THE ASSESSMENT OF ANAESTHETIC AGENTS FOR USE IN NEUROANAESTHESIA AND THE INTENSIVE CARE OF HEAD INJURIES

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D E C L A R A T I O N

I declare that I am the sole author of this thesis which contains original, investigative work organised and carried out by myself as a member of a research group, with advice and assistance of colleagues in the group, and that I have personally calculated the results.

Signed:

ABSTRACT

The relevant literature on the physiology and pathophysiology of the intracranial contents, the effects of anaesthetic agents on intracranial pressure (ICP) and cerebral blood flow (CBF) and the methodology of measurement of ICP is reviewed. The author's original work on the effect of anaesthetic agents and manoeuvres on ICP and cerebral perfusion pressure (CPP) in patients with intracranial pathology is described. The following results were obtained in patients who were about to undergo intracranial operations. The changes in ICP associated with intubation were small and were similar when thiopentone or Althesin were used together with d-tubocurarine for induction of anaesthesia even in patients with elevated ICP. Etomidate 0.2 mg/Kg intravenously caused a significant reduction in ICP ($0.01 > P > 0.001$) but caused no significant change in CPP. Tubocurarine 45 mg when given in combination with thiopentone or Althesin caused significant reductions in ICP ($0.05 > P > 0.02$), mean arterial pressure (MAP) ($P < 0.001$) and CPP ($P < 0.001$) and tubocurarine 15 to 20 mg caused a significant reduction in ICP ($0.05 > P > 0.02$) but caused no significant change in MAP or CPP. In hypocapnic patients fentanyl 0.2 mg caused small changes in ICP which could be in either direction and significant decreases in MAP ($0.01 > P > 0.001$) and CPP ($0.01 > P > 0.001$). Enflurane 2% also caused small changes in ICP which could be in either direction, and significant reductions in MAP ($P < 0.001$) and CPP ($P < 0.001$). In mechanically ventilated patients with head injury 50% nitrous oxide in oxygen increased ICP ($P < 0.001$) and exaggerated the increases in ICP associated with chest physiotherapy. Thiopentone and Althesin reduced the increases in ICP associated with chest

physiotherapy but did not prevent them. The relevance of these results to the anaesthetic and intensive care management of neurosurgical patients is discussed, and it is concluded that the information obtained helps the neuroanaesthetist to decide which anaesthetic agents are best used during intracranial surgery and the intensive care management of patients with head injury.

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ABBREVIATIONS

used in this thesis

B.P.	arterial blood pressure
BOC	British Oxygen Company
CBF	cerebral blood flow
CBV	cerebral blood volume
$CMRO_2$	cerebral metabolic rate for oxygen
CO_2	carbon dioxide
CPP	cerebral perfusion pressure
CSF	cerebrospinal fluid
CSFP	cerebrospinal fluid pressure
CT scan	computerised axial tomography scan
CVP	central venous pressure
CVR	cerebral vascular resistance
EDP	extradural pressure
EEG	electroencephalograph
Entonox	50% nitrous oxide in oxygen
F_IO_2	fractional inspired oxygen concentration
$[H^+]$	hydrogen ion concentration
ICP	intracranial pressure
KPa	Kilopascal(s)
MAC	minimal alveolar anaesthetic concentration
MAP	mean arterial pressure

Abbreviations (continued)

n	number of observations
$^{15}O_2$	^{15}oxygen-labelled oxygen
P	probability
$PaCO_2$	carbon dioxide tension in the arterial blood
PaO_2	oxygen tension in the arterial blood
PEEP	positive end expiratory pressure
Pvo_2	oxygen tension in the cerebral venous blood
rCBF	regional cerebral blood flow
SaO_2	oxygen saturation of the arterial blood
S.D.	standard deviation
S.E.M.	standard error of the mean
^{99}Tcm	^{99}technetium
VFP	ventricular fluid pressure
VPR	volume pressure response
$\bar{x}$	mean
^{133}Xe	^{133}xenon

I N T R O D U C T I O N

In order to make a rational choice of which anaesthetic agents to use during intracranial operations, the anaesthetist needs a thorough knowledge of the physiology and pathophysiology of the cranial contents, and of how they are affected by anaesthetic agents. The physiological parameters which are most important to the neuroanaesthetist are intracranial pressure (ICP), cerebral blood flow (CBF), cerebral blood volume (CBV), mean arterial pressure (MAP), cerebral perfusion pressure (CPP) and cerebral metabolic rate for oxygen ($CMRO_2$). In patients with intracranial pathology high ICP can cause brain shifts or reduction in CPP sufficient to cause cerebral ischaemia, thus it is necessary to minimise ICP changes during the anaesthetic and surgical care of such patients. In this thesis I will discuss the physiology and pathophysiology of the cranial contents, the effect of anaesthetic agents on ICP, CBF and CBV, the mechanisms whereby anaesthetics affect these parameters, and the influence on ICP of interactions between intracranial pathology and anaesthetic agents. Because the original work is concerned only with the measurement of ICP and MAP I will describe and discuss the methodology of ICP monitoring in detail and only briefly mention methods of measurement of CBF and CBV. I will then describe the original work and conclude by discussing the validity and clinical relevance of this work.

The original work deals with the effects of the intravenous anaesthetic agents thiopentone and Althesin on the changes in ICP and CPP during induction of anaesthesia and endotracheal intubation, and the effects of the intravenous induction agent etomidate, the narcotic analgesic fentanyl, the muscle relaxant d-tubocurarine and the volatile anaesthetic agent enflurane on ICP and CPP in patients

who were about to undergo intracranial surgery. It also includes investigations in patients with severe head injury who were being mechanically hyperventilated in which 50% nitrous oxide in oxygen (Entonox), thiopentone and Althesin have been used in an attempt to reduce the increase in ICP associated with chest physiotherapy, and the effect of Entonox on ICP has been measured in the absence of stimulation.

The aim of these investigations was to establish or confirm whether the anaesthetic agents investigated were suitable for use during intracranial surgery, and to determine whether particular anaesthetic agents were useful in preventing or attenuating changes in ICP associated with essential manoeuvres during anaesthesia and intensive care such as endotracheal intubation and chest physiotherapy. In the studies concerning fentanyl, d-tubocurarine and enflurane the work was done to clarify areas where the literature was contradictory, and the purpose of the other investigations was to provide information which was not available in the literature.

The work described in Chapters 4, 5, 7 and 9 has been published in the British Journal of Anaesthesia and Acta Anaesthesiologica Belgica, and reprints of these publications are included at the end of the thesis.

CHAPTER 1

FACTORS WHICH INFLUENCE INTRACRANIAL PRESSURE

(EXCLUDING DRUGS)

In order to make a rational assessment of studies of the effects of drugs on the cranial contents it is necessary to have a full understanding of the physiology and pathophysiology of the brain, cerebral circulation and cerebrospinal fluid. In this chapter I will therefore discuss the relevant physiology and pathophysiology of the cranial contents.

THE PHYSIOLOGY OF THE CRANIAL CONTENTS

The Contents of the Cranium

The adult cranium forms an almost rigid container which is in direct communication with the vertebral canal. It contains 1400 g. of brain, 130 ml. of blood (Hedlund and Nylin, 1962) and about 75 ml. of cerebrospinal fluid. About 14% of the brain volume is extracellular fluid (Woodward et al., 1967). 50% of the CSF is contained in the ventricles and cisterns and the rest covers the surfaces of the brain.

CSF is formed mainly in the choroid plexuses, which are present in all four ventricles, at a rate of about 0.4 ml./min. The rate of formation of CSF is independent of the age of the subject and of the level of ICP up to 15 mm Hg (Rubin et al., 1966; Cutler et al., 1968), except when autoregulation of CBF is impaired when the CSF formation rate may passively follow changes in CBF and CPP (Sklar et al., 1980). It is formed by an active secretion from the choroid plexus which is villous,

highly vascularised, and covered by a single layer of cuboidal cells supplied with various membrane elaborations and numerous mitochondria. Transependymal water follows the pumping of sodium (Pollay, 1975). This active transport of sodium into the CSF is inhibited by frusemide (Buhrley and Reed, 1972). CSF production is an energy-requiring secretory process involving at least two enzymes, carbonic anhydrase and an ouabain-sensitive sodium-potassium activated ATPase. The choroid plexus is supplied with an extensive system of autonomic nerves. Sympathetic stimulation causes a 32% reduction in the net rate of CSF production while sympathectomy gives a 33% increase (Lindvall et al., 1978). It is suggested that the sympathomimetic reduction in the rate of CSF production is the result of a combined β-receptor mediated inhibition of the secretion from the plexus epithelium, and a reduced blood flow in the choroid plexus tissue resulting from stimulation of the vascular α-receptors. CSF production rate is also reduced by cholinomimetic agents acting at receptors which appear to be of the muscarinic type (Lindvall et al., 1980).

The rate of CSF production is reduced by acetazolamide (Oppelt et al., 1963; Rubin et al., 1966; Cutler et al., 1968; Domer, 1969), frusemide (Reed, 1969; Buhrley and Reed, 1972), ethacrynic acid, triamterene and thiazide diuretics (Domer, 1969). Spironolactone significantly increases the rate of CSF formation (Domer, 1969). Metabolic and respiratory alkolosis reduce CSF production by 23% and 46% respectively, but metabolic and respiratory acidosis have no constant effect on CSF production (Oppelt et al., 1963).

CSF is mainly reabsorbed into the blood at the arachnoid

villi which consist of coiled microtubules without any membrane separating blood from CSF (Welch and Friedman, 1960). The process is mechanical depending on a pressure gradient between CSF and the blood of the venous sinuses. The minimum pressure gradient required for absorption is 5 mm Hg and at pressure gradients above this the rate of absorption is linearly related to the gradient (Rubin et al., 1966; Cutler et al., 1968). The absorption capacity exceeds the CSF production rate by at least four times (Rubin et al., 1966; Katzman and Hussey, 1970).

The resting level of CSF pressure is determined by the balance between formation and reabsorption. The rigid walls of the venous sinuses provide a resistance to blood flow and thus the venous sinus pressure is always greater than the intrathoracic pressure. The normal ICP is 0 to 10 mm Hg (Lundberg, 1960) and is the sum of the venous sinus pressure and the CSF to venous sinus pressure gradient. This pressure range is only valid for the horizontal position;if the head is on a pillow it is reduced by up to 2 mm Hg. Miller (1975) states that the normal ICP usually ranges between 0 and 10 mm Hg with an upper limit of 15 mm Hg, and Gilland and colleagues (1974) found an average lumbar CSF pressure in the horizontal position in young normal volunteers of 11.5 mm Hg (S.D. 2.7) with a maximum value of 17.7 mm Hg. Thus the upper limit of normal ICP can be taken to be approximately 15 mm Hg. The pressure fluctuates around the mean value.

The CSF pressure fluctuates with the heart beat and respiration. The transmission of the arterial pulse wave is believed to be produced partly by the pulsation of the intracranial arteries, particularly those at the base of the brain, and partly

by the pulsatile movements of the choroid plexuses. The amplitude of these pulsations increases when mean ICP is increased and when cerebral arterial vasodilatation occurs (both conditions may be present in diseased or damaged brain). The a-wave of the cerebral venous pressure (CVP) curve can also be identified in the CSF pressure curve as a small peak just before the arterial peak (Ponssen and Van den Bos, 1971). The height of the CSF pressure wave is dependent on the mean arterial blood pressure whilst the contour of the CSF pulse wave is shaped by rapid changes of cerebral blood volume (CBV) in the post-capillary cerebral vascular bed (Hamer et al., 1974).

The respiratory fluctuations in CSF pressure are in the same direction as the changes in intrathoracic pressure. Transmission of the intrathoracic pressure changes to the CSF may be partly through associated changes in systemic arterial pressure with respiration, but mostly via the jugular and vertebral veins because in animals CSF pressure variations continue with IPPV after death (Levinger and Kedem, 1972). Even after brain death when there is no blood flow through the brain, intracranial pulsations, with an amplitude as high as 10 to 30 mm Hg, may be seen in the ICP trace (Jorgensen et al., 1972).

A change in volume of any one of the intracranial contents must lead to a change in ICP unless compensatory changes in the volumes of the other constituents occur. Under normal circumstances compensation occurs and returns ICP to normal. The compensatory mechanisms include a reduction in intracranial blood volume due to the pressure exerted by the CSF on the thin-walled cerebral veins, displacement of CSF into the spinal subarachnoid space (which leads

to displacement of epidural venous blood from the vertebral canal), and increased reabsorption of CSF across the arachnoid villi. In dogs, 70% of the variation in volume in the craniospinal system was related to the spinal section and 30% to the cranial section, with the spinal compartment acting as an expansion vessel coupled to the rigid skull cavity (Lofgren and Zwetnow, 1973).

Interrelations between ICP, CBF and CBV

There is a linear correlation between changes in cerebral blood flow (CBF) and cerebral blood volume (CBV) (Risberg, 1969a; Smith et al., 1971; Phelps et al., 1973). Changes in CBF cause changes in CBV partly by changing the diameter of the arterioles and thus the volume of arterial blood in the brain, and partly by changing the volume of venous blood inside the cranium. The volume of venous blood will change because the resistance to flow through the almost rigid dural sinuses is virtually fixed. The cortical veins are readily distensible and if the outflow resistance remains constant whilst the blood flow changes, it follows that the pressure and thus the volume of blood in these veins will change. This explanation is supported by the observation of McDowall and colleagues (1966) that superior saggittal sinus pressure rises in parallel with ICP when halothane is administered to dogs. This change in volume of the venous blood in the cranium is the major cause of the change in CBV when CBF changes. If CBV increases then so will ICP, because the volume of one of the contents of the non-expansile cranium has increased. This increase in ICP will

last until compensatory mechanisms can return the volume of the intracranial contents to normal. A definite correlation between CBF and CSF pressure has been demonstrated (Shenkin et al., 1952; Hamer et al., 1974). Thus changes in CBF are accompanied by changes in CBV and ICP.

Physiological Influences on ICP

Changes in various physiological parameters may cause changes in CBF and ICP. Therefore, in order to study the effect on ICP of anaesthetic agents or techniques, it is necessary to know how these physiological influences may alter ICP and if possible eliminate their effects.

Arterial Blood Gas Tensions

Effect of $PaCO_2$ on ICP

CBF is very sensitive to changes in $PaCO_2$ (Smith et al.,1971). Hypocapnia causes a reduction and hypercapnia causes an increase in CBF (approximately 3%/KPa change in $PaCO_2$ (Okuda et al.,1974; Hauge et al., 1980)). The relationship appears to be linear over the physiological range (3.3 to 7.3 KPa) with a levelling off at very low $PaCO_2$ values (Hauge et al.,1980; Thoresen & Walloe,1980; Rhodes et al., 1981), although Brown and Donaldson (1976) found that the relationship was exponential. These latter authors reported that the response of CBF to changes in $PaCO_2$ was almost linear in the physiological range (4.8 to 5.3 KPa). Further evidence against a linear relationship between $PaCO_2$ and CBF is provided by Hayes and Tindall (1969), who

found only a small increase in CSF pressure between $PaCO_2$ values of 2.4 and 4.5 KPa, and the steepest increase between $PaCO_2$ values of 4.5 and 5.6 KPa in patients with cerebral tumours. Briggs and Adams (1973) found also that ICP changes may not always be linearly related to $PaCO_2$ in neurosurgical patients. No further increase in CBF occurs at a $PaCO_2$ greater than 10.6 KPa when CBF is increased by about 100% from normocapnic levels, and very little further decrease occurs at $PaCO_2$ values below 2.6 KPa, at which values CBF is reduced by about 40% from normocapnia (Harper, 1965; Harper and Glass, 1965; Thoresen and Walloe, 1980). This inability to reduce overall CBF below a certain level in response to a reduction in $PaCO_2$ may be due to blood flow levels being insufficient to remove acid metabolites (Cervos-Navarro et al., 1971-2). Alternatively, they may be explained by the exponential relationship between $PaCO_2$ and CBF, because the vessels have reached the limit of their responsiveness at such $PaCO_2$ values.

These CBF changes are accompanied by linearly related changes in CBV of approximately 3.75 ml/100 g./KPa change in $PaCO_2$ (Loehning et al., 1962; Greenberg et al., 1978), and these changes in CBV will in turn cause changes in ICP. Thus hypocapnia reduces ICP (Shenkin et al., 1952; Rich et al., 1953; Halldin and Wahlin, 1959; Lundberg et al., 1959; Greenbaum et al., 1975; Smith et al., 1981), and hypercapnia increases ICP (White et al., 1942; Shenkin et al., 1952; Rich et al., 1953; Small et al., 1960; Loehning et al., 1962; Hamer et al., 1974; Smith et al., 1981). Moderate hyperventilation in brain-injured patients or normal man causes a reduction in CBF and an increase in the cerebral arterio-venous oxygen difference, but causes no change in cerebral oxygen consumption

(McHenry et al., 1965; Gordon and Bergvall, 1973). The reduction in ICP with hypocapnia is a temporary effect lasting only 30 to 60 minutes in dogs (Rosomoff, 1963; Ueyama and Loehning, 1963) because reduced reabsorption of CSF returns the volume of the intracranial contents to normal. But the longer-lasting reduction in CBV tends to produce good neurosurgical operating conditions (Furness, 1957; Hayes and Slocum, 1962; Marrubini et al., 1964; Stern, 1972). Thus hyperventilation is routinely used for intracranial surgery today. During prolonged hyperventilation there is restoration of CSF pH to normal values and CBF to near normal values after 2 and 3-5 days respectively of hyperventilation produced by the hypoxia of altitude (Severinghaus et al., 1963, 1966). Normalisation of CBF therefore occurs within 3 days but the exact time course is unclear. In goats and baboons Alexander et al. (1968b)and McDowall and Harper (1968, 1970) found no return of CBF or cerebrovascular resistance (CVR) towards control values during 3 to 4 hours of hypocapnia despite return of CSF pH towards normal, while Raichle et al. (1970) showed that in conscious man CBF had returned to 90% of control values after 4 hours of hyperventilation, which is still considerably longer than the 30 minutes required for the restoration of normal ICP (Rosomoff, 1963). CBF overshot the control value by a calculated 31% when the original $PaCO_2$ was restored. It must be stressed that these observations were made in the absence of intracranial pathology and caution must be exercised in applying them in the presence of intracranial compression. Christensen (1973) showed that during controlled hyperventilation in patients with stroke, the CSF pH adapted with an estimated half time of 6 hours and was complete within 30 hours and the ICP changes showed a similar time

course, indicating that rapid normalisation of ICP does not occur during hyperventilation in patients with stroke.

Possible disadvantages of hyperventilation are that a high minute volume may increase ICP (Schettini et al., 1967) and extremely low $PaCO_2$ values (<2.67 KPa) may cause cerebral ischaemia as demonstrated by an increase in CSF lactate (Plum and Posner, 1967; Alexander et al., 1968c; Miller and Ledingham, 1971) and a reduction of cerebral venous PO_2 to less than 2.67 KPa in man (Wollman et al., 1965) and significant cerebral lactate production in children (Settergren et al., 1973) and in dogs (Alberti et al, 1975). There is limited evidence that extreme hyperventilation may increase the susceptibility to cerebral hypoxia when CPP is lower than 50 mm Hg (Harp and Wollman, 1973). Alexander and Granholm (1968) state that there seems to be conclusive evidence that hyperventilation to $PaCO_2$ values below 2.67 KPa causes a lowering of CBF of such a degree that tissue hypoxia ensues. Campkin et al. (1974) found no biochemical evidence of cerebral ischaemia at a $PaCO_2$ of 3.21 ± 0.39 KPa in normothermic neurosurgical patients receiving 50% oxygen, whereas Cohen et al. (1968) found that changes in cerebral metabolism indicative of cerebral hypoxia were beginning during mild hypocapnia, and that there was a significant degree of anaerobic metabolism during severe hypocapnia ($PaCO_2$ 1.35 KPa). Thus from the evidence currently available there appears to be little danger of cerebral hypoxia at $PaCO_2$ values of 3.3 KPa and above (Harp and Wollman, 1973).

During hypercapnia, as during hypocapnia, CSF pH and CBF adapt to the new $PaCO_2$ value, and this adaptation can be detected within 8 to 11 hours (Agnoli, 1968). After a brief period of uncomplicated hypercapnia a return of $PaCO_2$ to normal produces immediate restoration of normal ICP, but if acute hypertension occurs during hypercapnia

cerebral oedema may be produced causing a more prolonged elevation of ICP (Marshall et al., 1969).

Effect of PaO_2 on ICP

There is no change in CBF until the PaO_2 falls below 6.67 KPa, but major increases occur if the PaO_2 is reduced further (McDowall, 1966a; Kogure et al., 1970b). ICP changes will show a similar pattern with an increase occurring during severe hypoxia (Small et al., 1960). At a PaO_2 of about 4.67 KPa in conscious human volunteers CBF is nearly doubled (Cohen et al., 1968). The relationship between CBF and SaO_2 is linear in the hypoxic range of PaO_2 values (Stoyka et al., 1978), and maximum vasodilatation occurs at an arterial oxygen saturation of about 25% in dogs (Ekstrom-Jodal et al., 1979).

Following hypoxia CBV and ICP may not return to normal immediately after the restoration of normoxia (Freeman and Ingvar, 1968) because of cerebral hyperaemia, and even if ICP returns to normal values on restoration of normoxia it can increase again in the following few hours due to developing brain oedema (Loehning et al., 1962). Autoregulation to blood pressure changes may be impaired after hypoxia (Freeman and Ingvar, 1968; Kogure et al., 1970a).

80% oxygen did not significantly alter CBF from its value at normoxia in man (Turner et al., 1957), but 100% oxygen at 1 atmosphere pressure reduced CBF by 11 to 12% (Jacobsen et al., 1963; McDowall, 1966a) and ICP by 23% (Miller et al., 1970).

Combined hypoxia and $PaCO_2$ changes

In cats hypercapnia increases the sensitivity of the cerebral vessels to hypoxia with an increase in CBF occurring at higher PaO_2 values (Flohr et al., 1970), and combined hypoxia and hypercapnia has been shown to cause damage to the blood-brain barrier, cerebral oedema production and thus a sustained elevation in brain surface pressure (Schettini et al., 1972).

Conversely mild hyperventilation can completely overcome the vasodilator effect caused by a PaO_2 of 5.3 KPa (Shapiro et al., 1970).

Cerebral Perfusion Pressure

Before discussing autoregulation it is necessary to discuss the concept of cerebral perfusion pressure (CPP). Blood flows through the brain because there is a difference in pressure between the arteries and the veins. The veins on the brain surface are thin-walled and the pressure in these veins must closely approximate to CSF pressure, otherwise they would collapse. Greenfield and Tindall (1965) have shown that the cerebral veins within the sub-arachnoid space are not collapsed at a CSFP of 73.5 mm Hg in man. Thus in discussing cerebral perfusion the venous pressure in the thin-walled cerebral veins which drain into the venous sinuses must be considered. As this pressure approximates to CSF pressure it follows that CPP should be calculated by subtracting mean CSF pressure from mean arterial pressure (MAP). This concept of CPP has been confirmed by Johnston and Rowan (1974b)in studies on baboons. The normal cerebral perfusion pressure in man is approximately 85 to 95 mm Hg.

The concept of an overall CPP is probably too simplified particularly in patients with expanding intracranial space-occupying lesions. In such patients local tissue pressure will not be constant throughout the brain and thus local cerebral perfusion pressure will vary in different areas of the brain.

Autoregulation of CBF

CBF remains constant in normotensive man between mean arterial pressure values of approximately 60 and 130 mm Hg (Lassen, 1959; Strandgaard et al., 1973; Lassen, 1978). Above and below these limits CBF becomes pressure passive. When the MAP is 29 to 55 mm Hg and CBF is reduced to approximately 30 ml/100 g./min. clinical signs of cerebral ischaemia occur (sighing, syncope, dizziness, restlessness, disorientation and confusion) (Finnerty et al., 1954; Moyer et al., 1954b). During hypocapnic nitrous oxide halothane anaesthesia CBF can be reduced to 18 ml./100 g./min. before neurological damage can be demonstrated (Boysen et al., 1974). CBF also autoregulates in response to increasing levels of ICP with an increase in postcapillary resistance and a decrease in precapillary resistance (Shulman and Verdier, 1967) and does not become pressure passive until the cerebral perfusion pressure is reduced below 30 to 50 mm Hg in animals (Jennett et al., 1970; Johnston et al., 1972; Miller et al., 1972, 1973; Zwetnow, 1970a; Hamer et al., 1973; Haggendal et al., 1970a, 1970b), but in damaged brain when autoregulation is lost CBF will fall at lower levels of raised ICP (Miller et al., 1973). Jennett et al. (1970) found that the lower limit of autoregulation in baboons was the same regardless of whether the CPP was reduced by decreasing MAP

or by increasing ICP, whereas in monkeys Grubb et al. (1975) found that the limit was lower if CPP was decreased by increasing ICP (CPP of less than 30 mm Hg) than if it was reduced by decreasing MAP (CPP of 80 mm Hg). The difference in findings might be explained by the different methods used to reduce the MAP, as the former author used trimetaphan whilst the latter used trimetaphan in 50% of the animals and haemorrhage in the others and it is known that autoregulation is lost at a higher CPP during haemorrhagic hypotension than during drug-induced hypotension (Fitch et al., 1976). Autoregulation fails in baboons during haemorrhagic hypotension at an MAP of 65% of baseline whereas in drug-induced hypotension it fails at 35-45% of baseline (Fitch et al., 1976). After chemical or surgical sympathectomy autoregulation persists to significantly lower levels of MAP (approximately 35% of the baseline value) during haemorrhagic hypotension (Fitch et al., 1975). It is postulated that under conditions of haemorrhagic hypotension constriction of the extraparenchymal cerebral vessels in response to sympathetic stimulation reduces the possible range of autoregulation. This effect is less noticeable in hypertensive baboons (Fitch et al.,1978).

In man Greenfield and Tindall (1965) found that CBF was maintained up to CSF pressures of about 28 mm Hg which indicated a lower limit of autoregulation of 55 to 60 mm Hg. The rate of increase of ICP is important because if ICP is rapidly increased CBF declines immediately, but if the ICP increase is gradual no change in CBF will occur up to an ICP of 30 to 50 mm Hg (Langfitt, 1965a).

Elevation of the internal jugular venous pressure to 12.4 to 30 cm H_2O had no significant effect on CBF but caused a marked increase in ICP (Moyer et al., 1954a). Raisis et al. (1979) found

that monkey pial vessels dilated as cerebral venous pressure was increased and CBF remained constant up to a cerebral venous pressure of 75 mm Hg so there is autoregulation to an increase in cerebral venous pressure.

Several authors have reported a delayed response to a change in CPP of from 10 to 120 secs (but probably less than 60 secs) (Kogure et al., 1970a; Lassen and Agnoli, 1972; Ekstrom-Jodal, 1970; Symon et al., 1973). Lassen and Agnoli (1972) found that a sudden increase in B.P. may overcome autoregulation temporarily, while the same elevation more slowly does not overcome autoregulation. Thus autoregulation to a change in CPP is not immediate.

There are no significant biochemical changes suggestive of tissue hypoxia in the rat or dog brain until intracranial hypertension reduces CPP below 30 to 40 mm Hg (Siesjo and Zwetnow, 1970; Zwetnow, 1970a, 1970b; Hamer et al., 1973; Locke et al., 1971).

In dogs autoregulation was achieved in the major arteries supplying the circle of Willis and only when alterations of perfusion pressure were too large for the disturbance to be eliminated by the major arteries did resistance changes in smaller brain arteries become evident (Mchedlishvili et al., 1973).

Autoregulation of CBF occurs in all regions of the brain and spinal cord (including the brain stem and cerebellum) and during severe haemorrhagic hypotension redistribution of CBF occurs with preservation of flow to the cortical grey matter and brain stem (Heistad et al., 1977).

In hypertensive patients the CBF is the same as in normotensive patients but the CVR is increased in both grey and white matter, and the upper limits of autoregulation are shifted to a higher level,

with an upper limit of up to 160 mm Hg MAP (Strandgaard et al., 1973), depending on the severity of the hypertension. The range of blood pressure over which autoregulation occurs may be somewhat less in hypertensive patients than in normotensive individuals and the less distensible vessels in the elderly patient may reduce the range still further (Jones and Graham, 1978). A sudden reduction in blood pressure in the hypertensive patient may cause a marked reduction in CBF (Hansson, 1979), but if the blood pressure is gradually reduced over several months the autoregulation curve will tend to shift back towards normal (Hansson, 1979; Pistolese et al., 1977; Strandgaard, 1978). Some hypertensive patients, however, do not readapt their autoregulation towards normal during treatment (Strandgaard, 1978). Brain hypoxia occurs at an MAP of about 70 mm Hg in untreated hypertensive patients compared with 40 mm Hg in normotensives (Strandgaard et al., 1973).

An increase in MAP above the autoregulatory limit in animals, particularly during hypercapnia (which reduces the autoregulatory pressure range (Harper, 1966; Eckstrom-Jodal et al., 1971-2)) may cause distension of the cerebral arterioles and a large increase in CBF causing an increase in hydrostatic pressure in the capillaries and venules, focal disruption of the blood-brain barrier and oedema formation (Schutta et al., 1968). This has been termed 'breakthrough' of cerebral autoregulation by Lassen and Agnoli (1972). If the blood pressure increase is abrupt it may cause dysfunction of the blood-brain barrier and cerebral oedema even when the change is within the limits of autoregulation, and if autoregulation is impaired or abolished such damage could occur with less pronounced pressure changes (Haggendal and Johansson, 1971-2). The upper limit of autoregulation

may be lowered in the early stages of development of brain pathology, thus acute hypertension should be avoided during neurosurgical anaesthesia (Alexander and Lassen, 1970; Shapiro et al., 1972c; Leech et al., 1974).

During stimulation of cervical sympathetic nerves the upper limit of autoregulation is shifted upwards (Bill and Linder, 1976; Mackenzie et al., 1977) thus protecting against the increase in blood pressure during increased sympathetic activity, and preventing or reducing breakdown of the blood-brain barrier and formation of cerebral oedema (Beausang-Linder and Bill, 1981).

Fitch et al. (1976) showed that autoregulation was lost during haemorrhagic hypotension at a higher MAP (approximately 65 mm Hg) than with drug-induced hypotension (approximately 35 mm Hg) and α-adrenergic receptor blockade reduced the lower limit of autoregulation during haemorrhagic hypotension (Fitch et al., 1975) suggesting that cerebral vasoconstriction, due to sympathetic activity during haemorrhagic hypotension, reduces the range of autoregulation. This observation was confirmed by Hamar et al. (1979).

Hypercapnia narrows the range of autoregulation (Ekstrom-Jodal, 1971-2; Harper, 1966; Parolla and Beer, 1975), and autoregulation is lost at $PaCO_2$ values of 9 to 12 KPa in dogs (Harper, 1966). Autoregulation may be restored by hypocapnia (Paulson et al., 1972).

Autoregulation is impaired following hypoxia (Freeman and Ingvar, 1968) being lost only when PaO_2 is maintained below 3.3 KPa for 4 to 6 minutes (Kogure et al., 1970a). The fact that autoregulation is maintained even after hypoxia has produced an increase in CBF and decrease in cortical pH suggests that autoregulation is not due to parenchymal acidosis (Kogure et al., 1970a).

When hypotension is extreme and prolonged autoregulation may be abolished whether the hypotension is caused by bleeding (Freeman and Ingvar, 1968), by halothane anaesthesia (Keaney et al., 1973b), by nitroprusside infusion (Keaney et al., 1973a) or by trimetaphan infusion (Gamache et al., 1976) and impairment of autoregulation may last for more than 2 hours.

Dilatation of cerebral vessels in response to mass-induced intracranial hypertension has been demonstrated angiographically in dogs (Goodman and Wilson, 1971), and such hyperaemia may persist when the ICP is returned to normal after intracranial hypertension has caused a reduction of CPP to levels at which CBF was reduced (Haggendal et al., 1970b; Grubb et al. 1975). This hyperaemia lasts for up to 90 minutes and grossly coincides with the time taken for the disturbance of the energy metabolites to be corrected (Zwetnow, 1970a).

Mean CBF must be decreased to levels as low as 30% of normal for as long as 30 minutes in order to produce conditions which lead to brain oedema (Gamache et al., 1976).

There is a widespread clinical impression that 'brain bulk' is reduced by only moderate decreases in blood pressure during intracranial surgery (Mazzia et al., 1956). This is probably due to disturbance in autoregulation, caused by brain pathology or surgical manipulation, which allows the CBF, at least regionally, to follow the arterial pressure passively.

Neurogenic Influences on CBV

Stimulation of the sympathetic nerves supplying the cerebral vessels causes vasoconstriction and a reduction in CBV (Edvinsson, 1971-2; Harper et al.,1972; D'Alecy et al.,1979) and acetylcholine causes vasodilatation (Nielsen et al.,1973; Edvinsson and Owman,1973; Aoyagi et al.,1975; Matsuda et al.,1976; Toda,1979) as does stimulation of VII nerve when the centripetal effects of such stimulation are prevented (Salanga and Waltz, 1973). The extent of the change in CBF due to sympathetic stimulation is no more than 10% (Harper et al., 1972). Sympathetic stimulation increases the upper level of auto-regulation (Bill and Linder, 1976).

On morphological grounds and from physiological data it appears that there is a dual control of the cerebral circulation, the extra-parenchymal vessels being influenced by the sympathetic nervous system while the intraparenchymal vessels are under local intrinsic metabolic regulation. The pial vessels are possibly influenced by both systems (Harper et al.,1972; Ishii et al.,1975). It is possible that the increase in CBV which occurs in the early stages of brain swelling in patients with cerebral trauma is neurogenic in origin.

The Effects of CVP Changes

Changes in CVP or intrathoracic pressure can affect ICP by two mechanisms: firstly the increased pressure may be transmitted through the jugular and vertebral veins, thus increasing cerebral venous pressure, CBV and ICP; and secondly the pressure may be transmitted to the epidural veins in the thoracic vertebral canal, the distension of these veins may elevate CSF

pressure and displace CSF from the spinal to the cranial compartment (Hamilton et al., 1936; Williams, 1970, 1976). The latter mechanism is probably the most important particularly during rapid changes in intrathoracic pressure, for example due to coughing, which can cause significant increases in ICP (Brennan, 1938; Hunter, 1952; Stephen et al., 1954; Lundberg, 1960). Coughing causes CSF pressure below the foramen magnum to increase before ICP in the posterior fossa, and CSF pressure can exceed 100 mm Hg in the lumbar region (Williams, 1970, 1976). Thus the increase in ICP is probably caused by a wave of CSF passing upwards in the subarachnoid space, but part of the increase may be due to an increase in venous pressure around the cistern (Williams, 1976). Increases in intra-abdominal pressure, for example, due to incorrect prone positioning or straining due to inadequate doses of muscle relaxants, also act mainly through changes in epidural venous pressure and volume.

Lofgren (1976) has analysed the intracranial effects of central venous pressure changes. When the skull is closed isolated short-term increases in intrathoracic and systemic venous pressure may be of little consequence, because cerebral venous pressure and CSF pressure increase in parallel and the system remains balanced. If CPP is not significantly reduced there is no change in the relationships between the volumes of the cranial contents and there will be no volume displacements. The increase in CSF pressure will be slightly less than that in the central veins as there is a gradient of pressure along the veins. The head-down posture will similarly produce a balanced system when the cranium is closed because the effects on CVP and CSF pressure will balance each other. Elevation of the head of the bed leads to a decrease in ICP in most patients

with brain oedema (Shalit and Umansky, 1977; Abbushi, 1980).

However, any manoeuvre which increases intracranial venous pressure alone, for example compression of the neck veins, will cause the system to become unbalanced, there is a localised expansion of the veins, an increase in ICP (Moyer et al., 1954a; Stephen et al., 1954; Shalit and Umansky, 1977), and dislocation of CSF to the spinal compartment. Thus obstruction of the great veins of the neck, for example by extreme positions of the head, elevates cerebral venous pressure, CBV and ICP (Brennan, 1938; Hulme and Cooper, 1976). Head rotation of 90° to either side may partially or totally occlude the ipsilateral internal jugular vein, whereas flexion of the neck does not appear to affect internal jugular vein blood flow (Lipe and Mitchell, 1980). The increase in ICP on rotation of the head is associated with an increase in jugular venous pressure (Shalit and Umansky, 1977). In addition, when the craniotomy bone flap has been removed the balancing effect of the associated CSF pressure increase is removed, and changes in systemic venous pressure will produce changes of the relative volumes of the cranial contents. The cerebral congestion induced by coughing and straining when the cranium is open may persist for at least 30 minutes (Hunter, 1952).

When the cranium is closed an increase in CVP displaces the CSF pressure-volume curve in parallel along the pressure axis in proportion to the increase in venous pressure, but the elastance of the system is not appreciably affected. The volume change consequent upon an increase in systemic venous pressure results in a transient and reversible change in ICP, the magnitude of which depends on the value of the elastance at the pre-existing pressure level. The ICP then decays exponentially at a rate which is a

function of the ratio between the outflow resistance and the elastance of the system. If the elastance of the system is increased, an increase in CVP may cause very large increases in ICP which may be further augmented by transtentorial or foraminal herniation which shuts off the volume buffering action of the spinal compartment.

The different modes of controlled ventilation can alter CVP in different ways. Intermittent positive pressure ventilation (IPPV) causes an increase in intrathoracic pressure and CVP, and ventilation with excessive tidal volumes may lead to increases in ICP (Schettini et al., 1967). Negative phase can be used to achieve a lower CVP and ICP (Schettini et al., 1967), but Lundberg and colleagues (1959) suggest that it probably makes very little difference in practice. High frequency positive pressure ventilation has little effect on mean ICP or CPP even when ICP is high, but does reduce ventilator linked fluctuations in ICP and arterial pressure and thus may facilitate microsurgery (Todd et al., 1981). Positive end expiratory pressure (PEEP) increases systemic venous pressure which will tend to increase ICP, tends to reduce arterial pressure which reduces ICP, and causes cerebral vasodilatation because of the auto-regulatory response to the decrease in arterial pressure and increase in ICP. Several authors have shown significant increases in ICP when PEEP was applied (Apuzzo et al., 1977; Shapiro and Marshall, 1978; Abbushi, 1980; Kikuta et al., 1980), although the increases can be reduced or abolished by a head-up tilt (Frost, 1977;. Abbushi, 1980). Decreases in CPP have also been reported (Apuzzo et al.,1977; Shapiro and Marshall, 1978; Kikuta et al., 1980; Doblar et al., 1981). By increasing ICP PEEP may produce a critical reduction in blood flow in

regions of the brain where marginal conditions for tissue perfusion exist, for example, in focal expanding lesions caused by trauma or ischaemia in which existing vasodilatation reduces the capacity for further compensatory dilatation when the local tissue pressure is increased. This is particularly likely to occur if the PEEP causes hypotension. The presence of intracranial hypertension diminishes the increases in ICP seen at a given level of PEEP because there is greater compression of the cerebral veins as they enter the dural sinuses, thus the effect of an increase in CVP will be less (Huseby et al., 1981). Termination of PEEP tends to cause an overshoot in ICP because the arterial pressure increases and temporarily overcomes the autoregulation mechanisms. Neurological dysfunction has been demonstrated in cats during the application of PEEP (Aidinis et al., 1976). This could be explained by brain displacement or cerebral ischaemia.

The Influence of Hypothermia

Hypothermia lowers CBF and $CMRO_2$ (Stone et al., 1956; Rosomoff and Holaday, 1954; Michenfelder and Theye, 1968), brain volume (Rosomoff and Gilbert, 1955), and ICP (Rosomoff and Gilbert, 1955; McQueen and Jeanes, 1962).

Pain or Peripheral Stimulation

Pain and anxiety induce a marked increase in CBF and $CMRO_2$ (Ingvar, 1975; Kety, 1975). These effects are of an arousal nature and are probably related to enhanced neuronal function and

catecholamine release in the brain, because in rats stress causes a marked catecholamine mediated increase in CBF and $CMRO_2$ (Carlsson et al., 1977). ICP increases can be seen in head injured patients during painful stimulation such as arterial blood sampling and during application of a facemask to neurosurgical patients (Greenbaum et al., 1975). These increases are presumably due to arousal.

Surgical Manoeuvres

Surgical manoeuvres such as insertion of the Gigli saw guide and application of a head clamp can cause marked increases in ICP without increases in arterial or central venous pressures (Shapiro et al., 1972a, 1972c). Pressure on the brain substance during removal of the bone flap can also increase CSF pressure (Stephen et al., 1954).

* * * *

Thus during investigations into the effects on ICP of anaesthetic agents and techniques it is important to keep the $PaCO_2$, PaO_2, temperature, posture and inflation pressures constant, and to avoid surgical stimulation, because alteration of any of these factors will alter the ICP response. In the interpretation of the results it is important to take into account changes in CVP, arterial pressure and CPP.

PATHOPHYSIOLOGY OF THE INTRACRANIAL CONTENTS

Raised Intracranial Pressure

There is no evidence that increased hydrostatic pressure has a direct effect on neuronal function or structural integrity in the brain. The adverse effects of raised ICP produce neuronal damage indirectly, through cerebral ischaemia or because of brain shift, and in each of these mechanisms elevated ICP is only one of several factors that interact to injure the brain (Miller, 1975; Miller, 1979b). When the brain and cerebrovascular system are relatively normal, central nervous system function can continue in some patients despite ICP values in excess of 100 mm Hg and cerebral perfusion pressures of 10 mm Hg or less (Miller et al., 1972). In dogs , when CBF is reduced by elevating ICP, a CBF of 40 to 50% of control appears to be adequate to maintain normal brain energy metabolites while a lower CBF is not(Bruce et al.1972). When the brain is deformed and the cerebrovascular bed is structurally or functionally compromised much smaller increases in ICP may be associated with neurological deterioration. Chawla, Hulme and Cooper (1975) have reported that there is a decrease in CBF and cortical available oxygen when ICP is greater than 40 mm Hg, but this varies from patient to patient. Thus the level of ICP at which reduction should be attempted is uncertain. Repeated insults to the brain in the form of elevations of ICP ultimately impair autoregulation, even if none of the individual rises of pressure has been sufficient to cause cerebral ischaemia (Miller et al., 1973), and if autoregulation is impaired any increase in ICP will cause a fall in CBF (Miller et al., 1972). Locally expanding mass lesions may affect local CBF by producing tissue pressure differentials.

The Pressure-Volume Curve

The pressure-volume curve of the intracranial contents describes the ICP changes associated with increasing volume of one of the intracranial contents. Due to compensation for the change in volume the pressure remains fairly constant until all the compensation is used up when there is a steep rise in pressure. Even before the compensation is used up a rapid increase in volume of any one of the contents, for example an increase in CBV due to halothane administration, may cause a steep increase in ICP.

Thus when a space-occupying lesion begins to enlarge, there is little change in ICP, due to compensatory shifts of venous blood and CSF out of the skull. While this is occurring, however, the reserve of compensation is being used up, and any additional volume results in a large ICP increase. Most patients with intracranial pathology are on the flat compensated part of the pressure volume curve, though they are at various stages on the way to exhaustion of the compensating reserve. It is only at a very late stage, when all the compensation is used up, that patients (usually those with rapidly expanding space-occupying lesions) reach the steep section of the curve and ICP rises rapidly. At this stage there is cerebral vasomotor paralysis with loss of both autoregulation and responsiveness to $PaCO_2$ changes (Langfitt et al., 1965b) and ICP follows the arterial pressure passively.

Pressure Gradients and Brain Shifts

With any stimulus which causes an increase in ICP, pressure gradients must exist until equalisation of CSF pressure occurs and such gradients have been demonstrated between the supratentorial and spinal CSF spaces in patients with intracranial disease, particularly in relation to temporal lobe herniation through the tentorium (Smyth and Henderson, 1938; Kaufmann and Clark, 1970). Pressure gradients have also been demonstrated between the supratentorial and infratentorial CSF spaces in dogs (Fitch and McDowall, 1971) and in baboons (Johnston and Rowan, 1974a). Usually these gradients are compensated for by CSF pressure equalisation because this pressure remains essentially the same throughout the CSF space, but a point eventually occurs when CSF pathways become obstructed due to brain shift and impaction of the brain occurs. Brain shift occurs because the local tissue pressure around an expanding space-occupying lesion is greater than the pressure in other areas of the brain. This pressure is dissipated throughout the surrounding brain and CSF, and gradients are difficult to measure until brain shift has caused interruption of the CSF pathways. For brain shift to occur, however, there must be some pressure gradient and differential pressures must exist in relation to a rapidly expanding intracranial mass whose rate of expansion exceeds the rate of adjustment of the intracranial compensating mechanisms. As well as generating shearing forces and brain shift, such pressure gradients will favour propagation of oedema (Paulson, 1972). Actual shift of brain tissue may cause brain damage by direct compression, will lead to distortion of local blood supply and may cause obstruction of cerebral venous drainage by kinking of the cortical veins as they enter the venous sinuses.

In addition to pressure cones occurring through the foramen magnum (Cushing, 1902) and through the tentorium (Jefferson, 1938) when the cranium is intact, there is the danger of external herniation and upward shifts through the tentorium when external decompression is performed.

Intracranial Pressure Waves

Lundberg (1960) described three types of variations of ICP or pressure waves: A-waves or plateau waves which have an amplitude of 50 to 100 mm Hg lasting for 5 to 10 minutes (although it is now more generally accepted that these waves can last up to 20 minutes); B-waves, or one per minute waves (usual range $\frac{1}{2}$ to 2 per minute) with an amplitude of 20 to 25 mm Hg; and C-waves, or 6 per minute waves, which are related to rhythmic variations of the systemic arterial blood pressure (Traube-Hering waves). Risberg and colleagues (1969b) suggest that plateau waves are caused by an initial limited increase in ICP which may have been precipitated by a spontaneous variation in cerebrovascular resistance (Kjallquist et al., 1964) which in turn causes an increase in CBV and thus in ICP (Lundberg, 1972). This increase in ICP cannot be compensated for because of existing compression and leads to a further decrease in cerebrovascular resistance which in turn leads to a further increase in CBV and ICP. The cerebral vasodilatation allows the blood pressure to be transmitted straight through to the cerebral capillaries causing cerebral oedema and a further increase in ICP. Thus dilatation of the cerebral vessels seems to be of primary importance in the production of a plateau wave. The initial

limited increase in ICP will also induce compression of the outlets of the leptomeningeal veins (Laas and Arnold, 1981) which will lead to cerebral venous distension and contribute to the increase in CBV.

Tindall et al. (1972b) reported that a transient $PaCO_2$ increase often preceded the development of a plateau wave. This could be the cause of the initial decrease in CVR which precipitates the plateau wave.

Johnstone et al. (1975) found that CBF remained at control levels despite falling cerebral perfusion pressures during plateau waves, and that there was a marked cerebral hyperaemia between pressure waves.

Global Effects of Cerebral Pathology on the Circulation

If ICP is increased rapidly (for example by expanding an intracranial balloon) CBF declines (Langfitt, 1965a), and ceases when ICP exceeds the MAP, but with a gradual rise in ICP there is a minimal change in CBF until the CPP is reduced below the lower level of autoregulation. As ICP increases cerebral vasodilatation occurs (Goodman and Wilson, 1974) and eventually the associated increase in CBF increases CBV and thus ICP, so that a vicious circle develops until ICP equals MAP. Restoration of ICP to normal after a period of intracranial hypertension, for example by removal of an intracranial mass, may also cause cerebral vasodilatation (Langfitt et al., 1965a; Grubb et al., 1975; Zwetnow, 1970a) which usually lasts for 30 to 90 minutes.

Langfitt et al. (1965b) have described 4 stages of cerebrovascular compensation and decompensation in response to increasing intracranial space occupation:- Stage 1: a period of spatial compensation, loss of CSF and possibly blood from the cranium; Stage 2: when the intracranial volume is sufficiently increased to cause an increase in ICP leading to vascular dilatation which further increases volume and pressure; Stage 3: failure of the vasopressor mechanism (i.e. the increase in MAP in response to the increase in ICP) with a terminal pressure wave causing the arterial pressure to fall to the level of the ICP; Stage 4: vasomotor paralysis is complete with ICP and MAP becoming inseparable (which can only occur if respiration is being supported because apnoea occurs).

Trauma to the cat brain impairs cerebral autoregulation and under these conditions an increase in MAP is transmitted straight to the capillary bed producing acute cerebrovascular congestion and oedema (Marshall et al., 1969). Similar changes can occur when hypertension is combined with hypercapnia or follows a period of profound hypotension in the absence of trauma to the brain. Impairment of autoregulation which may be global or localised is also found in patients with head injuries (Enevoldsen and Jensen, 1978), ischaemic brain lesions (Fieschi et al., 1968; Hoedt-Rasmussen et al., 1967; Paulson, 1970; Zinke et al., 1979), subarachnoid haemorrhage (Heilbrun et al., 1972), cerebral tumours (Palvolgyi, 1969), except for meningiomas in which autoregulation is usually well preserved (Schmiedek et al., 1975) and during seizure activity (Plum et al., 1968). In severe head injury apparently preserved autoregulation is not always a good sign because it may not be a true autoregulation. It may be due to an increase in tissue pressure caused by raised

arterial pressure in the absence of normal autoregulation (Enevoldsen and Jensen, 1978). There is evidence that, in the presence of space-occupying lesions, there is more rapid exhaustion of autoregulatory capacity in the hemisphere subjected to greater compression (Symon et al., 1974).

Carbon dioxide reactivity is also altered in the presence of intracranial pathology. It is less commonly altered than autoregulation in patients with ischaemic lesions (Hoedt-Rasmussen et al., 1967; Fieschi et al., 1968; Paulson, 1970; Zinke et al.,1979). It is also altered in severe head injury, returning to normal as recovery occurs (Cold et al., 1977a, 1977b; Enevoldsen and Jensen, 1978; Nyary and Pasztor, 1978), in cerebral tumours (Palvolgli,1969; Schmeidek et al., 1975), and experimental subarachnoid haemorrhage (Hashi et al., 1972). Loss of autoregulation and cerebrovascular reactivity to CO_2 may not always occur in the same areas of brain (Fieschi et al., 1968). Acute brain injury tends to affect autoregulation first and all vasomotor control later (Alexander and Lassen, 1970).

This loss of autoregulation and carbon dioxide reactivity in relation to cerebral pathology has been termed the 'luxury perfusion syndrome' by Lassen (1966), because the CBF is in excess of that required to satisfy the metabolic requirements of the area of brain tissue involved. It may be due to the expanding mass lesion compressing vessels which leads to ischaemia and lactic acidosis which in turn causes vasoparalysis. It could, however, be due to abnormal brain metabolism leading to accumulation of acid metabolites.

It is of special practical importance that only very mild

local compression of brain tissue seems able to elicit the vicious circle of acidosis, hyperaemia, blood brain barrier damage, oedema, and local compression which creates further acidosis and so on. Thus, during neurosurgery, gentle retraction and manipulation of the brain is essential (Lassen, 1968a).

Cerebrovascular carbon dioxide reactivity can also be significantly impaired in hypertensive patients (Griffith et al., 1978) and diabetics (Dandona et al., 1978).

In diffuse chronic brain diseases, e.g., senile dementia, cortical blood flow is reduced (Bower et al., 1970; Ingvar and Gustafson, 1970) but cerebrovascular control is unaltered (Lassen, 1971; Simard et al., 1971) and in diffuse cerebrovascular disease the cerebrovascular response to CO_2 is largely maintained (McHenry et al., 1972).

Focal Effects of Cerebral Pathology on the Cerebral Circulation

Focal loss of autoregulation and carbon dioxide reactivity in the region of a cerebral tumour, infarct or area of oedema may lead to intracerebral steal when there is cerebral vasodilatation in normal brain tissue. This is a paradoxical decrease in flow through the damaged region when CBF through normal brain is increased for example by an increase in $PaCO_2$ (Fieschi et al., 1968; Palvolgyi, 1969; Paulson, 1970; Waltz, 1970). Several authors could not demonstrate intracerebral steal with volatile agents (Smith et al., 1973b; McKay et al., 1976). These authors showed an increase in CBF with halothane and enflurane in the ischaemic territory, but Hanson and colleagues (1975) and De Rood and co-workers

(1974) showed that halothane caused steal phenomena in ischaemic areas.

Conversely, if cerebral vasoconstriction is induced in normal brain tissue in the presence of focal vasoparalysis an increase in flow through the damaged region, which has been termed inverse intracerebral steal, can occur. Inverse intracerebral steal has been demonstrated during hypocapnia (Palvolgyi, 1969; Paulson, 1970; Cold et al., 1977b) and when anaesthetic drugs (e.g., Althesin) which cause cerebral vasoconstriction were administered (Renou et al., 1977a; Orgogozo et al., 1977; Rasmussen et al., 1978; Renou et al., 1978a).

It has been suggested that intracerebral steal is not caused by dilatation of the cerebral vessels causing a diversion of blood away from the diseased area, but by an increase in resistance to flow through the vessels in the lesion because an increase in $PaCO_2$ causes an increase in ICP and thus an increase in brain tissue pressure (Welch and Meyer, 1970; Lassen, 1971; Meyer et al., 1972). Therefore 'intracerebral squeeze' would be a better term. Inverse intracerebral steal could similarly be explained by the cerebral vasoconstriction causing a reduction in brain tissue pressure.

Hypocapnia does not, however, always improve the blood supply to an area of focal cerebral ischaemia. If the lesion is receiving a collateral blood supply from vessels which are still sensitive to carbon dioxide, hypocapnia may reduce the blood flow to the ischaemic area (Yamamoto et al., 1971).

Effects of ICP on Venous Pressure Gradients

When ICP increases, the pressure in the cerebral cortical veins increases and remains a few mm Hg above the ICP (Yada et al., 1973; Johnston and Rowan, 1974b). If this was not so these veins would collapse and cerebral venous drainage into the dural sinuses would be obstructed. The pressure in the superior sagittal sinus remains constant as ICP increases because it is virtually incompressible (Yada et al., 1973; Johnston and Rowan, 1974b). In fact Bedford (1942) described a small fall in sagittal sinus pressure when ICP was increased in dogs. The sagittal sinus pressure increases to levels approaching ICP only during the later stages of intracranial hypertension (Shulman et al., 1964; Johnston and Rowan, 1974b; Martins et al., 1974). The cavernous sinus in man cannot be compressed by an increase in ICP (Muller and Deck, 1975). Flow through the lateral lacuna decreases as ICP increases due to gradual stenosis of these vessels. Thus the regulatory mechanisms controlling intracranial venous pressure is located in the intradural portion of the drainage system next to the major dural sinuses. This mechanism prevents collapse of thin-walled cortical vessels during increased ICP but also leads to a decrease in CBF (Yada et al., 1973). Thus a considerable pressure gradient can develop between the cortical veins and the draining sinuses.

Permutt and Riley (1963) discussed the physics of flow through collapsible tubes which have a higher pressure surrounding them than their outflow pressure. These are the conditions which apply to the cerebral cortical veins, because the ICP is higher than the sagittal sinus pressure (Shulman et al., 1964), markedly so during intracranial hypertension. Under these circumstances a change in flow

has no influence on the pressure drop across the end of the tube, and a change in pressure drop across the end of the tube has no influence on flow. These are the characteristics of a waterfall and the effect has been termed a 'vascular waterfall'. The Poiseuille equation still holds for flow through the arteriole up to the vascular waterfall provided the proper driving pressure is used, i.e., the pressure at the arteriole minus the critical closing pressure of the cortical vein, thereafter the flow takes on the characteristics of a waterfall. As ICP increases the cerebral arterioles must dilate to maintain a constant cerebral blood flow against the increased resistance in the cerebral veins (Bloor, 1972).

Brain Swelling due to an Increase in CBV

Vascular factors appear to be very important in the early stages of brain swelling in patients with cerebral trauma, and the onset of vasomotor paralysis may be the turning point between reversible and irreversible swelling. The brain parenchyma becomes oedematous in the latter stages of brain swelling (Langfitt and Gennarelli, 1982). Barbiturate therapy may be effective when intracranial hypertension is due to vascular engorgement (Marshall et al., 1979).

Cerebral Oedema

Several types of cerebral oedema have been described (Miller, 1979a). From a neurosurgical point of view, the vasogenic

type of oedema is more common and important, since it is usually associated with brain tumours, head injury and brain inflammation (Reulen, 1976).

Vasogenic cerebral oedema

In vasogenic cerebral oedema the starting point is related to injury of the walls of cerebral blood vessels leading to an escape of water and plasma constituents into the surrounding parenchyma (Klatzo, 1967). The injury to cerebral vasculature is usually of a local character, such as occurs in the vicinity of brain tumours, traumatic lesions and inflammatory foci. It seems that in the majority of cases the vascular injury is severe enough to allow an indiscriminate escape of plasma components including serum proteins. The oedema is localised predominantly in the white matter where there is enlargement of the extracellular spaces which provide the pathway for the movement of oedema fluid. Any cellular swelling predominantly affects the astrocytes. The oedema is confined to the area of the lesion, and blood vessels outside the area of the lesion but within the oedema territory do not show an increased permeability. Oedema occurs because of damage to the blood brain barrier with an opening of the tight junctions allowing the passage of oedema fluid into the extracellular space. This has been observed in a variety of neuropathological conditions, such as malignant brain tumours, local injury, and experimental allergic encephalomyelitis (Reulen, 1976). The driving force for the extravasation of fluid is the capillary transmural pressure gradient (the difference between the intravascular and interstitial fluid

pressure). Thus an acute increase in the arterial pressure results in a dramatic increase in oedema formation (Schutta et al., 1968; Paulson, 1972) whilst a decrease in arterial pressure inhibits the development of oedema.

Oedema fluid probably moves by bulk flow because measurement of interstitial fluid pressure at various distances from the lesion showed the existence of hydrostatic pressure gradients during oedema with the highest pressure in the area of the lesion and decreasing pressure along the oedema pathway towards the normal tissue (Reulen, 1976).

An increasing interstitial fluid pressure, resulting from a pathological accumulation of oedema fluid in the extracellular space, may approach the intravascular pressure at the venous end of the capillary thus tending to collapse the vessel, increasing resistance to flow through it and decreasing local blood flow. Oedema per se does not appear to interfere with brain function, which is only disturbed when the volume of oedema is sufficient to reduce local blood flow by the mechanism described above, or to produce a generalised increase in ICP sufficient to reduce CPP to ischaemic levels (Langfitt, 1965b).

Cytotoxic cerebral oedema

In cytotoxic cerebral oedema a noxious factor (hypoxia or certain types of poisoning) directly affects the structural elements of the parenchyma producing intracellular swelling, vascular permeability remains relatively undisturbed (Klatzo, 1967). The cellular swelling itself is a non-specific reaction, which can

be induced by agents of varying nature all of which disturb cell osmoregulation. It may be caused by an interference with the sodium pump. Cytotoxic brain oedema is localised in the grey or white matter depending on the type of cytotoxic agent. Swelling of necrotic cells following ischaemic or hypoxic insults occurs in patients with cerebral infarcts. If vascular damage is also present at the edge of the infarct, vasogenic and cytotoxic oedema can co-exist.

Hydrostatic oedema

This type of oedema is produced by increases in intravascular pressure which are transmitted to the capillary bed because there is no compensatory increase in cerebrovascular resistance (Schutta et al., 1968; Marshall et al., 1969). The failure of autoregulatory compensation may be due to direct trauma, excessive arterial hypertension, hypercapnia or hypoxaemia. Water pours out into the extracellular space in the absence of damage to the vascular endothelium. The fluid is thus not protein rich and is forced out of the vessels by the high intravascular pressure which upsets the Starling equilibrium. Hydrostatic oedema is generally diffuse unlike vasogenic oedema which is focal. This form of oedema can occur during craniotomy when a rise in intravascular pressure is not balanced by an equivalent increase in ICP. It can also occur when a surgical decompression is performed on a patient with a mass lesion of long standing.

Interstitial oedema

This is a form of cerebral oedema which can be seen in the periventricular area in patients with obstructive high pressure hydrocephalus, and is caused by seepage of CSF through the ependyma and into the periventricular white matter (Fishman, 1975).

Hypo-osmotic oedema

This form of cerebral oedema, which is diffuse, occurs when plasma osmolality is reduced, and is thought to develop under circumstances in which hyponatraemia occurs, as in the syndrome of inappropriate ADH secretion or when excessive amounts of intravenous dextrose-water solutions have been infused.

Therapy

Osmotic diuretics will help in the treatment of cytotoxic cerebral oedema by reducing cellular oedema, but in vasogenic cerebral oedema they will reduce ICP by reducing the size of normal cells and may cause an increase in extracellular oedema by crossing the blood brain barrier and drawing in more water with them. Avoidance of agents which cause cerebral vasodilatation (hypoxia, hypercarbia, volatile anaesthetic agents and hyperthermia), control of hypertension, steroid therapy, hyperventilation and diuretics such as frusemide should prove to be more effective in the treatment of vasogenic cerebral oedema.

CHAPTER 2

THE EFFECTS OF ANAESTHETIC AGENTS ON ICP AND CBF

MECHANISMS OF ANAESTHETICALLY-INDUCED CHANGES IN ICP

Some anaesthetic agents produce major changes in ICP. Because of the speed of onset and the size of these ICP changes the only likely explanation for them is an alteration in CBV caused by a change in CBF. The fact that anaesthetic agents which alter ICP also alter CBF supports this explanation. No direct measurements of anaesthetically-induced CBV changes have been made, but Risberg (1969a) has shown a very high linear correlation between changes in CBF and CBV and a definite correlation between CBF and CSF pressure has been demonstrated (Shenkin et al., 1952; Hamer et al., 1974). As described in Chapter 1, an increase in CBF will increase the intracranial arterial blood volume to some extent but will increase the volume of blood in the readily distensible, thin-walled cerebral veins to a much greater extent. Another possible explanation for the ICP change associated with the administration of anaesthetic agents is a change in the rate of CSF formation. The rate of CSF formation has been shown to be influenced by drugs (see p. 6), cerebral blood flow changes, alterations in metabolic rate (Bering, 1959) and sympathetic activity (Lindvall et al., 1978). The rate of CSF production is 0.35 to 0.37 ml./min.(Rubin, 1966; Cutler,1968) and the resistance to reabsorption of CSF is so low that a three-fold increase in CSF formation rate would only raise ICP to 14.7 mm Hg (Cutler et al., 1968). Thus this mechanism is too slow, and is probably incapable of producing changes of sufficient magnitude, to explain the ICP changes associated with the administration of anaesthetic agents.

The most important mechanism whereby ICP can be increased by anaesthetic agents is through a change in CBF and CBV, but there are other possible mechanisms. Many anaesthetic drugs will depress the myocardium and will increase central venous pressure and thus cerebral venous pressure which will lead to an increase in ICP. Cyclopropane increases central venous pressure (Price et al., 1953; Thompson et al., 1957);although deep halothane anaesthesia may increase CVP, appreciable increases do not occur with the inspired concentrations required for surgical anaesthesia (Adams et al.,1972).

Most anaesthetic agents cause central respiratory depression and thus will cause an increase in $PaCO_2$. This $PaCO_2$ increase will in turn cause an increase in CBF and ICP.

In patients with cerebral pathology in which autoregulation is defective, an increase in MAP caused by some anaesthetic agents may lead to an increase in CBV, cerebral oedema and an increase in ICP.

One further mechanism by which the administration of an anaesthetic agent leads to an increase in ICP is by the diffusion of nitrous oxide into the ventricles when air has been used for pneumoencephalography. The nitrous oxide increases ICP by causing the air space to expand because nitrous oxide diffuses into the space more rapidly than nitrogen diffuses out.

The mechanism whereby anaesthetic agents alter CBF is uncertain. Considerable differences in CBF, which are closely related to local increases in neuronal activity and metabolism, can occur in localised areas (Olesen, 1971), and there are increases in regional oxygen uptake which parallel these changes in CBF (Raichle, 1975). In addition, abnormal increases in cerebral metabolism occur during seizure activity (Plum et al., 1968; Sakabe et al., 1974;

Brodersen et al., 1973), and by producing an increase in CBF cause an increase in CSF pressure (Stephen et al., 1954). Thus changes in cerebral metabolism can alter CBF. Anaesthetic agents have been shown to alter $CMRO_2$ and this may be the mechanism whereby they alter CBF.

The mechanism whereby CBF is controlled at cellular level is uncertain. It is now accepted that the pH hypothesis (i.e., that a change in hydrogen ion concentration in the cerebral extracellular fluid around pial and parenchymal vessels will influence the tone of the vascular smooth muscle), cannot explain all the experimental observations, and that no simple hypothesis can be advanced to explain the relationship between CBF and cerebral metabolism (Cameron, 1977; Astrup et al., 1978; Purves, 1978). Purves (1978) suggests that in addition to the system of rapid regulation of CBF in response to systemic disturbances such as hypoxia, hypocapnia and hypotension, which threaten the supply of oxygen and substrate and the immediate chemical environment of the neurones, there could be a second system which acts as a fine tuner to make local adjustments of perfusion to metabolic rate. This system may involve factors very different from those known to dilate pial or extraparenchymal vessels which include potassium ions (Baldy-Moulinier, 1971-2; Kuschinsky et al., 1972; Heuser et al., 1977; Astrup et al., 1978; Heuser, 1978), hydrogen ions (Lassen, 1968b; Kuschinsky et al., 1972; Heuser et al., 1977; Astrup et al., 1978), and adenosine (Wahl and Kuschinsky, 1976; Cameron, 1977; Purves, 1978).

The effects of pH, potassium ions, and adenosine on the vascular muscle may eventually be explicable in terms of their influence on the entry of calcium ions into the cell, one of the

essential steps in smooth muscle contraction (Cameron, 1977; Purves, 1978).

Prostaglandin $F_{2\alpha}$ causes cerebral vasodilatation and may be involved in the control of CBF (Emerson et al., 1976; Vlahov, 1976). It has been suggested that cyclic AMP may be involved in cerebrovascular dilatation (Wahl and Kuschinsky, 1976), and MacMurdo and colleagues (1981) claim to show a dose-related increase in brain cyclic AMP levels with the administration of ether and halothane, which suggests a causal relationship between their effect on cyclic AMP and their cerebrovascular effects. Scrutiny of the latter author's results, however, reveals that the difference between the results with halothane and pentobarbitone was small, and the results with halothane were of borderline significance.

So there is a multifactorial control mechanism for CBF, with the brain having at its disposal several potent and independent local vasodilatory mechanisms including hydrogen ions and potassium ions which, together with the perfusion pressure, control CBF.

Keaney and colleagues (1978) have shown that the cerebrovascular response to Althesin occurred approximately 2 seconds after the arrival of the drug in the brain, and within 1 second of the onset of the electroencephalogram (EEG) depression. From calculations of the change in cortical carbon dioxide tension and hence tissue $[H^+]$ they concluded that this was too small to be the factor linking metabolism and flow. By repeating the experiment in baboons after acute cervical sympathectomy and α-adrenergic blockade, they also excluded the involvement of the sympathetic nervous system in the vasoconstrictor response. The calculations have been confirmed by the measurement of cortical extracellular fluid pH during Althesin administration (McDowall et al., 1979). Perhaps the most likely

mechanism causing the initial change in flow is a decrease in extracellular fluid potassium ion concentration due to depression of neuronal function. The decrease in extracellular fluid pH may play a part in the maintenance of the change in CBF. Another explanation is the removal of tonic activity in a vasodilator pathway. Extracellular potassium ions also act as a vasodilator initiating hyperaemia in seizures, and extracellular hydrogen ions seem to be important in maintaining the hyperaemia, but hyperaemia may be initiated and maintained by other mechanisms as in amphetamine activation and hypoglycaemia (Astrup et al., 1978).

Most inhalational anaesthetics uncouple the relationship between cerebral metabolism and CBF so they cannot alter CBF by their effect on cerebral metabolism. Stullken et al. (1977) have shown that, during anaesthesia with enflurane, halothane, isoflurane and thiopental in dogs, there is an abrupt metabolic depression when the EEG pattern changes to an "anaesthetic" pattern, and that this change occurs at concentrations well below 1 MAC. This indicates that the metabolic depression is caused by the anaesthetic state. It is unknown whether the increased CBF to $CMRO_2$ ratio with deep inhalation anaesthesia indicates an improved safety margin or whether the higher tissue PO_2 is somehow necessitated by a block in oxygen utilisation or uptake (Smith and Wollman, 1972).

Because the maximum effect of halothane on CBF occurred 4 to 5 minutes after the arterial halothane concentration had reached a maximum, Smith (1973a) suggested that the increase in CBF during halothane anaesthesia is not due to a direct effect of halothane but due to halothane altering PVo_2, with an increase in CBF and a decrease in CVR following as secondary effects. It seems more likely,

however, that the altered PVO_2 is just another manifestation of altered cerebral metabolism.

TIME COURSE OF ANAESTHETICALLY-INDUCED CHANGES IN ICP

Compensatory mechanisms would be expected to return ICP to its initial value and this can be shown to occur after 52 minutes of 0.5% halothane administration in dogs (McDowall et al., 1966), after 10 to 30 minutes in man with halothane 0.5 to 1% (Adams et al., 1972), after 10 to 20 minutes with isoflurane (Adams et al., 1981) and after 10 to 15 minutes with ketamine (Sari et al., 1972).

EFFECTS ON ICP OF INTERACTION BETWEEN ANAESTHETICS AND BRAIN PATHOLOGY

In the presence of an intracranial space-occupying lesion the changes in ICP can be accentuated. Anaesthetic agents which increase ICP have a greater effect when the ICP is elevated before administration (Jennett et al., 1969), and those which reduce ICP cause a greater reduction in patients with higher initial ICP values (Turner et al., 1973). This is due to the nature of the pressure volume curve of the intracranial contents described on page 29. If a standard volume increment is added to the intracranial contents e.g., the administration of halothane, the increase in ICP is gradually accentuated as the intracranial contents become more compressed (Fitch and McDowall, 1971). If halothane is given when compensation has been overcome and/there is cerebral vasomotor paralysis, the ICP will fall as the arterial pressure falls. Anaesthetic agents do not appear to precipitate plateau waves (Jennett et al.,1969).

INTERACTION OF HYPERVENTILATION WITH ANAESTHETIC DRUGS

Adams and his colleagues (1972) showed that CSF pressure increases associated with the administration of halothane 0.5 to 1% were small when hyperventilation ($PaCO_2$ less than 4 KPa) was established for 10 minutes prior to the introduction of halothane, but Gordon (1970) found that hyperventilation did not fully protect against increases in ICP during the administration of halothane in patients with very high initial ICP values, a finding which was supported by the work of Jennett and colleagues (1969). Simultaneous introduction of isoflurane and hyperventilation ($PaCO_2$ 3.3 to 4 KPa) prevented increases in lumbar CSF pressure with this agent, and initiation of hyperventilation during isoflurane anaesthesia reduced CSF pressure to control levels (Adams et al., 1981). The influence of anaesthesia on cerebrovascular reactivity to CO_2 will be discussed separately.

INTERACTION OF OSMOTIC AGENTS WITH ANAESTHETIC DRUGS

Osmotic agents reduce the volume of the intracranial contents and thus one would expect the effects of volatile agents on ICP to be less after the osmotic agents have been given.

THE EFFECT OF ANAESTHESIA ON CEREBROVASCULAR REACTIVITY TO CARBON DIOXIDE

The cerebral circulation retains its responsiveness to changes in $PaCO_2$ during halothane anaesthesia (Alexander et al., 1964; McHenry et al., 1965; Christensen et al., 1967; Okuda et al., 1976) except during profound hypotension (systolic B.P. = 60 mm Hg) (Okuda et al., 1976), although Alexander and colleagues (1964) found that the shape of the $PaCO_2$ response curve was altered, showing an increase in cerebrovascular sensitivity to changes in $PaCO_2$, a finding confirmed by Scremin and colleagues (1978). With 1.2% halothane the CBF response to CO_2 tends to diminish at a $PaCO_2$ of about 6.7 KPa because the cerebral vessels are nearly maximally dilated (Alexander et al.,1964). Carbon dioxide reactivity is also markedly increased during 21% cyclopropane anaesthesia (Alexander et al., 1968a;Smith and Wollman, 1972).

Carbon dioxide reactivity is not altered by thiopental anaesthesia deep enough to reduce $CMRO_2$ by 40% (Schieve and Wilson, 1953; Pierce et al., 1962), by Althesin anaesthesia (Sari et al., 1976), by ketamine anaesthesia (Sari et al., 1972a),or by etomidate anaesthesia (Renou et al., 1978c). Carbon dioxide reactivity was significantly greater in patients anaesthetised with methohexitone, nitrous oxide, oxygen and neuroleptanalgesia than in awake subjects (Iliff et al., 1976), and was reduced by a combination of diazepam and fentanyl according to Renou and colleagues (1977b)but unchanged by this combination according to Vernhiet and co-workers (1978). Diazepam alone does not affect cerebral vaso-reactivity to carbon dioxide (Cotev and Shalit, 1975).

Reactivity to carbon dioxide is also preserved during

isoflurane (Cucchiara et al., 1974), methoxyflurane (Michenfelder and Theye, 1973), enflurane (Michenfelder and Cucchiara, 1974; De Rood et al., 1980a), trichloroethylene (McDowall et al., 1964), and chloroform anaesthesia (McDowall, 1965). It is unaltered by 70% nitrous oxide (Wollman et al., 1965) or nitrous oxide, oxygen and neuroleptanalgesia (Wilkinson and Browne,1970). Fentanyl and fentathienyl increase cerebral vascular reactivity to carbon dioxide (Vernhiet et al., 1977).

THE EFFECT OF ANAESTHESIA ON AUTOREGULATION OF CBF

Autoregulation is preserved during light general anaesthesia with both nitrous oxide and cyclopropane, but impaired at deeper levels of cyclopropane anaesthesia (20%) during arterial hypotension (Smith et al., 1970; Smith and Wollman, 1972). It is also preserved during nitrous oxide anaesthesia supplemented with fentanyl, Althesin and halothane or enflurane (Farrar et al.,1981).

In baboons disturbance of autoregulation has been observed following deep halothane anaesthesia when the blood pressure had been restored to normal (Keaney et al., 1973b), and following the restoration of the blood pressure after nitroprusside hypotension (Keaney et al., 1973a). This impairment of autoregulation can last for at least 100 minutes. The slow return to normal could be due to the gradual correction of an undetected cerebral extracellular fluid acidosis. In the monkey autoregulation remained intact during nitrous oxide/oxygen anaesthesia supplemented with 0.5% halothane, but when the halothane concentration was increased to 1% autoregulation was impaired and with 2% halothane autoregulation was

completely lost (Morita et al., 1977). Morphine 2 mg/Kg during 70% nitrous oxide administration does not affect cerebral autoregulation in man (Jobes et al., 1975).

Okuda and colleagues (1976) observed that after restoration of the blood pressure to normal following deep halothane anaesthesia in the baboon, the response to changes in $PaCO_2$ was still preserved, which suggests that post-operative hyperventilation may protect against cerebral hyperaemia and possible oedema formation.

Autoregulation fails in baboons during haemorrhagic hypotension at an MAP of 65% of baseline, whereas in drug-induced hypotension it fails at 35 to 40% of baseline (Fitch et al., 1976). After chemical or surgical sympathectomy autoregulation persisted to significantly lower levels of MAP (approximately 35 mm Hg) during haemorrhagic hypotension (Fitch et al., 1975). It is postulated that, under conditions of haemorrhagic hypotension, constriction of the extraparenchymal cerebral vessels in response to sympathetic stimulation reduces the possible range of autoregulation. This effect is less noticeable in hypertensive baboons (Fitch et al.,1978).

THE EFFECT OF ANAESTHESIA ON THE CEREBROVASCULAR RESPONSE TO HYPOXIA

Anaesthesia with pentobarbitone, Althesin or 0.3% methoxyflurane did not interfere with the dogs' response to severe arterial hypoxaemia to an extent that impaired cerebral oxygen transport (Cohen et al., 1973). Gray and co-workers (1971a) found that anaesthesia with low concentrations of volatile agents had very little effect on the CBF response to hypoxia in dogs, but at high

concentrations the response was variable and frequently resulted in insufficient oxygen transport to maintain cerebral metabolism. Halothane anaesthesia was associated with a better oxygen supply to demand ratio than methoxyflurane or trichloroethylene anaesthesia, when these agents were given in higher concentrations during hypoxaemia.

THE EFFECT OF ANAESTHETIC AGENTS ON OPERATING CONDITIONS

Anaesthetic agents which alter ICP do so by altering CBV, so brain bulk is influenced by anaesthetic agents. When the cranium is opened at craniotomy there is an external decompression of the cranial contents and the ICP falls to zero. Thus the balancing effect of the ICP is lost, so that when the initial ICP is elevated, the decompression may lead to an increase in brain bulk (due to the removal of the restraints of the intact cranium) and the brain tissue will be forced against the edges of the craniotomy defect, with the danger of herniation through the craniotomy site (Jennett at al., 1969). These events will cause trauma to the brain tissue. A lesser manifestation of the same process is the greater difficulty the surgeon experiences in retracting the brain, thus making the operation difficult or even impossible. The greater the pressure required to retract the brain, the greater the degree of ischaemia and trauma to the brain underlying the retractor, and to the surface of the contralateral hemisphere. If an anaesthetic agent produces arterial hypotension as well as an increase in brain bulk and retraction pressure, the risk of cerebral ischaemia will be even greater because the local

CPP will be reduced further (Albin et al., 1980). In addition the vascular congestion caused by those agents which increase CBF will increase the amount of surgical bleeding. Thus operating conditions can be affected by the anaesthetic agents given.

EFFECTS OF INDIVIDUAL ANAESTHETIC AGENTS ON CBF, ICP AND CPP

In this chapter I have discussed in general terms how anaesthetic agents can affect CBF, ICP and CPP and the potential harmful or beneficial effects of the changes produced. In order to avoid repetition, the effects of individual anaesthetics on CBF, ICP and CPP will be discussed in chapters 4 to 9, which deal with the original work, the discussion sections of which will include reviews of the relevant literature. Unless otherwise stated, the literature quoted refers to investigations in man, and when adequate information is available from investigations in humans similar results from animal studies will not be mentioned.

CHAPTER 3

METHODS OF ASSESSING THE EFFECTS OF ANAESTHETIC AGENTS ON THE DYNAMICS OF THE CRANIAL CONTENTS

MEASUREMENT OF ICP

Before Guillaume and Janny (1951) described the continuous measurement of ICP using transducers and Lundberg (1960) comprehensively reviewed the technique, knowledge about ICP had been obtained from discrete measurements of lumbar CSF and ventricular fluid pressure performed during lumbar puncture or craniotomy. The relative ease with which ICP can be measured, the continuous nature of the information obtained, and the minimal risk to the patient have made it a useful method for assessment of the effects of anaesthetic agents and techniques on intracranial dynamics. Consequently, this is the method of measurement which was used in the original work described in this thesis.

Attempts have been made to record changes in ICP by non-invasive methods such as echoencephalography and impedance plethysmography, but all techniques which give useful measurements require the insertion of a measuring device into the cranial cavity.

There are four recognised sites for ICP monitoring; firstly a lateral ventricle, secondly the intracranial subdural space, thirdly the intracranial extradural space, and fourthly the intracranial subarachnoid space. In addition, CSF pressure can be measured from the lumbar subarachnoid space. In steady state conditions ICP measured outside the CSF space closely approximates to CSF pressure, but under changing conditions this may not be the case because of the viscoelastic nature of the brain tissue, its membranes and blood vessels.

ICP Measurement from a Lateral Ventricle

A catheter is introduced under sterile conditions into a lateral ventricle through a burr hole or twist drill hole. Care is taken to lose as little CSF as possible so that the baseline ICP can be obtained accurately.

This method gives the most reliable readings of ICP, it reflects global ICP, and is the standard by which the others are judged. Other advantages include minimal damping of the respiratory and pulse waveforms, and the ability to withdraw CSF to improve surgical access, to reduce ICP, or to allow biochemical or bacteriological examination.

The disadvantages are that the brain must be punctured and thus it is more invasive than the other methods, it may cause intracranial haemorrhage (less than 1% chance) (Fleischer et al., 1976), and there is the danger of introducing infection into the ventricular system. In addition, cannulation of a lateral ventricle can be technically difficult, and it can be difficult to keep the catheter patent because of partial or complete blockage by collapse of the ventricular surface with either damping or loss of the pressure recording (Turner et al., 1975).

The ventricular catheter is connected to an electrical transducer and the signal is amplified and recorded. Transducers incorporated into the catheter tip are available, but have not yet reached the required degree of reliability for long-term measurements.

ICP Measurement from the Intracranial Extradural Space

Dorsch and Symon (1975a) have discussed the theory of extradural measurement of ICP. The pressure within a hollow organ can be measured from outside its enclosing membrane provided that the membrane is not indented by the pressure sensor (i.e., it is coplanar with the outer surface of the membrane). Any forces due to changes in the tension of the membrane which accompany changes in intracavity pressure must act in the plane of the membrane, while the force due to pressure inside the cavity can be taken to act along a radius from the centre of the cavity. These two forces act at right angles, so the force due to tension in the membrane has zero component with regard to the pressure sensor because this has maximum sensitivity along the line of action of the intracavity pressure. However, if the surrounding membrane is indented by the pressure sensor then the forces will not be at right angles and the tension in the membrane will have an effect on the pressure recorded by the sensor. Thus it is critical that the pressure sensor is correctly placed. With an implanted transducer the sensing diaphragm must be exactly flush with the inner surface of the skull and perpendicular to a line extending from the centre of the brain. Provided that the dural membrane is absolutely flat against the transducer sensing surface, the internal pressure will be fully transmitted irrespective of the tension in the membrane. To satisfy these conditions, Ream and colleagues (1979) have developed an implantable transducer with a guard ring which holds the membrane flat. This ring has to be sufficiently distant from the sensing surface to avoid edge-loading. The sensing area of the transducer must be large enough to average out the effects of less than ideal smoothness and non-uniform

thickness of the dura, and the maximal allowable transducer displacement must be very small. Any epidural transducer or device must be rigidly fixed in place once in the correct position.

For measurement from this site one can use a fluid-filled adaptor such as the device described by Coroneos et al. (1973), which is a hollow metal screw with a base-plate and side-holes rather than an end-hole to minimise blockage of the measurement holes by the dura mater, or a specially designed transducer which lies against the dura mater. Many different devices have been described for measurement of ICP from the extradural space (Nornes and Serck-Hanssen, 1970; Dorsch and Symon, 1975b; Beks et al., 1977; Levin, 1977; Wald et al., 1977; Ream et al., 1979; Gjerris et al., 1980; Koster and Kuypers, 1980; Corbin et al., 1980). The main problem with an implanted transducer is zero drift, although some transducers can be re-zeroed in situ. The measuring instrument is inserted into a burr-hole or twist-drill hole, which must be at right angles to the plane of the dura, and there must be a watertight seal round the bolt or transducer in order to obtain correct measurements (Coroneos et al., 1972a).

The advantages of this site of measurement are that insertion of the measuring implement is straightforward, the dura mater is not breached so that infection, if it does occur, is less serious (the dura is an excellent barrier against infection), and patency can usually be maintained without difficulty for prolonged periods.

There are several disadvantages of this site of measurement. CSF cannot be removed, implanted transducers may be subject to zero drift (although some can be calibrated in situ) and there is also

evidence of gradients of pressure occurring between the ventricles and the brain surface when there are acute relative changes of the cerebral constituents. Thus values of extradural pressure should be treated with caution (Cooper and Nornes, 1972), A further disadvantage is that the dura mater tends to damp the pressure signal, and although there is a linear relationship between extradural pressure (EDP) and ventricular fluid pressure (VFP), the measurements of pressure from the extradural space tend to be higher than the pressures recorded simultaneously from a ventricular catheter, particularly at high pressures (Gobiet et al., 1972; Coroneos et al., 1972a, 1972b, 1973; Jorgensen and Riishede, 1972; Nornes and Sundbarg, 1972; Sundbarg and Nornes, 1972; Turner et al., 1975; Gobiet et al., 1974; Gjerris et al., 1980; Nagai et al., 1980), and high EDP has been reported in the presence of a normal VFP (Turner et al., 1975). Some hours may be needed after implantation before pressures are recorded which are reasonably close to CSF pressure, and even then there is still considerable scatter of VFP and EDP values, and VFP may exceed EDP (Coroneos et al., 1973).

The VFP/EDP regression line does not pass through zero and shows an error of the EDP reading up to 10 mm Hg when the VFP is zero. Zattoni and colleagues (1973) state that EDP reads higher than the pressure in the subdural space only when the epidural devices are shaped or placed in such a way as to displace the surrounding dura mater from the bone surface. However, possible reasons for the EDP reading higher than the VFP include the following methodological errors (Dorsch and Symon, 1975a). Firstly, the construction of the measuring device may allow the sensing portion to project beyond the rest of the device, thus indenting the dura, so

that the additional stress force causes the measured extradural pressure to read higher. Secondly, and for similar reasons, implantation of the transducer at an angle to the dura mater or indenting it will give a falsely high reading of EDP. An 8 degree change in the angle of insertion of the transducer will produce differences in pressure readings of more than 20% (Zierski, 1980). Thirdly, undue trauma during the insertion of the measuring device may lead to a localised increase in pressure without affecting the general ICP. Fourthly, in comparative studies if the zero reference points for the two forms of measurement are different a constant differential will occur. The existence of true pressure differentials can be explained by the dura, because of its relative thickness, causing a distortion of the pressure transmitted through it (Cooper and Nornes, 1972; Zierski, 1980), so that, in disturbed physiological conditions, the deviations between EDP and VFP may be considerable (up to 20 mm Hg). In addition, factors causing an increase in CBF which increase brain bulk and only increase VFP secondarily may lead to pressure gradients which could explain the difference between these two measurements (Schettini and Walsh, 1974; Dorsch and Symon, 1975a). The true extradural to ventricular pressure differentials at higher ICP levels could be explained by increasing contact of the dura with the sensor thus converting the system to a stress/force rather than a fluid-filled system (Jennett, 1972); the time at which this change occurs cannot be determined. The work of Esparza et al. (1980), showing an EDP to VFP gradient only when CSF circulation over the cerebral hemispheres was impeded, appears to support this hypothesis. At low pressures the dura might not always be pressed against the sensing membrane and would therefore record a falsely low ICP.

Miniature transducers have been slipped under the inner table of the skull for measuring extradural pressure, but sources of inaccuracy must include indentation into the subarachnoid and subpial regions and the transducer not being flush with the inner table of the skull. Guha and Anand (1979), however, have suggested that their non-coplanar transducer of rectangular design, which is inserted between dura and skull, will be more accurate than the traditional coplanar transducer for long-term monitoring, because its position will be more constant than that of a coplanar transducer. Such a transducer must, however, be calibrated initially against the reading from a coplanar transducer.

Zierski (1980) concluded that the range of discrepancies between EDP and VFP was too disturbing for routine clinical use because he could not confirm the tendency of EDP to read higher at higher VFP values.

ICP Measurement from the Intracranial Subdural Space

ICP can be measured from this site using a 3-way tap or the end of an intravenous giving set pushed into an appropriately-sized hole in the skull after the dura has been incised (Gosch and Kindt, 1972; Kindt, 1975), or a plastic catheter inserted below the dura mater which can be made in a ribbon-shaped design (Wilkinson, 1977), or a bolt (as described above for extradural pressure measurement, the only difference being that the dura mater is incised leaving the arachnoid mater intact). In addition, transducers have been specially designed for insertion into a burr hole for subdural pressure measurement (Eversden,1970; Richardson et al., 1970; Tindall et al., 1972a).

The advantages of this site of measurement are that the damping effect of the dura mater is removed but the arachnoid mater is not breached, thus the chance of serious infection is reduced, siting of the measuring device is technically easier than placing a ventricular catheter, placement is independent of brain shift or small ventricular size, the brain is not punctured and the patency of the measuring device is maintained quite easily (particularly if the Leeds bolt (Coroneos, 1973) is used because it has a footplate to protect the measuring holes from blockage).

The disadvantages are that CSF cannot be removed, blockage may occur at high ICP levels, particularly when a catheter is used because the arachnoid mater is forced against it by the underlying brain, and surface bleeding may be caused by opening the dura. In measuring subdural pressure Mendelow (1982) found that both the single lumen screw as described by Vries and colleagues (1973) and the Leeds type screw may give unreliable results which may differ from VFP in either direction, more commonly by underestimating the occurrence of high ICP. This tendency was seen more frequently with the open ended screw than with the Leeds type screw, but both can show errors which become greater as ICP exceeds 20 mm Hg.

ICP Measurement from the Intracranial Subarachnoid Space

Sometimes it is technically impossible to avoid incising the arachnoid mater along with the dura mater so that subarachnoid pressure is measured. Some workers deliberately incise the arachnoid mater in order to measure supratentorial subarachnoid pressure. Vries and colleagues (1973) described a hollow screw

designed for measurement of pressure from the subarachnoid space which gave pressure measurements which were identical with VFP in 12 patients and gave satisfactory readings up to 100 mm Hg in cats. The tip of the screw projected 1 mm below the surface of the dura mater. Winn and colleagues (1977) found that subarachnoid pressure measurement through a screw was a reliable method of recording ICP clinically with a low failure rate. In patients VFP and convexity subarachnoid pressure were similar except for a slight difference in waveform which could be partly due to the distensibility of the ventricular catheter. In swine, however, Davis et al. (1981) found that subarachnoid screw-type devices consistently underestimated the brain tissue pressure measured from an intracerebral microtransducer, which confirms the findings of Schettini and Walsh (1974).

Measurement of ICP in Infants

In infants with an open fontanelle a transducer can be applied directly over the fontanelle to measure ICP either using pneumatic pressure to balance a mirror (Vidyasagar and Raju, 1977) or the aplanation principle (Wealthall and Smallwood, 1974). The pressures obtained correlate well with simultaneously measured CSF pressure.

Measurement of CSF Pressure from the Lumbar Subarachnoid Space

In many studies of the effects of anaesthetic agents on CSF pressure this pressure has been measured by cannulation of the lumbar subarachnoid space. However, the spinal CSF pressure will only be the same as the ventricular CSF pressure under steady state conditions, and when there is no obstruction to the flow of CSF between the intracranial and the spinal CSF compartments (Shenkin, 1952). In normal patients, and the majority of patients with intracranial tumours, the lumbar and ventricular CSF pressures are identical and show identical responses to jugular vein compression and withdrawal of CSF, but in some there is a difference of up to 7.5 mm Hg with VFP reading higher. In these latter patients jugular compression revealed partial block between the cranial and spinal compartments (Smyth and Henderson, 1938). This is the least invasive method of measuring CSF pressure and the only one justifiable in normal subjects, but it does penetrate the subarachnoid space and there is a danger of meningitis. Free communication between the cranial and spinal subarachnoid space must be demonstrated before lumbar CSF pressure can be taken to reflect ICP. When performing lumbar puncture in the presence of intracranial space-occupying lesions and raised ICP, there is a considerable danger of inducing brain shift and impaction at the foramen magnum.

Measurement of Lumbar Epidural Pressure

Recently it has been suggested that CSF pressure can be measured from a catheter placed in the lumbar epidural space (Shah, 1981). It seems unlikely, however, that lumbar epidural pressure will accurately reflect CSF pressure.

* * * *

From the above discussion it is obvious that there is no one method of ICP measurement which is ideal in all circumstances, but that measurement of the pressure from a lateral ventricle will give the most accurate values. In the original work described in this thesis a ventricular catheter was used for ICP measurement in patients scheduled for craniotomy (with the exception of one patient), and an extradural or subdural device (Coroneos, 1973) or subdural catheter was used in the studies undertaken in patients with head injury. The zero reference point for ICP was the external auditory meatus, except in the patients with head injury in which the zero reference point was the level of the transducer which was mounted on the patient's head.

Recording the ICP

If an implanted device (catheter, bolt or 3-way tap) is used this is filled with sterile saline and connected through a saline-filled column to a suitably calibrated arterial range electrical pressure transducer sited outside the cranium. The signal from the external or internal transducer is amplified and recorded on a chart recorder. All joints in the system must be watertight and air must be completely removed from the system. The author used

an externally mounted transducer connected to a Devices amplifier and chart recorder which employs a heated stylus on a knife-edge to provide a linear response. During the studies the chart was set to run at an appropriate speed (usually 1 mm/second) and ICP values were read directly from the analogue signal on the chart. For clinical investigations the ICP range of the recording system normally should be 0 to 50 mm Hg but if the pressure is very high a range of 0 to 100 mm Hg is required. The transducer was calibrated against a sterile saline column exerting a known pressure (usually 34 cm H_2O which equals 25 mm Hg) immediately before the measurements were made, and the calibration was checked after the period of measurement. Regular zero checks are necessary during a long period of measurement to check that significant zero drift has not occurred. The transducer is sterilised before use by filling the dome with Cidex and waiting at least 2 hours. The Cidex is then flushed out with liberal amounts of sterile saline.

In the results included in this thesis mean ICP has been defined as half-way between the systolic and the diastolic pressures. Figures so obtained were rounded to the nearest 0.5 mm Hg.

The recording system can be made more sophisticated by feeding the amplified signal into an analogue-to-digital converter, and from there into a suitably programmed computer or micro-processor where the data can be manipulated and stored.

Telemetry

Telemetry allows continuous measurement of ICP in ambulant patients and many implantable devices have been developed for this purpose. The technique is of use for long-term observations of ICP in experimental situations but is not usually used for measurement of the effects of anaesthetic agents on ICP.

Infection

Intracranial infection rarely occurs during short-term ICP monitoring for studies of drug effects on ICP. It does, however, occur during long-term monitoring particularly when this is continued for more than 3 days (Rosner and Becker, 1976). Under these conditions the incidence of infection is usually between 1 and 4% (Lundberg, 1972; Sundbarg et al., 1972; Winn et al., 1977) but can be as high as 10% (Fleischer et al., 1976). In order to reduce the incidence of infection during long-term ICP monitoring from a ventricular catheter, Fleischer and colleagues (1975) developed a system in which an intraventricular catheter was connected to an implanted Rickham reservoir, and a 23 gauge needle was inserted percutaneously into the reservoir.

Volume-Pressure Testing

Another test relating to ICP which has been found useful in the prediction of the response of ICP to increasing volume of one of the intracranial components is the volume-pressure test (Miller and Garibi, 1972). In this test a known volume of sterile

saline (usually 1 ml) is injected into (or withdrawn from) the CSF space through a ventricular catheter and from the height of the resultant increase in ICP and the rate of decline towards the baseline after injection indices can be derived which relate both to absorption rates for CSF and brain stiffness (Marmarou et al., 1975). There is a positive correlation between the height of the resting level of ICP and the volume pressure response which supports the concept of an exponential relationship between intracranial volume and pressure (Miller and Garibi, 1972). An increase or decrease in ICP of 2 mm Hg or more is taken to indicate reduced intracranial compliance and thus a reduced ability to compensate for further changes in volume of the intracranial contents. Pronounced enlargement of the ventricles interferes with the test (Miller and Leech, 1975; Rowed et al., 1975).

The VPR is closely correlated with the ventricular fluid pressure (VFP) immediately before the test and can be dissimilar at the same VFP depending on whether the increase in VFP was produced by a mass lesion or by a diffuse process such as an increase in MAP (Leech and Miller, 1974), and the test is useful in determining which agents improve intracranial compliance (Miller and Leech, 1975).

An increase in pulse amplitude of the ICP trace occurs with increasing ICP and is mainly explained by the decrease of the intracranial compliance (Nornes et al., 1977). The increment of blood volume that is added to the intracranial compartment with each heart beat acts as the volume stress of a volume-pressure test. Van Eijndhoven and colleagues (1980) found that in individual patients the CSF pulse pressure is a reliable parameter for monitoring alterations in intracranial elastance, but that the volume change

underlying the CSF pulse pressure varies considerably between patients and may be affected by haemodynamic changes. According to Szewczykowski et al. (1977) calculation of intracranial elastance from the pulse pressure and the basic level of ICP needs an on-line computer for clinical use. Ikeyama et al. (1980) suggest that the function of the intracranial veno-sinus junction is the most important factor in causing the increase in pulse pressure associated with intracranial hypertension.

A further test of ICP reserve has been developed by Wilkinson et al. (1978) in which increments of saline were injected subdurally at one minute intervals for not more than 5 injections. Using this test in dogs, baboons and man they found a linear response of ICP to an increase in volume (Wilkinson et al., 1981). They claimed that the linear response was a response to intermittent injections allowing compensation to occur in between injections, whereas continuous or rapid infusion would be expected to cause an exponential response because there was less time for compensation to occur.

A marked increase in CSF pulse pressure to ICP ratio may indicate a loss of autoregulation and under these circumstances the CSF pulse pressure is a better parameter of the clinical state than the VPR (Avezaat et al., 1979).

MEASUREMENT OF OTHER PRESSURES WITHIN THE CRANIAL CAVITY

Brain Tissue Pressure

Brain tissue pressure can be measured using wicks which consist of a thin polythene catheter with a wick of long-stranded combed cotton wool at its tip preventing obliteration of the catheter tip by the surrounding tissue (Brock et al., 1972b).

Pressure-Depth Measurements

Schettini and Walsh (1974) devised a method of simultaneously measuring pressure and the depth of that measurement, using a transducer with a small pressure-sensing element mounted at the end of a cylindrical piston which was coupled to a finely-threaded plunger. For continuous insertion or withdrawal at a constant rate an adjustable drive system was used, and accurate measurement of the depth of the plunger from the initial position could be made using a rotational potentiometer. Using this system, inserting the transducer at a constant rate to a depth corresponding to a preset pressure (usually 30 mm Hg), with the point of dural contact taken as the zero position, subarachnoid CSF pressure can be measured when the dura is flattened against the transducer, a point can be identified which represents contact with the brain surface, and insertion after this gives pressure changes associated primarily with compaction of the brain tissues of the subpial region. The pressure-depth test reflects principally the behaviour of the subpial tissue, and Schettini and Walsh (1974) suggest that it is more meaningful to record surface brain pressure than CSF pressure, because the latter does not always correlate with the condition of the brain. Because of the rich vascular supply to the brain, changes in cerebral circulation will primarily affect the subpial compartment and only secondarily be reflected in the CSF pressure which, in spite of an expanded brain, may be abnormally low due to CSF absorption to compensate for the increase in brain volume. In fact it is possible that methods which were thought to be measuring epidural ICP may have been recording subpial rather than subarachnoid CSF pressure if the dura was pressed against the brain tissue. The slope of the

pressure increase as the transducer is advanced in the subpial region gives a measure of the stiffness of the brain, and the subpial region exhibits relaxation and creep behaviour similar to that observed with viscoelastic materials (Schettini and Walsh,1973,1975). Using this method of measurement with the transducer placed at a depth corresponding to the initial subpial contact in dogs, Schettini and Moreshead (1978) showed that halothane in concentrations greater than 1% caused a sustained increase in surface brain pressure, and that thiopentone narcosis reduced this pressure. The increase in surface brain pressure may have been due to an increase in brain water, because the electrical impedance of the brain was also increased.

Measurement of Brain Retraction Pressure

An instrument has been devised which measures the pressure required to retract the brain (Albin et al., 1980). This could prove useful in determining which anaesthetic agents are best used for maintenance anaesthesia during neurosurgical operations. Those agents which were associated with the lowest brain retraction pressure would be the best agents to use, provided that MAP and thus CPP was not markedly reduced at the same time.

MEASUREMENT OF THE DIAMETER OF CEREBRAL VESSELS

Pial vessels may be observed directly and photographed through the microscope before and after the administration of the agent being studied. From the photographs the vessel diameter can be measured. In addition, the change in diameter of the cerebral vessels, before and after an agent is introduced,

can be measured from X-ray films taken during carotid angiography (Fischgold et al., 1968). Certain / contrast media may affect CBF (Brown and Donaldson, 1976), so this could be a source of error. This method has been used in the author's department to assess the effects of carbon dioxide and etomidate on cerebral vessel diameter.

MEASUREMENT OF ARTERIAL PRESSURE

In the investigations described in this thesis, arterial pressure was measured continuously from a radial artery cannula filled with saline and connected to an appropriately calibrated electrical transducer and recorder system. Calibration was checked before each investigation. The zero for the arterial pressure was at the level of the heart. Before a cannula was placed in a radial artery, Allen's test was performed to establish that there was adequate ulnar collateral circulation. MAP was measured from the chart recordings by adding one-third of the pulse pressure to the diastolic pressure. CPP was calculated by subtracting mean ICP from MAP.

STATISTICAL METHODS

In these investigations Student's t-test was used to test for significant differences between the test groups in Chapters 4 and 9, and a paired t-test was used to test for significant changes from the control values of the different parameters measured in the studies described in Chapters 5, 6, 7, 8 and 9.

MEASUREMENT OF CBF

Knowledge of the effects of anaesthetic agents on CBF is necessary to explain the effects of these agents on ICP. I have not measured CBF in any of the investigations described in this thesis, so I will only refer briefly to the methods used for the measurement of CBF in man. These methods employ diffusible indicators which are delivered to the brain tissue and subsequently are removed by the blood stream. The first such method, described by Kety and Schmidt (1945), uses nitrous oxide as the indicator. The subject inhales a constant low concentration (10 to 15%) of nitrous oxide over a 10-minute period, and during this 10-minute inhalation period a series of blood samples are taken from an artery and the internal jugular vein. From these measurements CBF can be calculated. This method was modified by the substitution of ^{85}Krypton for the nitrous oxide because the analysis of the blood samples was easier. Further technical improvement was made by McHenry (1964) who suggested looking at desaturation curves as opposed to saturation curves. One advantage of the Kety Schmidt and similar methods is that cerebral metabolism can be calculated by multiplying the flow by the appropriate arteriovenous difference. The methods used currently in man for measurement of CBF involve the systemic administration of the radioactive inert gas ^{133}Xenon, and recording the washout of radioactivity from the brain using external scintillation detectors. Administration of the ^{133}Xe into the internal carotid or vertebral artery gives the most accurate results because extracerebral contamination of the clearance curve is avoided. The intraarterial ^{133}Xe method gives a clearance curve which is biexponential. However, this route of administration is

very invasive, and less invasive techniques have been developed in which the ^{133}Xe is given by inhalation (Mallett and Veall, 1963), or by intravenous injection (Agnoli et al., 1969). Using the inhalation and intravenous methods there is contamination of the extracerebral tissues, and when the cerebral curves are corrected for arterial recirculation three exponentials can be extracted (Obrist et al., 1967). The third component of the clearance curve causes the calculated value of CBF to be about 14% low on average. The methods of calculating CBF from the clearance curves were reviewed by James (1979). Although the results obtained using the intraarterial method are the most accurate, the inhalation and intravenous methods give results which are of the same magnitude, and because these methods are less invasive they are the ones most commonly used in clinical practice at present. Lenzi and colleagues (1978) have developed a new technique for assessing cerebral oxygen utilisation and blood flow relationships, using two separate inhalation periods of 6 minutes, one of $^{15}O_2$ and the other of ^{15}O-labelled carbon dioxide with a 15-minute break between the periods for washout. This technique is interesting because it gives an index of the regional oxygen supply to demand relationships.

MEASUREMENT OF CBV

CBV can be measured using the intravenous injection of $^{99}Tc^m$-labelled red blood cells and an emission tomographic brain scanner (Greenberg et al., 1978), or by following the clearance of intravenously administered $^{99}Tc^m$ using a gamma camera. The CT scan can be used to estimate CBV by superimposing scans performed before and

after the intravenous injection of sodium iothalamate (Ladurner et al., 1976), and a photoelectric technique for measurement of CBV has been described (Kuyama et al., 1980).

CHAPTER 4

THE EFFECTS OF TRACHEAL INTUBATION ON ICP FOLLOWING INDUCTION OF ANAESTHESIA WITH THIOPENTONE OR ALTHESIN IN PATIENTS UNDERGOING NEUROSURGERY

INTRODUCTION

Laryngoscopy and intubation are associated with increases in ICP and MAP. The increases in ICP are likely to be more marked in neurosurgical patients with raised ICP (Shapiro et al., 1972a, 1972c), and such increases in ICP may lead to transcompartmental brain tissue herniation. The increase in MAP may accentuate brain oedema in patients with intracranial pathology. Both thiopentone and Althesin decrease ICP (see Chapter 5), and thus might reduce or prevent the above changes. In this chapter I will describe a randomised trial comparing the effects of thiopentone with those of Althesin on ICP and MAP during the induction of anaesthesia.

METHOD

Twenty patients who were about to undergo craniotomy were studied. All gave their informed consent for the study. Each patient was premedicated with diazepam 10 mg. intramuscularly, except for one patient who received papaveretum 10 mg. and hyoscine 0.2 mg. Anaesthesia was induced in 10 patients with thiopentone and in 10 with Althesin, the choice of agent being randomised. Before induction of anaesthesia arterial and venous cannulae were inserted under local analgesia. A burr hole was made under local analgesia, and a catheter was inserted into a lateral ventricle for measurement of ICP.

Once MAP and ICP were stable, d-tubocurarine 45 mg was given

(40 mg. in one frail woman). This was followed immediately by an induction dose of thiopentone (range 250 to 400 mg.) or Althesin (range 3 to 5 ml.), the drug being given until there was loss of the eyelash reflex. The patients were then hyperventilated moderately with nitrous oxide and oxygen for 2 minutes, via a facemask, by hand compression of the reservoir bag. Exactly 2 minutes after the completion of the thiopentone or Althesin injection, laryngoscopy and intubation were performed. After intubation the patient was ventilated mechanically and a pharyngeal pack was inserted. Ventilation was adjusted to produce moderate hypocapnia by reference to an infra-red carbon dioxide analyser. In all patients arterial blood gas tensions were estimated once the patient was established on the ventilator. In addition, in the last 6 patients in the series the arterial blood gas tensions were estimated immediately before the induction of anaesthesia, and immediately before intubation. From the chart records the following measurements of MAP and ICP were made: 1) for the 5 minutes immediately before induction of anaesthesia (hereafter described as control MAP and ICP) and at 1, 2, 3, 4 and 5 minutes after induction; 2) immediately before laryngoscopy; 3) at the point of maximum ICP in the first 60 seconds after intubation, and 4) at the point of maximum ICP during and in the first 60 seconds after packing the pharynx.

RESULTS

Table 1 shows the pathology for which craniotomy was being performed and the ICP values for the individual patients. There was no significant difference in control mean ICP (10 ± 4 cf. 11 ± 4) between the two groups. However, two patients (one in each group)

TABLE 1a. Intracranial pathology and mean intracranial pressure (mm Hg) - Thiopentone group

Patient (age, yr)	Diagnosis	Control (before induction)	1 min.	2 min.	Maximum ICP in 1st min. after intubation	3 min.	4 min.	5 min.
ø/ A (59)	Glioblastoma	22.5	8.5	9	13	15	16	12
*/ B (47)	Metastatic carcinoma	13	11	11	14	14	14	13
* C (46)	Pituitary tumour	3	2.5	4	9	8	8	7
D (41)	Dural repair	15	13	15	28	28	19	16.5
E (61)	Pituitary tumour	9	11	8	10	10	9	9.5
?/ F (66)	Metastatic carcinoma	10	9.5	9	12	10	10	15
G (49)	Meningioma	9	15	15	16	13	13	13.5
H (63)	Metastatic carcinoma	5	4	3	4.5	4	4	3.5
I (33)	Aneurysm	15.5	8.5	9.5	17	15.5	19	28
*/ J (46)	Aneurysm	12.5	9	8.5	8	7.5	9.5	9.5
$\bar{x}$		10.2						
S.D.		4.27						
S.E.M.		1.42						

* Papilloedema pre-operatively
/ Dexamethasone pre-operatively
ø Patient A was excluded from the statistical analysis (see text)
? Fundus could not be visualised

TABLE 1b. Intracranial pathology and mean intracranial pressure (mm Hg) - Althesin group

Patient (age, yr)	Diagnosis	Control (before induction)	1 min.	2 min.	Maximum ICP in 1st min. after intubation	3 min.	4 min.	5 min.
ø K (60)	Glioblastoma	30	10	9	15	12	14	13
L (59)	Meningioma	18	12	12	15	12	10	11
M (47)	Aneurysm	14	11	12	15	12	10	10
N (56)	Pituitary tumour	9	9	8	10	9	8	9
O (57)	Aneurysm	6.5	5	5	6	5	5	2
P (45)	Pituitary tumour	6	5.5	2	4.5	3.5	2	4.5
* Q (43)	Meningioma	16	17	14	15.5	15.5	15	15
R (54)	Aneurysm	11.5	8.5	6	13	11	12.5	14.5
/ S (59)	Meningioma	12.5	14	9.5	11.5	10.5	10	9
T (71)	Meningioma	9.5	9	12.5	37	34.5	27.5	13
	$\bar{x}$	11.4						
	S.D.	4.11						
	S.E.M.	1.37						

ø Patient K was excluded from the statistical analysis (see text)
* Papilloedema pre-operatively
/ Dexamethasone pre-operatively

TABLE 2a. Mean blood pressure (mm Hg) - Thiopentone group

Patient		Control (before induction)	1 min.	2 min.	Maximum MAP reached in 1st min. after intubation	3 min.	4 min.	5 min.
ø/	A	95	65	55	68	70	73	70
*/	B	123	110	107	112	112	110	103
*	C	120	67	63	100	87	95	130
	D	107	38	48	87	87	100	90
	E	90	58	53	57	57	57	55
?/	F	103	53	52	31	48	53	67
	G	97	43	48	48	43	42	40
	H	107	73	53	52	63	95	108
	I	83	25	13	25	22	28	35
*/	J	127	105	65	73	63	73	77
	$\bar{x}$	106.3						
	S.D.	15.01						
	S.E.M.	5.0						

ø Patient A was excluded from the statistical analysis (see text)
* Papilloedema pre-operatively
/ Dexamethasone pre-operatively
? Fundus could not be visualised

TABLE 2b. Mean blood pressure (mm Hg) - Althesin group

Patient		Control (before induction)	1 min.	2 min.	Maximum MAP reached in 1st min. after intubation	3 min.	4 min.	5 min.
ϕ	K	103	88	70	110	113	113	98
	L	112	55	70	93	93	105	103
	M	135	73	88	93	102	112	117
	N	98	35	30	33	31	28	27
	O	100	70	40	70	80	100	-
	P	113	107	93	133	133	120	123
*	Q	77	77	63	113	113	92	87
	R	148	113	107	200	200	170	200
∤	S	110	96	57	88	93	120	123
	T	117	92	63	117	117	132	127
	$\bar{x}$	112.2						
	S.D.	20.67						
	S.E.M.	6.89						

ϕ Patient K was excluded from the statistical analysis (see text)
* Papilloedema pre-operatively
∤ Dexamethasone pre-operatively

TABLE 3a. ICP - changes from control and changes following intubation compared with pre-laryngoscopy value (mm Hg) - Thiopentone group

Patient		1 min.	2 min.	Max. change from control in 1st min. after intubation	3 min.	4 min.	5 min.	Changes from pre-laryngoscopy value following intubation
ø/	A	-14	-13.5	-9.5	-7.5	-6.5	-10.5	+12
*/	B	-2	-2	+1	+1	+1	0	+3
*	C	-0.5	+1	+6	+5	+5	+4	+5
	D	-2	0	+13	+13	+4	+1.5	+13
	E	+2	-1	+1	+1	0	+0.5	+2
?/	F	-0.5	-1	+2	0	0	+5	+3
	G	+6	+6	+7	+4	+4	+4.5	+1
	H	-1	-2	-0.5	-1	-1	-1.5	+1.5
	I	-7	-6	+1.5	0	+3.5	+12.5	+7.5
*/	J	-3.5	-4	-4.5	-5	-3	-3	-0.5
	$\bar{x}$	-0.9	-1	+2.9	+2.0	+1.5	+2.6	+3.9
	S.D.	3.58	3.35	5.06	5.02	2.74	4.61	4.12
	S.E.M.	1.19	1.12	1.69	1.68	0.91	1.54	1.37

ø Patient A was excluded from the statistical analysis (see text)
/ Dexamethasone pre-operatively
* Papilloedema pre-operatively
? Fundus could not be visualised

TABLE 3b. ICP - changes from control and changes following intubation compared with pre-laryngoscopy value (mm Hg) - Althesin group. (The probability values shown below are for comparison between thiopentone and althesin groups.)

Patient	1 min.	2 min.	Max. change from control in 1st min. after intubation	3 min.	4 min.	5 min.	Changes from pre-laryngoscopy value following intubation
ϕ K	-20	-21	-15	-18	-16	-17	+6
L	-6	-6	-3	-6	-8	-7	+3
M	-3	-2	+1	-2	-4	-4	+3
N	0	-1	+1	0	-1	0	+2
O	-1.5	-1.5	-0.5	-1.5	-1.5	-4.5	+1
P	-0.5	-4	-1.5	-2.5	-4	-1.5	+2.5
* Q	+1	-2	-0.5	-0.5	-1	-1	+1.5
R	-3	-5.5	+1.5	-0.5	+1	+3	+7
≠ S	+1.5	-3	-1	-2	-2.5	-3.5	+2
T	-0.5	+3	+27.5	+25	+18	+3.5	+25
$\bar{x}$	-1.3	-2.4	+2.7	+1.1	-0.3	-1.7	+5.2
S.D.	2.35	2.69	9.40	9.13	7.34	3.48	7.6
S.E.M.	0.78	0.90	3.13	3.04	2.45	1.16	2.54
P						0.05>P>0.02	

ϕ Patient K was excluded from the statistical analysis (see text)

* Papilloedema pre-operatively

≠ Dexamethasone pre-operatively

were noted to have control ICP values of greater than 20 mm Hg; these results have been excluded from the statistical analysis and are discussed separately later. The two groups were similar with regard to age and sex distribution. The thiopentone group had an average age of 51.1 years (range 33-66 years), the Althesin group 55.1 years (range 43-71 years).

The values of MAP obtained in the individual patients are given in Table 2. The difference in control MAP between the two groups (106 (S.D. 15) cf. 112 (S.D. 21) mm Hg)was not statistically significant. In 5 of the 20 patients, MAP decreased to less than 50 mm Hg following induction, in one patient to 13 mm Hg. At 5 mins after induction MAP was greater than 50 mm Hg in all except three patients.

Table 3 shows the changes in ICP with intubation related to the control value and to the value obtained immediately before laryngoscopy. In each group mean ICP decreased following the induction of anaesthesia and increased slightly following laryngoscopy and intubation. There was no significant difference between the two groups except at 5 min. after induction, when mean ICP was significantly less in the Althesin group ($0.05 > P > 0.02$). There was no significant difference between the groups in the response of ICP to intubation. There was a significant correlation between the pre-induction ICP and the increase in ICP associated with intubation in the thiopentone group ($0.05 > P > 0.02$), but there was no such correlation in the Althesin group.

The control MAP values for the two groups were very similar but the reduction in MAP after induction of anaesthesia with tubocurarine and thiopentone was at each stage greater than that

TABLE 4a. MAP - changes from control and changes following intubation compared with pre-laryngoscopy value (mm Hg) - Thiopentone group.

Patient	1 min.	2 min.	Max. change from control in 1st min. after intubation	3 min.	4 min.	5 min.	Changes from pre-laryngoscopy value following intubation
ϕ A	-30	-40	-27	-25	-22	-25	+15
*/ B	-13	-16	-11	-11	-13	-20	+20
* C	-53	-57	-20	-33	-25	+10	+37
D	-69	-59	-20	-20	-7	-17	+32
E	-32	-37	-33	-33	-33	-35	+12
?/ F	-50	-51	-72	-55	-50	-36	+1
G	-54	-49	-49	-54	-55	-57	0
H	-34	-54	-55	-44	-12	+1	+10
I	-58	-70	-58	-61	-55	-48	+12
*/ J	-22	-62	-54	-64	-54	-50	+8
$\bar{x}$	-42.8	-50.6	-41.3	-41.66	-33.8	-28.0	15.0
S.D.	18.42	15.87	20.99	18.60	20.23	23.21	12.43
S.E.M.	6.14	5.29	6.99	6.20	6.74	7.74	4.14

ϕ Patient A was excluded from the statistical analysis (see text)
* Papilloedema pre-operatively
/ Dexamethasone pre-operatively
? Fundus could not be visualised

TABLE 4b. MAP - changes from control and changes following intubation compared with pre-laryngoscopy value (mm Hg) - Althesin group. (The probability values shown below are for comparison between thiopentone and althesin groups.)

Patient	1 min.	2 min.	Max.change from control in 1st min. after intubation	3 min.	4 min.	5 min.	Changes from pre-laryngoscopy value following intubation
ø K	-15	-33	+7	+10	+10	-5	+40
L	-57	-42	-19	-19	-7	-9	+30
M	-62	-47	-42	-33	-23	-18	+20
N	-63	-68	-65	-67	-70	-71	+3
O	-30	-60	-30	-20	0	-	+30
P	-6	-20	+20	+20	+7	+10	+40
* Q	0	-14	+36	+36	+15	+10	+45
R	-35	-41	+52	+52	+22	+52	+93
≠ S	-14	-53	-22	-17	+10	+13	+36
T	-25	-54	0	0	+15	+10	+55
$\bar{x}$	-32.4	-44.3	-7.8	-5.3	-3.4	-0.4	39.1
S.D.	23.90	17.71	38.06	36.70	28.40	35.09	25.09
S.E.M.	7.97	5.90	12.69	12.23	9.47	12.41	8.36
P			0.05>P >0.02	0.05>P >0.02	0.02>P >0.01		0.02>P >0.01

ø Patient K was excluded from the statistical analysis (see text)
* Papilloedema pre-operatively
≠ Dexamethasone pre-operatively

TABLE 5

Changes in ICP and MAP related to packing the pharynx (mm Hg)

Patient		ICP before pack	Change in ICP	MAP before pack	Change in MAP
THIOPENTONE					
*⁄	A	14	0	112	+15
*	B	8	+0.5	97	+23
	C	24.5	-1	100	0
	D	9.5	0	57	0
?⁄	E	10.5	0	55	+5
	F	13	0	45	-5
	G	4	0	68	+20
	H	17	+3	25	+5
*⁄	I	7.5	+1.5	63	+5
⁄	J	15	+2	72	-5
$\bar{x}$			+0.6		+6.3
S.D.			1.20		9.90
S.E.M.			0.38		3.13
ALTHESIN					
	K	11.5	0	97	+16
	L	12.5	-0.5	110	+8
	M	10	0	30	-3
	N	5	0	80	+10
	O	5.5	+1.5	113	+12
*	P	10	0	92	+11
	Q	12.5	+2	175	+25
⁄	R	10	-0.5	95	+23
	S	27.5	+2	118	+19
	T	15	-2.5	110	0
$\bar{x}$			+0.2		+12.1
S.D.			1.36		9.10
S.E.M.			0.43		2.89

* papilloedema preoperatively
⁄ dexamethasone preoperatively
? fundus could not be visualised

obtained following tubocurarine and Althesin (Table 4). This difference reached significance ($0.05 > P > 0.02$) at approximately 3 min. after the induction of anaesthesia which, incidentally, was the time at which the maximum MAP was reached after intubation, and remained significant ($0.02 > P > 0.01$) at 4 min., but not at 5 min. The increase in arterial pressure which followed within 60 sec. of intubation was significantly greater in the Althesin group ($0.02 > P > 0.01$).

There were no significant differences between the two groups in mean $PaCO_2$ at the time of intubation (thiopentone 4.0 ± 1.2 KPa, Althesin 4.5 ± 1.1 KPa) or at 5 min. after induction (thiopentone 3.8 ± 0.9 KPa, Althesin 4.2 ± 0.8 KPa).

The changes in MAP and ICP caused by packing the pharynx were minimal and there was no statistically significant difference between the two groups (Table 5).

In the two patients with control ICP values greater than 20 mm Hg the changes in MAP were similar to those noted in patients with control ICP values of less than 20 mm Hg. In these two patients ICP decreased markedly following the administration of the induction agent and tubocurarine (by 44 mm Hg and 20 mm Hg; see Table 3) and did not increase above the control value with intubation.

DISCUSSION

Increases in ICP at the time of laryngoscopy and intubation were described first by Stephen and colleagues (1954), and since then many other workers have reported such ICP increases in normal and neurosurgical patients (Lundberg, 1960; Marx et al., 1962; Adams et al., 1972; Hulme and Cooper, 1972; McLeskey et al., 1974;

Misfeldt et al., 1974; Burney and Winn, 1975; Greenbaum et al.,1975). De Vault and colleagues (1960) found that tracheal intubation under light general anaesthesia was consistently accompanied by a pressor response, tachycardia, and in some instances cardiac arrhythmias. These circulatory changes were not affected by the administration of atropine but were reduced by phentolamine, indicating that they could be mediated by the sympathicoadrenal system. This conclusion is supported by the data of Reves and colleagues (1981) who found a transient increase in arterial noradrenaline levels during intubation which suggested an adrenergic neuronal reflex pathway. The ICP increase is not caused by changes in CVP because only small changes in CVP occur during intubation (Shapiro et al., 1972c). The likely mechanism of the increase in ICP is that a loss of autoregulatory control (or a change in MAP which is too rapid for autoregulation to cope with), allows the increase in MAP to cause an increase in CBF, CBV and ICP, although it is possible that the increase in ICP is not secondary to an increase in MAP (Greenbaum et al., 1975). Distortion of the jugular veins during laryngoscopy may be a contributing factor.

The ICP changes associated with this increase in MAP are likely to be more marked in neurosurgical patients, especially those with increased ICP caused by tumour or other intracranial space-occupying lesion, and these increases could lead to transcompartmental herniation of brain tissue (Shapiro et al., 1972a; Greenbaum et al., 1975).

In this investigation the increases in ICP associated with intubation were small. For the 18 patients included in the statistical analysis (ICP less than 20 mm Hg) there was a mean increase in ICP from the control level of 2.8 mm Hg (range -4.5 to

27.5 mm Hg) and the mean increase from the prelaryngoscopy value was 4.6 mm Hg (range=0.5 to 25 mm Hg). With the exception of 2 patients the increases in ICP from control level following intubation were 7 mm Hg or less (7.5 mm Hg or less from the prelaryngoscopy value). One patient showed an increase in ICP from control of 13 mm Hg but this was related to coughing and straining on the endotracheal tube. Another patient showed an increase of 27.5 mm Hg. This patient had a large meningioma and probably had a very low intracranial compliance, and the $PaCO_2$ increased by 1.1 KPa between induction of anaesthesia and laryngoscopy. The $PaCO_2$ was 5.2 KPa at the time of intubation and this may have been the reason for the marked increase in ICP, as this was the only patient who showed an increase in $PaCO_2$ between induction of anaesthesia and intubation.

There are several reports on the changes in ICP occurring with intubation. Shapiro and colleagues (1972c) found, in patients intubated with suxamethonium, that the increases were greater in patients who had symptoms or signs of increased ICP before operation (increases from the pre-induction value of 19 to 30 mm Hg) than in patients with "normal ICP" (increases from preinduction value of -7 to +5 mm Hg). The changes did not, however, relate to the measured ICP values immediately before induction of anaesthesia. Burney and Winn (1975), who also used suxamethonium, showed increases in ICP similar to those of Shapiro and colleagues, and their data appeared to show no correlation between the initial values of ICP and the increase associated with intubation. The variable response of ICP to intubation in patients with similar ICP values before intubation may be explained by the pressure/volume relationship of the cranial contents. Thus, when intracranial compliance is reduced a stimulus

which affects ICP will produce a greater response than it would if the compliance had been normal.

Other studies, in which suxamethonium was used as the relaxant, have shown increases in ICP of up to 80 mm Hg, with peaks of 100 mm Hg (Misfeldt et al., 1974; Greenbaum et al., 1975). Workers who compared the increases of ICP following intubation under relaxation with suxamethonium and pancuronium, found much smaller increases in ICP when pancuronium was used, provided that adequate time was allowed for it to act (McLeskey et al., 1974; Lewelt et al., 1976). Despite using very large doses of thiopentone, McLeskey and colleagues found marked increases in MAP in their suxamethonium group. Lewelt and colleagues (1976) did not record arterial blood pressure during induction. The ICP changes recorded in the last two studies are closest to those described by the author, probably because a non-depolarising relaxant was used in all three studies. Suxamethonium may be associated with greater increases in ICP during intubation because it causes muscle fasciculations, or because of a direct action of the drug on the cerebral vessels (preliminary work by the author suggests that suxamethonium has very little direct effect on ICP (see Chapter 6)), or because the duration of hyperventilation before intubation will be shorter than when a non-depolarising muscle relaxant is used. The longer period of hyperventilation before intubation in patients receiving a long-acting muscle relaxant produces hypocapnia, which may partially restore defective auto-regulation (Paulson et al., 1972), and thus protect the cerebral circulation against any sudden increase in MAP, which would otherwise increase CBV and could promote the formation of cerebral oedema.

Large increases in ICP associated with intubation should be

avoided in neurosurgery because they may cause transcompartmental pressure gradients and so induce brain shifts, may precipitate cerebral oedema if secondary to an acute episode of arterial hypertension, or may result in an inadequate CPP. Misfeldt and colleagues (1974) stated that increases in ICP associated with intubation were harmless, but they concentrated only on CPP, (which was always adequate in their investigations), and did not consider the other factors discussed above, which are probably more important in this context.

Several methods of reducing the increases in MAP and ICP with endotracheal intubation have been suggested. King and colleagues (1951) showed that deepening anaesthesia to the second or third plane of surgical anaesthesia obtunded or abolished the increase in arterial pressure. Thiopentone can be used to deepen anaesthesia before intubation (Shapiro et al., 1972c), and the intravenous administration of a β-adrenergic blocking agent before intubation has been suggested (Greenbaum et al., 1975), although this has caused cardiovascular collapse in a patient with subarachnoid haemorrhage (Farnon and Curran, 1981). Shapiro and colleagues (1972c) suggested the use of fentanyl before intubation to attenuate the associated ICP increase, and Dahlgren and Messeter (1981) have shown significant attenuation of the MAP response to laryngoscopy and intubation by the administration of fentanyl 5 μg/Kg intravenously 3 min. before intubation in patients about to undergo elective intracranial surgery. Davies and colleagues (1981) have shown that pretreatment with hydrallazine 0.4 mg/Kg caused a significant reduction in the maximum MAP changes at intubation in patients undergoing intracranial surgery, but the average MAP change over the intubation period

was no different from that in the control patients, and the administration of hydrallazine 12.5 mg intravenously has been shown to increase CBF and ICP in patients with intracranial pathology (Overgaard and Skinhøj, 1975). Local anaesthesia of the larynx and trachea would prevent coughing on intubation, but transtracheal injection of lignocaine caused a greater increase in MAP than intubation alone (Ward et al., 1965), and laryngoscopy for spraying the vocal cords will itself increase ICP. Hyperventilation before spraying the cords may prevent any associated increase in ICP (Sondergard, 1961).

Intravenous injection of lignocaine 1.5 mg/Kg during thiopentone, nitrous oxide, oxygen anaesthesia has been shown to prevent the ICP increase after intubation under suxamethonium (Bedford et al., 1980). From the author's results and those of other similar investigations, it appears that the increases in ICP associated with intubation are smaller when a non-depolarising relaxant is used.

Tubocurarine was used in this study, since it is commonly used in neurosurgery, partly because the hypotension produced (Thomas, 1957) may reduce bleeding from skin and muscle and aids in the avoidance of hypertensive episodes during surgery. In this respect it may have an advantage over pancuronium which can produce increases in arterial pressure (Kelman and Kennedy, 1971; Gordon, 1975).

In this study tubocurarine and an intravenous induction agent produced significant decreases in MAP, an effect which lasted for only a few minutes. MAP decreased to a similar degree with thiopentone and Althesin, but recovery was more rapid and complete

in the Althesin group. CPP was reduced to less than 60 mm Hg in 75% of the patients and to less than 40 mm Hg in 20%. A CPP of 50 mm Hg is at the lower end of the autoregulation range (Olesen, 1973), thus tubocurarine can cause potentially dangerous reductions in CPP which, even though short-lived, might be considered to be a disadvantage of the drug. However, there was no clinical evidence in the period after operation that this decrease in CPP affected the recovery of the patient in any way, and it may have been a factor in preventing large increases in ICP with intubation. The wide inter-patient variation in MAP response to tubocurarine is in agreement with the results of Thomas (1957).

Four of the patients were receiving dexamethasone before operation, but their ICP response to intubation did not appear to differ from the other patients.

There had been no previous reported comparison between thiopentone and Althesin for the induction of anaesthesia for craniotomy. The author's results show that there was no significant difference between these two agents in their effects on ICP when combined with tubocurarine, and that there was no difference between the two groups with regard to the change in ICP following intubation or packing the pharynx.

The positive correlation between control ICP and the increase in ICP associated with intubation in the thiopentone group only just reached statistical significance, and the increases in ICP with intubation in this series were small. Thus the changes in ICP at intubation are similar when thiopentone and Althesin are used for induc tion of anaesthesia, even in patients with elevated ICP.

SUMMARY

In this chapter an investigation is described in which intracranial pressure and mean arterial pressure were studied in 20 patients during the induction of anaesthesia for craniotomy, using tubocurarine as the muscle relaxant and either thiopentone or Althesin for induction of anaesthesia. No significant differences were found between the thiopentone and the Althesin groups in the ICP changes with induction, intubation or pharyngeal packing. Except for two cases (one in each group) the increases in ICP associated with intubation were small. In these two patients moderate increases from normal levels to 28 and 37 mm Hg were recorded, but in one of these cases coughing and straining followed intubation. Marked decreases in MAP were noted in both groups, but the recovery of MAP was significantly more rapid in the Althesin group. Only two patients had ICP values greater than 20 mm Hg before operation and in neither did ICP increase above control values during induction and intubation. Packing the pharynx produced minimal changes in ICP in all patients. These findings are discussed and compared with those of other authors.

CHAPTER 5

THE EFFECT OF ETOMIDATE ON ICP AND CPP

INTRODUCTION

At the time this study was started it was known that, of the drugs used to induce anaesthesia, thiopentone, methohexitone and Althesin caused a reduction in ICP and CBF, propanidid could have variable effects on these parameters, and ketamine increased them (see below). Etomidate is an intravenous agent for induction and maintenance of anaesthesia which causes a reduction in CBF in normal man (Herrshaft et al., 1975) and thus it would be expected to reduce ICP also. This study was undertaken to determine the effect of etomidate on ICP in patients with intracranial pathology who were about to undergo craniotomy, and thus to determine its suitability for use in patients with intracranial space-occupying lesions.

METHODS

Ten patients with intracranial lesions requiring craniotomy were investigated. All gave their informed consent for the study. If considered necessary, the patients were premedicated with diazepam 10 mg. intramuscularly. Anaesthesia was induced with thiopentone given until the eyelash reflex was lost, and was maintained with nitrous oxide (70%) in oxygen. Ventilation was controlled and tubocurarine 45 mg. was administered to produce neuromuscular blockade. The volume of ventilation was adjusted

to produce normocapnia, and was maintained constant throughout the period of the study. Arterial pressure was recorded from a radial artery cannula and ICP from a catheter inserted into a lateral ventricle. The patients were supine and tilted 10° head-up during the investigations. The arterial and intracranial pressure traces were observed for 5 minutes before the intravenous injection of etomidate 0.2 mg/Kg (given over a period of 10 seconds), and for 10 minutes after the administration of etomidate. Surgery was then continued. From the chart recordings, the following measurements were made: 1) MAP, mean ICP and CPP in the 5 minutes before the injection of etomidate (control values for MAP, mean ICP and CPP); 2) MAP, mean ICP and CPP at one-minute intervals for 10 minutes after the administration of the etomidate . (Only the results obtained at 2-minute intervals are tabulated, as there was no further information to be obtained from the more frequent measurements.)

Samples were taken for measurement of arterial blood-gas tensions just before the administration of the etomidate (initial $PaCO_2$) and at 10 minutes after etomidate administration (final $PaCO_2$). The end-tidal carbon dioxide concentration was monitored continuously with an infra-red gas analyser during the period of measurement.

RESULTS

Table 6 gives the ages and diagnoses of the patients and the mean ICP during the control period and at 2-minute intervals after the administration of etomidate. ICP decreased initially in all the patients and then started to increase, but in only 2 patients it returned to control levels within 10 minutes. This decrease

TABLE 6

The mean intracranial pressure (mm Hg), diagnoses and ages (yr.) of the 10 patients. Control indicates the mean pressure in the 5 minutes before administration of etomidate. The probability values represent the significance of the changes in ICP from the control value.

Patient and age (yr.)	Diagnosis	Control ICP	Time after etomidate (min.)				
			2	4	6	8	10
A (51)	Aneurysm	14	9	9	6	8	8
B (46)	Pituitary tumour	28	22	22	23	23	23
C (35)	Glioblastoma	16	10	11	12	14	16
D (22)	Glioblastoma	16	11	11	11	12	13
E (66)	Pituitary tumour	9	4	4	4	5	6
F (71)	Pituitary tumour	9	6	5	6	6	6
G (70)	Pituitary tumour	13	6	6	6	6	6
H (33)	Pituitary tumour	26	11	11	12	11	13
I (61)	Glioblastoma	21	8	7	8	8	9
J (51)	Meningioma	12	9	10	10	11	11
$\bar{x}$		16.4	9.6	9.6	9.8	10.4	11.1
S.D.		6.62	4.93	5.08	5.43	5.32	5.43
S.E.M.		2.09	1.56	1.61	1.72	1.68	1.72
P			<0.001	<0.001	<0.001	0.01>P >0.001	0.01>P >0.001

from control was statistically significant ($0.01 > P > 0.001$) at the first minute after injection, and remained significant at the 1% level or greater for the 10 minutes of measurement.

There was a small decrease in MAP in 8 patients (Table 7). This decrease was statistically significant at 3 and 4 minutes after the administration of etomidate ($0.05 > P > 0.02$). The heart rate decreased slightly in 8 patients but did not differ significantly from the control level at any time.

On average the CPP decreased slightly but this decrease was not statistically significant (Table 8). The CPP decreased to less than 60 mm Hg in one patient (patient B, minimum CPP = 54 mm Hg).

In 4 patients $PaCO_2$ was in the normal range and in 5 patients was just below the lower limit of normal. One patient was markedly hypocapnic (Table 9). In most patients there was a slight decrease in $PaCO_2$ over the 10-minute period of measurement so that the mean $PaCO_2$ decreased by 0.23 KPa (stastical significance $0.01 > P > 0.001$). The decrease in end-tidal carbon dioxide concentration usually occurred at between 2 and 7 minutes after the administration of etomidate.

Fig. 1 shows the scatter diagram and regression line for the decrease in ICP after the administration of etomidate plotted against the initial ICP value. The correlation ($r = 0.624$) between the decrease in ICP and initial ICP was not statistically significant.

TABLE 7

The mean arterial pressure (mm Hg) of the 10 patients. 'Control' indicates the mean pressure in the 5 minutes before the administration of etomidate. The probability value represents the significance of the change in MAP from the control value.

Patient	Control MAP	Time after etomidate (min.)				
		2	4	6	8	10
A	183	185	175	180	180	180
B	102	87	78	77	83	90
C	123	123	122	128	133	135
D	108	108	108	108	108	103
E	87	83	78	83	85	85
F	115	107	107	122	125	120
G	102	93	95	95	90	90
H	133	128	130	140	133	137
I	107	107	105	105	100	100
J	143	112	105	98	103	103
$\bar{x}$	120.3	113.3	110.3	113.6	114.0	114.3
S.D.	27.39	29.03	28.10	30.47	29.68	29.42
S.E.M.	8.66	9.18	8.89	9.64	9.39	9.31
P			0.05>P >0.02			

TABLE 8

The cerebral perfusion pressure (mm Hg) of the 10 patients. 'Control' indicates the mean cerebral perfusion pressure in the 5 minutes before the administration of etomidate

Patient	Control CPP	Time after etomidate (min.)				
		2	4	6	8	10
A	169	176	166	174	172	172
B	74	65	56	54	60	67
C	107	113	111	116	119	119
D	92	97	97	97	96	90
E	78	79	74	79	80	79
F	106	101	102	116	119	114
G	89	87	89	89	84	84
H	107	117	119	128	122	124
I	86	99	98	97	92	91
J	131	103	95	88	92	92
$\bar{x}$	103.9	103.7	100.7	103.8	103.6	103.2
S.D.	28.37	29.72	29.07	32.43	31.02	30.27
S.E.M.	8.98	9.41	9.20	10.26	9.82	9.58

TABLE 9

The $Paco_2$ values (KPa) of the 10 patients immediately before the administration of etomidate (inicial $Paco_2$) and at 10 minutes after administration of etomidate (final $Paco_2$). The probability value refers to the significance of the change in $Paco_2$ during the period of measurement.

Patient	Initial $Paco_2$	Final $Paco_2$
A	4.67	4.13
B	4.80	4.80
C	4.40	4.40
D	4.13	4.0
E	4.53	4.27
F	4.93	4.67
G	4.53	4.27
H	4.80	4.67
I	5.60	5.33
J	3.07	2.67
$\bar{x}$	4.55	4.32
S.D.	0.65	0.70
S.E.M.	0.21	0.22
P	0.01>P>0.001	

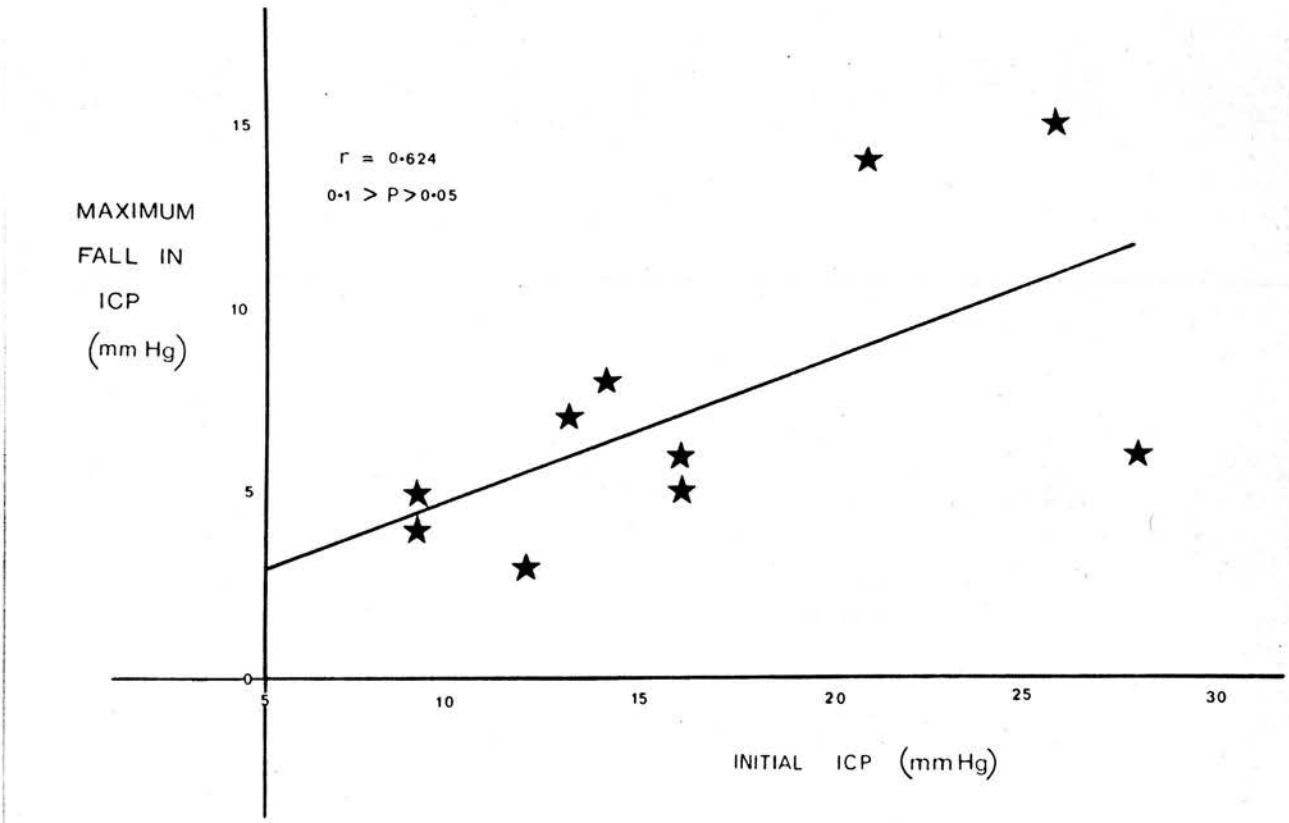

Figure 1. Scatter diagram and regression line for the maximum decrease in ICP (mm Hg) following the administration of etomidate 0.2 mg/Kg plotted against the initial ICP.

DISCUSSION

There have been many investigations on the effect of intravenous anaesthetic agents on ICP, CBF and CPP. Doses of barbiturates which do not cause unconsciousness do not alter CBF, $CMRO_2$ (Kety et al., 1948), or lumber CSF pressure (Horsley, 1937), but, provided that respiratory depression does not occur, barbiturates in doses sufficient to produce light anaesthesia cause a highly significant decrease in $CMRO_2$ and a significant reduction in CBF (McCall and Taylor, 1952b). ICP is reduced by thiopentone (Horsley, 1937; Sondergard, 1961; Zattoni and Siani, 1969, 1972; Shapiro et al., 1973; Cunitz et al., 1978; Schulte am Esch et al., 1978a, 1978b; Nayak et al., 1980), methohexitone (Hunter, 1972b; Takasaki et al., 1973; Cunitz et al., 1978; Cunitz and Gaab, 1980), and Althesin (Turner et al., 1973; Takahashi et al., 1973; Takasaki et al., 1973; Rasmussen et al., 1978; Zattoni, 1980). (Nayak and colleagues (1980) found no significant change in lumber CSF pressure in normal patients following Althesin 0.05 ml/Kg but there was coughing, muscle rigidity and tremors during the measurements.) In normal patients propanidid had no effect on CSF pressure (Takasaki et al., 1973), but in patients with intracranial pathology its effect was variable (Zattoni and Siani, 1972). Schulte am Esch and colleagues (1978b) found that propanidid 7 mg/Kg reduced ICP, but that there were fluctuations of ICP up to the third mimute after its administration. Ketamine causes an increase in ICP (Bock et al., 1972; Gardner et al., 1972; Gibbs, 1972; Shapiro et al., 1972b), CBF is reduced by thiopentone (Pierce et al., 1962; Herrschaft et al.,1975; Van Aken, 1976b; Coté et al., 1979), methohexitone (Herrschaft et al., 1974, 1975), and Althesin (Sari et al., 1976; Rasmussen et al., 1978).

Propanidid caused a reduction in CBF in man (Herrschaft et al., 1975), but in dogs CBF increased insignificantly for the first 1 to 2 minutes and then decreased until the MAP returned to normal (Takeshita et al., 1973; Miyauchi et al., 1973). Ketamine causes an increase in CBF in man (Takeshita et al., 1972b),which Hougaard and colleagues (1974) found to be localised particularly to the fronto-temporal and parieto-occipital regions, and in dogs (Dawson et al., 1971;Bazaugour et al., 1975). Thus the effects of these anaesthetic agents on CBF parallels their effect on ICP, which supports the concept that anaesthetic drugs alter ICP by altering CBF and CBV (see Chapter 2).

Thiopentone, by reducing MAP, can cause a significant reduction in CPP (Schulte am Esch, 1978a, 1978b, 1980) although smaller doses (3 mg/Kg) produced only minimal changes (Shapiro et al., 1973; Cunitz et al., 1978). CPP is only minimally reduced by methohexitone (Cunitz et al., 1978) or Althesin (Turner et al., 1973). Propanidid causes a reduction in CPP (Schulte am Esch et al., 1978b) as does ketamine (Bock et al., 1972; Schulte am Esch et al., 1978b).

The cerebral metabolic rate for oxygen ($CMRO_2$) is also affected by the intravenous agents used for induction of anaesthesia. $CMRO_2$ is reduced by thiopentone (Pierce et al., 1962; Coté et al.,1979) and similar dose-dependent decreases have also been reported with phenobarbitone in rats. It appears that little further reduction in $CMRO_2$ can be expected once it has been reduced to about 50% of normal (Nilsson and Siesjö, 1975). Acute tolerance to the depressant effect of thiopentone on $CMRO_2$ can be demonstrated in dogs (Altenburg et al., 1969). $CMRO_2$ is also reduced by Althesin (Sari et al., 1976; Rasmussen et al., 1978), by propanidid in dogs (Takeshita et al., 1973;

Miyauchi et al., 1973) and etomidate (Van Aken and Rolly, 1976; Renou et al., 1978b, 1978c). Ketamine caused no significant change in $CMRO_2$ in healthy patients (Takeshita et al., 1972b), but increased $CMRO_2$ in anaesthetised dogs (Dawson et al., 1971; Bazaugour et al., 1975). The changes in CBF associated with the administration of these intravenous anaesthetic agents closely parallel the changes in $CMRO_2$, which suggests that the change in CBF is caused by the change in $CMRO_2$.

In this study there was a decrease in ICP in all 10 patients following the administration of etomidate intravenously. The change in ICP for the group was statistically significant ($P < 0.001$). This reduction can be explained by the rapid decrease in CBF, and thus CBV, which is known to occur after the administration of etomidate (Herrschaft et al., 1975; Van Aken and Rolly, 1976; Renou et al., 1978b, 1978c). The studies of Herrschaft and colleagues were in normal patients anaesthetised with propanidid, suxamethonium, nitrous oxide, oxygen and halothane 0.1 to 0.4 vol.%. The use of halothane may explain the more short-lived reduction in CBF that they observed (less than 5 minutes) as compared with the duration of the decrease in ICP that was observed in this study (more than 10 minutes). The duration of the decrease in ICP seen in the author's study is more in keeping with the duration of action of etomidate reported in the literature by both Doenicke (1974), who reported that the time to complete recovery after the administration of etomidate 0.3 mg/Kg was approximately 12 minutes, and by Lewi and Heykants (1978) who found that the plasma concentration fell by approximately 90% in 16 minutes after a dose of 0.21 mg/Kg.

There was no significant correlation between initial ICP and

change in ICP following etomidate. These results differ from those of Turner and colleagues (1973) with Althesin. There was, however, a tendency for a greater fall in ICP if the initial ICP was higher, and in a larger series the correlation might have proved significant.

The small decrease in $PaCO_2$ (average 0.23 KPa), which occurred in most of the patients during the period of measurement, occurred during constant ventilation which had been established for at least 30 minutes before the administration of etomidate. It may have been due to a reduction in metabolic rate, and thus a reduction in carbon dioxide production. With one exception this decrease in $PaCO_2$ occurred between 2 and 7 minutes after the administration of etomidate, whereas the maximum change in ICP occurred within 90 seconds and by 7 minutes ICP was beginning to increase again. Thus the influence on ICP of this small change in $PaCO_2$ was probably minimal.

The MAP decreased in all except 2 patients, but the lowest MAP recorded was 77 mm Hg which was above the value at which auto-regulation of CBF ceases and CBF becomes pressure-dependent. The CPP increased in 50% of the patients and decreased in 50%, remaining adequate in all patients. The heart rate decreased slightly in most of the patients, but the change was not statistically significant. These findings confirm the cardiovascular stability found with etomidate (Doenicke, 1974; Morgan et al., 1975; Holdcroft et al., 1976; Rifat et al., 1976; Famewo and Odugbesan, 1977; Ghoneim and Yamada, 1977; Lees and Hendry, 1977; Patschke et al., 1977).

Etomidate has other possible advantages which were not assessed in this study. Plasma histamine concentration does not increase after its administration (Doenicke et al., 1973), (whereas

it does after Althesin and propanidid), and there is no reported case of allergic reaction to the drug. In the dose required for anaesthesia, respiratory depression is not a problem (Doenicke, 1974; Morgan et al., 1975, 1977; Famewo and Odugbesan, 1977, 1978; Ghoneim and Yamada, 1977), although this property is not so important in neuroanaesthesia as ventilation is usually controlled. Etomidate is metabolised quickly and has been shown to be suitable for maintenance of anaesthesia by a total intravenous technique, when given in a dose of 100 μg/Kg for 10 minutes followed by 10 μg/Kg for the remainder of the operation, and supplemented with fentanyl as required (Boyes et al., 1981). It has no toxic effects when given in large doses, and patients are usually rouseable within 5 minutes of terminating the infusion. Some patients do, however, take some time to wake and most are drowsy for several hours afterwards. Thus its use by continuous intravenous infusion may have a place as an alternative to thiopentone, methohexitone (Hunter, 1972a, 1972b) or Althesin, in maintaining anaesthesia in patients with intracranial space-occupying lesions. It has no analgesic properties so analgesic supplementation is essential. The rapid metabolism of the drug and its ability to reduce ICP suggest that it would be suitable for rapid reduction of ICP in head injured patients, or for prophylactic use before chest physiotherapy or other procedures known to increase ICP in this group of patients.

Patel (1980) reported that the involuntary movements caused by etomidate could cause ICP to increase. This would appear to mitigate against its use in neuroanaesthesia, but involuntary movements are rare when anaesthesia is induced over a period of 90 to 120 seconds by infusion of etomidate (Boyes et al., 1981), and

will not be a problem when the patient is under the influence of a muscle relaxant.

From the results of this study it can be concluded that etomidate is a useful addition to the drugs available to the neuroanaesthetist for induction of anaesthesia. This conclusion is supported by the results of other authors (Cunitz et al., 1978; Schulte am Esch et al., 1978a, 1978b, 1980; Cunitz and Gaab, 1980), which were published after this investigation was completed. In addition, etomidate could be used as an agent for the rapid reduction of ICP and for maintenance of anaesthesia by continuous infusion.

SUMMARY

Ten patients with intracranial lesions, anaesthetised with thiopentone, d-tubocurarine, and nitrous oxide (70%) in oxygen (30%) received etomidate 0.2 mg/Kg intravenously. Ventilation was controlled in each patient. ICP and MAP were recorded. ICP decreased significantly in all patients ($0.01 > P > 0.001$). Although $PaCO_2$ decreased during the period of measurement, the extent and time-course of this change suggested that it was not mainly responsible for changes in ICP. MAP decreased in most patients, but the decrease was statistically significant only at 3 and 4 minutes after the administration of etomidate ($0.05 > P > 0.02$). The changes in CPP and heart rate were not clinically or statistically significant. Thus etomidate can be used for the induction of anaesthesia in patients with intracranial space-occupying lesions without increasing ICP or seriously reducing CPP.

CHAPTER 6

THE EFFECTS OF TUBOCURARINE ON ICP AND CPP

INTRODUCTION

Although d-tubocurarine is commonly used in neuroanaesthesia the literature on its effect on ICP and CBF is contradictory. Alexander and colleagues (1964) stated that it had no direct effect on the cerebral circulation, a finding which has been supported by the results of other workers (see below). There are, however, very few reports of the effect of tubocurarine on ICP. Tarkkanen and colleagues (1974) reported that tubocurarine could cause significant increases in ICP during normocapnia in neurosurgical patients. This finding is contradictory to all previous reports and does not agree with the author's experience. In this chapter I will describe the results of studies of the effect on ICP of d-tubocurarine 45 mg. given with thiopentone or Althesin, and of smaller incremental doses of d-tubocurarine in patients who were receiving nitrous oxide relaxant anaesthesia.

METHODS

In these investigations ICP was measured from a ventricular catheter, which had been inserted for other ICP studies, and arterial pressure was measured from a radial artery cannula. The patients were placed supine with a 10° head-up tilt. The patients gave their informed consent.

The first investigation involves the 20 patients described in Chapter 4. Each patient was premedicated with diazepam 10 mg. intramuscularly, except for one patient who received papaveretum 10 mg and hyoscine 0.2 mg. intramuscularly. Ten patients received

thiopentone (range 250 to 400 mg), preceded by d-tubocurarine 45 mg and 10 received Althesin (range 3 to 5 ml) preceded by d-tubocurarine 45 mg (40 mg in one frail patient). The patients were then hyperventilated moderately with 70% nitrous oxide in oxygen for 2 mins. via a facemask by hand compression of the reservoir bag until intubation. End-tidal carbon dioxide concentration was observed on an infra-red analyser throughout this period, and an arterial blood sample was taken for determination of blood gas tensions 2 mins. after the administration of d-tubocurarine in 6 of the patients. ICP and MAP were measured for 5 mins. before induction of anaesthesia and for the 2 mins. between induction and laryngoscopy and intubation.

In the second investigation, 10 patients who were about to undergo intracranial operations for cerebral tumour or aneurysm were studied. If premedication was required this was with diazepam 10 mg. intramuscularly or orally. The patients were anaesthetised with thiopentone or Althesin followed by d-tubocurarine, intubated, and maintained with 70% nitrous oxide in oxygen supplemented with fentanyl. The ventilator was adjusted to give a constant end-tidal carbon dioxide concentration by reference to an infrared carbon dioxide analyser. Once ICP and MAP had been stable for 5 min, d-tubocurarine 15 to 20 mg was given intravenously, and ICP and MAP were recorded for 5 min before any further drugs were given and before surgery was continued. Arterial blood gas tensions were measured within 5 min. of the administration of tubocurarine.

RESULTS

When d-tubocurarine 45 mg was given immediately before thiopentone or Althesin at induction of anaesthesia there were significant reductions in ICP, MAP and CPP (Tables 10, 11 and 12). ICP was reduced in 14 out of the 20 patients and the maximum increase in ICP was 6 mm Hg. CPP was reduced to less than 50 mm Hg in 11 patients. The $PaCO_2$ at 2 minutes after the administration of tubocurarine was 3.76 (S.D. 0.80) KPa (range 2.1 to 5.3 KPa).

The administration of tubocurarine 15 to 20 mg intravenously resulted in a statistically significant reduction in ICP at 4 and 5 minutes after its administration compared with the control value ($0.05 > P > 0.02$) (Table 13). In this dosage it also caused small reductions in MAP and CPP which were not statistically significant (Tables 14 and 15). The mean $PaCO_2$ at the time of the administration of the tubocurarine was 4.76 (S.D. 0.96) KPa (range 3.7 to 6.7 KPa).

DISCUSSION

With the exception of suxamethonium which has been shown to increase lumber CSF pressure by up to 23.5 mm Hg (Halldin and Wahlin, 1959; Sondergard, 1961; Marx et al., 1962), the muscle relaxants appear to have no primary effect on ICP. Greenbaum and colleagues (1975) found that alcuronium appeared to have no direct effect on ICP and, during induction of anaesthesia, McLeskey and colleagues (1974) found that pancuronium had no effect on ICP. It is the author's experience that ICP does not change when pancuronium 2 to 4 mg is given to mechanically-

TABLE 10

Mean ICP before (control) and 1 and 2 min. after thiopentone or Althesin and d-tubocurarine 45 mg. intravenously.

(Significance values are for comparison with the control values.)

Patient	Control (before induction)	1 minute	2 minutes
A	22.5	8.5	9
B	13	11	11
C	3	2.5	4
D	15	13	15
E	9	11	8
F	10	9.5	9
G	9	15	15
H	5	4	3
I	15.5	8.5	9.5
J	12.5	9	8.5
K	30	10	9
L	18	12	12
M	14	11	12
N	9	9	8
O	6.5	5	5
P	6	5.5	2
Q	16	17	14
R	11.5	8.5	6
S	12.5	14	9.5
T	9.5	9	12.5
n	20	20	20
$\bar{x}$	12.38	9.65	9.1
S.D.	6.26	3.63	3.76
Σx	247.5	193	182
Σx^2	3806.8	2113.5	1925
P		0.05>P >0.02	0.02>P >0.01

TABLE 11

MAP before (control) and 1 and 2 min. after thiopentone or Althesin and d-tubocurarine 45 mg. intravenously.

(Significance values are for comparison with the control values.)

Patient	Control (before induction)	1 minute	2 minutes
A	95	65	55
B	123	110	107
C	120	67	63
D	107	38	48
E	90	58	53
F	103	53	52
G	97	43	48
H	107	73	53
I	83	25	13
J	127	105	65
K	103	88	70
L	112	55	70
M	135	73	88
N	98	35	30
O	100	70	40
P	113	107	93
Q	77	77	63
R	148	113	107
S	110	96	57
T	117	92	63
n	20	20	20
$\bar{x}$	108.3	72.2	61.9
S.D.	17.17	26.35	23.47
Σx	2165	1443	1238
Σx^2	239961	117309	87096
P		<0.001	<0.001

TABLE 12

CPP before (control) and 1 and 2 min. after thiopentone or Althesin and d-tubocurarine 45 mg. intravenously.

(Significance values are for comparison with the control values.)

Patient	Control (before induction)	1 minute	2 minutes
A	72.5	56.5	46
B	110	99	96
C	117	64.5	59
D	92	25	33
E	81	47	45
F	93	43.5	43
G	88	28	33
H	102	69	50
I	67.5	16.5	3.5
J	114.5	96	56.5
K	73	78	61
L	94	43	58
M	121	62	76
N	89	26	22
O	93.5	65	35
P	107	101.5	91
Q	61	60	49
R	136.5	104.5	101
S	97.5	82	47.5
T	107.5	83	50.5
n	20	20	20
$\bar{x}$	95.9	62.5	52.8
S.D.	19.23	27.05	24.14
Σx	1917.5	1250	1056
Σx^2	190867.8	92026.5	66829
P		<0.001	<0.001

TABLE 13

ICP values (mm Hg) before (control) and after d-tubocurarine 15 to 20 mg intravenously. (Significance values are for comparison with the control values.)

Patient	Control	After d-tubocurarine				
		1 min	2 min	3 min	4 min	5 min
A	6.5	6.5	6.5	6.5	5.5	5.5
B	13.5	13.5	13.5	13	13	13.5
C	23	23	23.5	23	21	22.5
D	4.5	4	4	4	4	4
E	21.5	21.5	20.5	20.5	20	19
F	50	47.5	44	44	45	47.5
G	7.5	7	6	6	6	6
H	11.5	11.5	9	10	11	11
I	7.5	8	7.5	7.5	7.5	8
J	-1.5	-1.5	-1.5	-1.5	-1.5	-1.5
n	10	10	10	10	10	10
$\bar{x}$	14.4	14.1	13.3	13.3	13.2	13.6
S.E.M.	4.61	4.41	4.16	4.14	4.18	4.40
P					0.05>P >0.02	0.05>P >0.02

TABLE 14

MAP values (mm Hg) before (control) and after d-tubocurarine 15 to 20 mg intravenously.

Patient	Control	After d-tubocurarine				
		1 min	2 min	3 min	4 min	5 min
A	90	90	90	90	90	90
B	137	137	132	132	125	132
C	107	102	102	100	100	107
D	117	122	122	122	112	112
E	100	105	105	100	102	100
F	85	84	80	80	80	84
G	62	62	62	62	67	68
H	140	132	130	123	118	117
I	100	100	100	98	93	93
J	88	82	68	63	68	73
n	10	10	10	10	10	10
$\bar{x}$	102.6	101.6	99.1	97	95.5	97.6
S.E.M.	7.57	7.46	7.75	7.65	6.29	6.34

TABLE 15

CPP values (mm Hg) before (control) and after d-tubocurarine 15 to 20 mg intravenously

Patient	Control	After d-tubocurarine				
		1 min	2 min	3 min	4 min	5 min
A	83.5	83.5	83.5	83.5	84.5	84.5
B	123.5	123.5	118.5	119	112	118.5
C	84	79	78.5	77	79	84.5
D	112.5	118	118	118	108	108
E	78.5	83.5	84.5	79.5	82	81
F	35	36.5	36	36	35	36.5
G	54.5	55	56	56	61	62
H	128.5	120.5	121	113	107	106
I	92.5	92	92.5	90.5	85.5	85
J	89.5	83.5	69.5	64.5	69.5	74.5
n	10	10	10	10	10	10
$\bar{x}$	88.2	87.5	85.8	83.7	82.4	84.05
S.E.M.	9.18	8.90	8.88	8.70	7.48	7.53

ventilated patients with head injuries, unless the patient has been straining against the ventilator, in which case ICP decreases after the administration of pancuronium. The latter is an example of a secondary effect of muscle relaxants on ICP caused by a reduction in muscle tone, mainly in the abdominal muscles, and CVP. Studies in man showed that tubocurarine had no effect on ICP provided that $PaCO_2$ was not allowed to increase (Sondergard, 1961). However, in 20 patients with normal ICP, Tarkkanen and co-workers (1974) showed increases in ICP of 8.1 (S.D. 6.8) mm Hg with doses of 0.6 (S.D. 0.1) mg/Kg of tubocurarine, which they attributed partly to histamine release causing cerebral vasodilatation. Tubocurarine is known to cause histamine release and, in patients with intracranial tumours, histamine has been shown to cause a rapid increase in internal carotid blood flow of about 60%, lasting for approximately 1 minute (Tindall and Greenfield, 1973). Histamine also increases lumbar CSF pressure in patients suffering from headaches (Engel, 1970). Tarkkanen and colleagues allowed the patients to breathe spontaneously for 1 to 2 minutes after the administration of tubocurarine and the $PaCO_2$ increased by 0.6 (S.D. 0.5) KPa, which was sufficient to account for an increase in ICP of about 20%. The patients were either sedated or only very lightly anaesthetised, and some of the increase in ICP could have been due to an arousal effect as $PaCO_2$ increased and respiration became more difficult. An incremental dose of tubocurarine of 0.2 ± 0.1 mg/Kg administered during respirator-assisted respiration caused smaller increases in ICP.

None of the muscle relaxants have been shown to affect CBF (Alexander et al., 1964; Wollman et al.,1964, 1965; Gauch et al.,

1973), but the former group provided no results to support their statement.

In the author's investigations there were significant reductions in ICP when d-tubocurarine 45 mg was given before an induction dose of thiopentone or Althesin. However, several different events were occurring at the same time. More than one drug was given, there was a change from spontaneous respiration to controlled ventilation and $PaCO_2$ may have been changing. So any change in ICP cannot be solely attributed to tubocurarine, but if it did cause a marked increase in ICP one would have have expected to see evidence of it in these results. The maximum increase in ICP seen in this investigation was small (6 mm Hg). CPP was considerably reduced and was less than 50 mm Hg in 11 patients at some time during the first 2 minutes after the administration of tubocurarine. This pressure is at the lower limit of the autoregulation range (Olesen, 1973), so there is a danger of producing cerebral ischaemia.

In the second investigation these variables were eliminated by administering the tubocurarine to patients who were already anaesthetised, paralysed with tubocurarine and mechanically ventilated. Tubocurarine 15 to 20 mg caused a small reduction in ICP which was statistically significant at 4 and 5 minutes. This smaller dose did not affect MAP or CPP, thus it might be safer to give this agent in smaller incremental doses as suggested by Savarese (1975). The small decrease in ICP is probably due to increased muscle relaxation and a reduction in CVP, and not to a direct effect on the cerebral vasculature.

The fact that suxamethonium does not influence CBF supports

the view that the increase in CSF pressure associated with its administration is due to the muscle fasciculations causing an increase in intra-abdominal, intrathoracic and central venous pressures. This view is also supported by the author's investigations in 5 patients. These patients were receiving a standard relaxant anaesthetic with tubocurarine and nitrous oxide in oxygen supplemented with fentanyl. When ICP had returned to normal after a previous study, suxamethonium 1.5 mg/Kg was administered intravenously. The maximum changes in ICP in the first 5 mins. after the administration of suxamethonium were minimal (mean = 1.4 mm Hg, range = 1 to 2.5 mm Hg). Thus even if there is a direct effect of suxamethonium on the cerebral vessels, which might be expected because of its structural resemblance to acetyl choline, it is very small, and if muscle fasciculations are abolished, any effect of suxamethonium on ICP should be clinically insignificant.

In conclusion, the results reported here indicate that tubocurarine has no direct effect on the cerebral circulation and ICP. The marked reduction in CPP, which it causes when given in large doses with intravenous anaesthetic agents at the induction of anaesthesia is a major disadvantage in some patients, but it may help to avoid excessive arterial pressure increases during laryngoscopy and intubation, which in turn may reduce increases in ICP and the formation and propagation of cerebral oedema. In smaller doses it can be used safely during anaesthesia for intracranial operations, where it has the advantages of a long duration of action, and of causing some reduction in blood pressure, which helps in arterial pressure control. It can, however, cause bronchoconstriction (Weiss et al., 1974), and is best avoided in patients who are prone to bronchospasm.

SUMMARY

Thirty patients who were about to undergo craniotomy were studied. All were anaesthetised with thiopentone or Althesin preceded by d-tubocurarine 4.5 mg and hyperventilated moderately with 70% nitrous oxide in oxygen. In 20 patients ICP and MAP were measured during induction of anaesthesia. In these patients there were significant reductions from the control values in average ICP ($0.05 > P > 0.02$), MAP ($P < 0.001$) and CPP ($P < 0.001$) in the 2 mins between induction of anaesthesia and intubation. In the other 10 patients, once intubation had been performed and anaesthesia was established with 70% nitrous oxide supplemented with fentanyl, an incremental dose of d-tubocurarine 15 to 20 mg was administered. Ventilation was controlled to maintain a constant mean $PaCO_2$ of 4.76KPa (range 3.7 to 6.7 KPa). Tubocurarine 15 to 20 mg caused a reduction in ICP from the control value which was statistically significant ($0.05 > P > 0.02$) at 4 and 5 minutes after its administration, and small reductions in MAP and CPP which were not statistically significant. These results indicate that d-tubocurarine has no direct effect on ICP. The literature about the effects of muscle relaxants on ICP and CBF is reviewed.

CHAPTER 7

THE EFFECTS OF FENTANYL ON ICP AND CPP DURING HYPOCAPNIA

INTRODUCTION

The narcotic analgesics do not have any significant effect on CBF or ICP provided that the $PaCO_2$ does not increase following their administration (see below). Fentanyl and droperidol in combination have been shown to not alter or decrease slightly the ICP during controlled ventilation (Fitch et al., 1969a), and to have no effect on CBF (Sari et al., 1972b). Because fentanyl is short-acting, it has been widely used, sometimes with droperidol, to supplement nitrous oxide, relaxant anaesthesia for neurosurgery. However, Misfeldt and colleagues (1976) observed a marked increase in ICP when they used droperidol and fentanyl for induction of anaesthesia and, from the results of systematic investigations during controlled ventilation, concluded that these drugs were contra-indicated in neurosurgery unless hypocapnia was established and the arterial pressure was normal or increased. Because this latter report appears to contradict earlier work, this study was conducted on the effect of fentanyl on ICP in neurosurgical patients during controlled ventilation.

METHODS

Ten patients with intracranial lesions presenting for craniotomy were studied. Diazepam 10 mg intramuscularly was administered for premedication, if this was considered necessary. Following the induction of anaesthesia with thiopentone (5 patients) or Althesin (5 patients), which was given until the eyelash reflex was lost, tubocurarine (45 mg) was administered. Anaesthesia was

maintained with 70% nitrous oxide in oxygen. The ventilation was adjusted to maintain the $PaCO_2$ at between 2.7 and 4.0 KPa. ICP was measured from a catheter in a lateral ventricle and arterial pressure was measured from a radial artery cannula. The studies were performed with the patient supine and tilted 10° head-up. When ICP and arterial pressure had remained stable for 5 minutes, fentanyl 0.2 mg was given intravenously. The ICP and arterial pressure recordings were followed for 10 minutes before surgery was continued. End-tidal carbon dioxide concentration was maintained constant by reference to an infra-red carbon dioxide analyser, and arterial blood gas tensions were measured at the beginning and end of the 10-minute period.

The following measurements were obtained from the chart recordings:

1) MAP and mean ICP in the 5 minutes before administration of fentanyl (termed control MAP and control ICP);
2) MAP and mean ICP at 1 minute intervals for the first 10 minutes after the administration of the fentanyl;
3) CPP at 1-minute intervals for 10 minutes after the administration of the fentanyl.

RESULTS

For brevity, the measurements in the tables are at 2-minute intervals, as there was no additional information in the values at 1 minute intervals.

The ages of the patients, their intracranial pathology,

and the effects of fentanyl on mean ICP are presented in Table 16. The average ICP for the group decreased initially from the control value after the administration of fentanyl. ICP decreased in most patients but increased in 3 patients, and in one patient ICP decreased initially but increased after the head was turned. The ICP changes after the administration of fentanyl ranged from -5 to 6 mm Hg. The maximum increase in ICP recorded was 6 mm Hg, and in 3 of the 4 patients showing an increase in ICP after fentanyl, the ICP did not reach the pre-induction level; the fourth patient had no pre-induction measurement for comparison. The changes in ICP from the control level were not statistically significant for the group.

In all the patients MAP decreased after the administration of fentanyl (Table 17), and was less than 60 mm Hg in 2 patients (55 and 53 mm Hg). These decreases in MAP were statistically significant from 2 minutes after the administration of fentanyl until the end of the period of measurement ($0.01 > P > 0.001$). CPP was less than 60 mm Hg in 4 patients (39, 55, 43 and 51 mm Hg), but less than 40 mm Hg in only 1 patient (Table 18), and this for less than 1 minute. The changes in CPP from control were statistically significant at 1 minute after the administration of fentanyl ($0.02 > P > 0.01$), but from 2 minutes onwards were of greater significance ($0.01 > P > 0.001$).

Table 19 shows the $PaCO_2$ measurements obtained at the time of the injection of fentanyl and 10 minutes after the injection. These values showed little change during the period of measurement. Although most of the $PaCO_2$ values were between 2.7 and 4.0 KPa (the range aimed for), one was 5.5 KPa and another 2.5 KPa. In each

TABLE 16

Diagnosis and mean ICP values (mm Hg) before (control) and after the administration of fentanyl 0.2 mg.

Patient (age, yr)	Diagnosis	Control (value before induction if known)	Time after fentanyl (min)				
			2	4	6	8	10
A (42)	Pituitary tumour	12	10	8	7	8	7
B (71)	Meningioma	15 (10)	13	10	14	10	10
C (59)	Meningioma	10 (13)	8	9*	11	11	12
D (59)	Glioblastoma	10 (23)	11	10	16	15	15
E (47)	Aneurysm	20 (17)	-	-	19	20	19
F (59)	Meningioma	9 (17)	8	9	10	10	11
G (33)	Aneurysm	11 (15)	10	9	9	8	8
H (62)	Glioblastoma	16	16	19	19	19	19
I (50)	Acoustic neuroma	9	9	9	9	8	8
J (64)	Spontaneous intracerebral haemorrhage	9	8	8	8	8	8
Mean		12.1	10.3	10.1	12.2	11.7	11.7
S.E.M.		1.2	0.9	1.1	1.4	1.5	1.4

* Head turned at this time.

TABLE 17

Mean arterial pressure (mm Hg) before (control) and after the administration of fentanyl 0.2 mg.

Patient	Control	Time after fentanyl (min.)				
		2	4	6	8	10
A	113	93	83	70	70	75
B	105	98	98	-	83	85
C	127	102	88	82	80	82
D	73	55	65	55	58	65
E	113	115	105	105	98	98
F	100	80	70	65	72	75
G	63	53	60	57	63	63
H	83	72	70	70	70	70
I	115	95	85	80	90	95
J	107	97	92	90	90	88
Mean	99.9	86.0	81.6	74.9	77.4	79.6
S.E.M.	6.5	6.5	4.7	5.4	4.1	3.8

TABLE 18

Cerebral perfusion pressure (mm Hg) before (control) and after the administration of fentanyl 0.2 mg.

Patient	Control	Time after fentanyl (min.)				
		2	4	6	8	10
A	101	83	75	63	62	68
B	90	85	88	-	73	75
C	120	94	79	71	69	70
D	63	44	55	39	43	50
E	93	-	-	86	78	79
F	91	72	61	55	62	64
G	52	43	51	48	55	55
H	67	56	51	51	51	51
I	106	86	76	71	82	87
J	98	89	84	82	82	80
Mean	88.1	72.4	68.9	62.9	65.7	67.9
S.E.M.	6.7	6.6	4.8	5.3	4.2	4.1

TABLE 19

$Paco_2$ values at the time of injection of fentanyl 0.2 mg and 10 min. after injection

Patient	Initial $Paco_2$ (kPa)	Final $Paco_2$ (kPa)
A	2.7	2.8
B	3.7	3.7
C	2.9	2.9
D	3.3	2.9
E	4.0	4.0
F	5.2	5.5
G	2.8	2.8
H	3.2	3.2
I	3.1	3.1
J	2.5	2.5

patient the end-tidal carbon dioxide concentration remained constant during the period of the study.

DISCUSSION

The narcotic analgesics have little effect on CBF and ICP provided that respiration is not depressed and the $PaCO_2$ does not increase. Thus if $PaCO_2$ remains constant morphine has no effect on CBF (McCall and Taylor, 1952a; Moyer et al., 1957; Jobes et al., 1977) or ICP (Keats and Mithoefer, 1955; Stullken and Sokoll,1975a), but if the $PaCO_2$ rises ICP increases (Gurdjian et al., 1939; Keats and Mithoefer, 1955). At constant $PaCO_2$ pentazocine produces small decreases in ICP in patients undergoing intracranial surgery, but when given to spontaneously breathing patients with 'brain damage' the ICP and $PaCO_2$ increase (Barker et al., 1972). When phenoperidine is given in combination with droperidol at constant $PaCO_2$, changes in CSF pressure are small and can be in either direction (Barker et al., 1968; Fitch et al., 1969a), and there is no effect on CBF (Barker et al., 1968; Wilkinson and Browne, 1970). The narcotic antagonist nalorphine causes CSF pressure to increase if given to patients who have not previously received a narcotic analgesic (Keats and Mithoefer, 1955), and levallorphan reduces CSF pressure when given to dogs which are under the influence of morphine (Weitzner et al., 1963).

Droperidol is often administered in combination with a narcotic analgesic to supplement nitrous oxide relaxant anaesthesia. When given on its own droperidol reduces CBF in dogs (Michenfelder

and Theye, 1971). In man, Misfeldt and colleagues (1976) demonstrated a small but not significant increase in ICP following the administration of droperidol, R.Miller and coworkers (1975) found that a similar dose of droperidol had no effect on lumbar CSF pressure and Cunitz and Gaab (1980) showed a significant reduction in ICP with a larger dose. On balance, it appears that droperidol has very little effect on ICP.

Morphine 0.6 mg/Kg decreases $CMRO_2$ in dogs (Takeshita et al., 1972a), but in man the reports are conflicting. Moyer and colleagues (1957) found that morphine 60 mg intravenously caused a significant reduction in $CMRO_2$, but Jobes et al. (1977) found that a dose of 1 to 3 mg/Kg had no effect on cerebral metabolism when given during nitrous oxide anaesthesia. Pethidine reduces $CMRO_2$ in dogs which are lightly anaesthetised with halothane (Messick and Theye, 1969). When fentanyl is given to dogs anaesthetised with nitrous oxide in oxygen it causes a reduction in $CMRO_2$ (Michenfelder and Theye, 1971), but when it is given in combination with droperidol $CMRO_2$ is either slightly reduced (Michenfelder and Theye, 1971), or not affected (Miller and Barker, 1969). Droperidol alone has no effect on $CMRO_2$ in dogs (Michenfelder and Theye, 1971). In man $CMRO_2$ is unaffected by fentanyl combined with droperidol (Sari et al., 1972b).

In dogs anaesthetised with nitrous oxide in oxygen fentanyl 0.006 mg/Kg caused a reduction in CBF of 47% (Michenfelder and Theye, 1971), but in man Sari and colleagues (1972b) found that CBF was unaffected by fentanyl and droperidol in combination. Fitch and coworkers (1969a) reported that, in patients with space-occupying lesions ventilated with nitrous oxide and oxygen at normocapnia, the intravenous administration of droperidol 5 mg together with fentanyl

0.1 mg led to small decreases in ICP in 8 out of 9 patients. Adams and colleagues (1972), however, found that droperidol and fentanyl had no effect on ICP. The effect of these drugs on ICP was also assessed by Misfeldt and coworkers (1976), who reported that fentanyl 0.2 to 0.3 mg given after droperidol 7.5 to 12.5 mg intravenously resulted in increases in ICP in 5 patients and decreases in 3. These latter authors concluded that they could not explain the difference between their results and those of Fitch and colleagues. However, the disagreements appear to be small because, of the 5 patients with increases in ICP reported by Misfeldt and coworkers, 3 had very small increases (1, 2 and 3 mm Hg). In the other 2 patients the increases were greater (8 and 9 mm Hg), but the methodology employed by these workers would bias the results towards the finding of increases in ICP, because they measured the highest ICP achieved at an undefined time more than 10 minutes after the administration of the drugs. Patients with space-occupying pathology show 'spontaneous' variations in ICP, so that in any group of such patients a method which selects the highest ICP value reached will include increases in ICP which are not a result of the previous drug administration, and the effect will increase the longer the period of observation after the administration of the drug. In the study of Misfeldt and colleagues, the 2 patients with the greatest increases in ICP following the injection of fentanyl had plateau waves recorded before the induction of anaesthesia, which indicates that ICP in these patients was unstable before the administration of fentanyl.

The changes in ICP caused by supplementation of nitrous oxide/oxygen anaesthesia with neuroleptanalgesic drugs are very small in comparison with the large and consistent increases in ICP associated

with the administration of some volatile anaesthetics to normocapnic patients (Jennett et al., 1969; Adams et al., 1972). However, the changes in ICP associated with the administration of enflurane, during both normocapnia and hypocapnia, are very similar to those seen with fentanyl (see Chapter 8).

Most neurosurgical operations are conducted during hypocapnia, and the present study extends the information available in the literature about neuroleptanalgesic drugs by reporting measurements made at hypocapnia. Furthermore, since fentanyl is a short-acting drug with a plasma half-life of 2 minutes (Schleimer et al., 1978), the measurements were made during the first 10 minutes after drug administration, at a time when the maximum effect of the drug is seen clinically. This increased the likelihood that the changes observed were causally related to the drug administered. During hypocapnia fentanyl 0.2 mg caused small changes in ICP which could be in either direction. The mean ICP decreased for 4 minutes after the administration of fentanyl, but this fall was not statistically significant.

The present results on the effect of fentanyl on MAP and CPP are in complete agreement with those of other authors (Misfeldt et al., 1976; Cunitz and Gaab, 1980), and emphasize the point made by the former authors, that fentanyl should not be given to patients who are hypotensive already, otherwise low CPP may result. In the author's study values of CPP of less than 50 mm Hg were observed in 2 patients, both of whom were moderately hypotensive when the drug was given (MAP = 73 and 63 mm Hg).

The author's finding of a variable response of ICP following the administration of fentanyl is supported by the work of Vernhiet

and colleagues (1977). This showed that fentanyl caused no significant change in CBF, but that the individual response was very variable. The variations in CBF correlated perfectly with individual variations in $CMRO_2$. Fentanyl produces no obvious regional modification of CBF (De Rood et al., 1974; Vernhiet et al., 1977). Fentathienyl, a new agent with a structure similar to fentanyl, causes no significant changes in CBF and $CMRO_2$ and, when compared with fentanyl, shows less variability of response between patients (Vernhiet et al., 1977), and may prove to have a more predictable effect on ICP.

It must be emphasised that this discussion of the effect of neuroleptanalgesic drugs on ICP and CBF refers to the administration of the drugs to patients whose ventilation is controlled. In spontaneously breathing patients fentanyl 0.1 mg and droperidol 5 mg may cause an increase in lumbar CSF pressure because of an increase in $PaCO_2$ (Miller, R., et al., 1975).

The results of the investigation described here allow the following conclusions to be made. In hypocapnic patients with intra-cranial space-occupying lesions, changes in ICP following the administration of fentanyl are small and may be in either direction. Fentanyl causes decreases in MAP and CPP, but unless the patient is already hypotensive the changes are small. The establishment of hypocapnia before the administration of fentanyl does not provide complete protection against a fall in CPP to less than 50 mm Hg if the patient is already hypotensive (see patients D and G). In the author's view fentanyl is a valuable adjunct to nitrous oxide/oxygen relaxant anaesthesia in patients with intracranial space-occupying lesions, provided that it is not used in patients who are hypotensive. Its effect on ICP in hypocapnic patients is small and, both clinically and statistically insignificant.

SUMMARY

Ten patients who were about to undergo craniotomy were studied. Each was anaesthetised with thiopentone or Althesin followed by tubocurarine, and the lungs were hyperventilated with nitrous oxide in oxygen. Fentanyl 0.2 mg was administered intravenously and ICP and MAP were recorded continuously for 10 minutes. At the time of administration of fentanyl 9 out of the 10 patients were hypocapnic ($PaCO_2$ less than 4 KPa). The changes in ICP were small and could be in either direction. Cerebral perfusion pressures of less than 50 mm Hg were observed in 2 patients, who had moderate hypotension before the drug was given. Thus fentanyl is a valuable supplement to nitrous oxide/oxygen relaxant anaesthesia with hyperventilation in patients with intracranial space-occupying lesions, provided that hypotension is absent. The literature concerning the effects of narcotic analgesics and neuroleptanalgesic agents on ICP and CBF is reviewed.

C H A P T E R 8

THE EFFECTS OF 2% ENFLURANE ON ICP AND CPP

INTRODUCTION

Enflurane is a volatile anaesthetic agent which has been introduced into anaesthetic practice in Britain fairly recently. The literature regarding its effect on ICP and CBF is conflicting. In dogs the administration of enflurane produces cerebral metabolic depression, cerebral vasodilatation and an increase in ICP which is less than that caused by the administration of halothane (see below). In man, however, most workers have found that the administration of enflurane has very little effect on ICP and CBF provided that the $PaCO_2$ remains constant, but some investigations have shown substantial increases in ICP in some patients (see below). Enflurane causes a substantial reduction in arterial pressure and thus reduces CPP. This investigation was performed in order to determine the effect of enflurane on ICP and CPP in patients with cerebral tumours.

METHODS

Ten patients with cerebral tumours were studied. All were about to undergo intracranial surgery. Informed consent was obtained for all the investigations. If considered necessary, the patients were premedicated with diazepam 10 mg orally. Anaesthesia was induced with thiopentone and maintained with nitrous oxide 70% in oxygen supplemented with fentanyl to a maximum dose of 0.2 mg. Muscle relaxation was achieved with d-tubocurarine 45 mg and ventilation was controlled so as to maintain a $PaCO_2$ as near as possible to the normal range. ICP was measured from a ventricular

catheter in 9 patients and a subarachnoid bolt in 1 patient (patient J) because the lateral ventricles were compressed. Arterial pressure was measured from a radial artery cannula. During the investigation the patients were supine with a 10^{o} head-up tilt except for 1 patient who was studied in the prone position (patient B). Once stable, ICP and arterial pressure were recorded for 5 minutes (control readings), 2% enflurane was then administered (from an enfluratec vaporizer) in 70% nitrous oxide in oxygen for 15 minutes (if CPP was reduced to a level which was considered unacceptable the enflurane was stopped after less than 15 minutes).

After 15 minutes the enflurane was stopped, and ICP and arterial pressure were recorded for a further 10 minutes. At the end of the study, pressure/volume testing was performed by measuring the ICP response to 1 ml injections of saline into the lateral ventricle to a maximum of 3 injections, or until ICP exceeded 20 mm Hg, whichever was the first. Arterial blood samples were taken for measurement of blood gas tensions just before the enflurane was started, and at the time when the administration of enflurane was stopped. During the period of measurement the end-tidal carbon dioxide concentration was continuously displayed on an infra-red carbon dioxide analyser. Arterial blood samples were taken for measurement of enflurane concentration (using a gas chromatograph) at 5, 10 and 15 minutes after the start of the administration of enflurane.

RESULTS

There was no significant change in ICP during the administration of 2% enflurane (Table 20). The ICP changes ranged from -18.5 to 5.5 mm Hg. MAP and CPP were reduced by the administration of 2% enflurane (Tables 21 and 22). These changes were stastically significant ($P < 0.001$). Neither MAP nor CPP were significantly different from control 10 minutes after the administration of enflurane was stopped. CPP was reduced to less than 40 mm Hg in 3 patients and in another 3 patients the administration of enflurane was prematurely stopped because CPP was approaching this value.

$PaCO_2$ values were the same before and at the end of the enflurane administration, but although the mean $PaCO_2$ was in the hypocapnic range there was a considerable scatter of $PaCO_2$ values from 3.7 to 6.7 KPa (Table 23). Of the 7 patients with normal initial ICP values, 2 had an increased pressure/volume response (2 mm Hg or more (Miller and Leech, 1975)), and the test was not performed on 2 (Table 23). One of the latter patients had an excessive increase in ICP when the $PaCO_2$ was increased into the normocapnic range, and was therefore studied during hypocapnia.

The blood enflurane concentrations are shown in Table 24; they were not measured in patient A.

TABLE 20

ICP values (mm Hg) before (control), during and after the administration of 2% enflurane

Patient	Control	During enflurane administration			After enflurane stopped	
		5 min	10 min	15 min	5 min	10 min
A	2	2	2	2	2	2
B	18	19	20	19.5	21	21.5
C	58.5	43.5	40	40	48	50
D	10	10.5	9.5	9.5	9.5	9.5
E	7.5	7.5	8	9.5	8.5	6.5
F	4.5	5	5	-	5.5	5
G	7.5	8	8.5	-	6.5	5.5
H	8.5	11.5	12.5	-	11	10
I	-1	0	0	0	0.5	0.5
J	22.5	20.5	19	-	18	18.5
n	10	10	10	6	10	10
$\bar{x}$	13.8	12.8	12.5	13.4	13.4	12.9
S.E.M.	5.44	4.00	3.69	6.01	4.38	4.64

TABLE 21

MAP values (mm Hg) before (control), during and after the administration of 2% enflurane. (Significance values are for comparison with the control values.)

Patient	Control	During enflurane administration			After enflurane stopped	
		5 min	10 min	15 min	5 min	10 min
A	115	97	87	53	67	102
B	102	92	87	90	97	100
C	100	80	70	75	85	85
D	98	70	63	57	55	63
E	91	62	43	48	55	67
F	78	62	50	-	55	55
G	77	67	60	-	82	100
H	93	73	63	-	95	108
I	85	63	53	50	52	62
J	83	60	50	-	62	73
n	10	10	10	6	10	10
$\bar{x}$	92.2	72.6	62.6	62.2	70.5	81.5
S.E.M	3.78	4.14	4.77	6.83	5.57	6.26
P		<0.001	<0.001	0.01>P >0.001	0.01>P >0.001	

TABLE 22

CPP values (mm Hg) before (control), during and after the administration of 2% enflurane. (Significance values are for comparison with the control values.)

Patient	Control	During enflurane administration			After enflurane stopped	
		5 min	10 min	15 min	5 min	10 min
A	113	95	85	51	65	100
B	84	73	67	70.5	76	78.5
C	41.5	36.5	30	35	37	35
D	88	59.5	53.5	47.5	45.5	53.5
E	83.5	54.5	35	38.5	46.5	60.5
F	73.5	57	45	-	49.5	50
G	69.5	59	51.5	-	75.5	91.5
H	84.5	61.5	50.5	-	81	98
I	86	63	53	50	51.5	61.5
J	60.5	39.5	31	-	44	54.5
n	10	10	10	6	10	10
$\bar{x}$	78.4	59.9	50.2	48.8	57.15	68.6
S.E.M.	5.99	5.19	5.33	5.08	4.99	7.18
P		<0.001	<0.001	0.02>P >0.01	0.01>P >0.001	

TABLE 23

$Paco_2$ values (kPa) immediately before and at the end of the administration of enflurane, and the response of ICP (mm Hg) to intraventricular injection of 1 ml saline.

Patient	$Paco_2$ before enflurane	$Paco_2$ when enflurane stopped	ICP response to saline injection
A	3.7	3.7	1
B	5.8	5.7	2.5
C	6.3	6.7	5
D	5.3	5.4	1
E	4.3	4.2	2
F	5.2	5.4	2
G	3.9	3.6	-
H	4.5	4.9	-
I	4.5	4.7	0
J	4.7	4.2	-
n	10	10	
$\bar{x}$	4.8	4.8	
S.E.M.	0.26	0.31	

TABLE 24

Blood enflurane concentrations (mg %) at 5, 10 and 15 minutes after the commencement of the administration of 2% enflurane.

Patient	5 min.	10 min.	15 min.
A	-	-	-
B	4.5	7.4	6.6
C	3.5	7.4	8.5
D	10.6	10.1	8.9
E	8.3	6.0	7.9
F	11.8	9.6	-
G	5.9	7.5	-
H	12.6	8.2	-
I	8.4	8.0	8.8
J	6.9	7.6	-

DISCUSSION

All the volatile anaesthetic agents which have been investigated have been shown to increase CBF and ICP and decrease $CMRO_2$. In man CBF is increased by diethyl ether in certain concentrations (Smith and Wollman, 1972), and halothane (Wollman et al., 1964; Christensen et al., 1967; De Rood et al., 1974). In dogs CBF is increased by chloroform (McDowall and Harper, 1965), trichloroethylene (McDowall, 1966b), and isoflurane (Cucchiara et al., 1974). Methoxyflurane increases CBF according to Michenfelder and Theye (1973) but other authors found a decrease in CBF with methoxyflurane (McDowall and Harper, 1965; Gray et al., 1971b). McDowall and Harper (1965), who measured CBF at 30 minutes after the commencement of methoxyflurane administration, may have missed an early increase, and the results of Gray and colleagues (1971b) may be explained by the fall in CBF which occurs with time in the anaesthetised dog (Raichle et al., 1970). Thus it is most likely that methoxyflurane causes an increase in CBF because otherwise it would be difficult to explain its effect on ICP. In man $CMRO_2$ is decreased by diethyl ether (Smith and Wollman, 1972) and halothane (Wollman et al., 1964; McHenry et al.,1965; Christensen et al.,,1967). In dogs $CMRO_2$ is reduced by trichloroethylene (McDowall et al.,1964), methoxyflurane (Michenfelder and Theye,1973), and isoflurane (Cucchiara et al.,1974).

In man ICP is increased by diethyl ether (Lundberg, 1959; Sondergard, 1961), trichloroethylene (Jennett et al., 1969), methoxyflurane (Fitch et al., 1969b; Jennett et al., 1969), halothane (Sondergard, 1961; Marx et al., 1962; Jennett et al., 1969; Gordon, 1970; Adams et al.,1972; Zattoni and Siani,1972; Stullken and Sokoll, 1975a), isoflurane (Adams et al., 1981) and fluroxene (Jorgensen and

Henriksen, 1973). Chloroform increases ICP in cats (Finesinger and Cobb, 1935). The changes in ICP during the administration of volatile agents are generally greater in patients with initially increased ICP than in patients with normal ICP (Fitch et al.,1969b; Jennett et al.,1969; Gordon, 1970; Richardson et al., 1970; Shapiro et al., 1972c; Zattoni and Siani, 1972). Most volatile anaesthetic agents also reduce CPP because they both increase ICP and reduce MAP.

The anaesthetic gas cyclopropane has a biphasic effect on CBF; 5 and 13% cyclopropane decrease CBF, 20 and 37% increase it (Alexander et al., 1968a). This is probably due to changes in plasma catecholamine levels during cyclopropane administration (Michenfelder and Theye, 1972). Cyclopropane increases ICP (Sondergard, 1961), and in certain concentrations (5, 13 and 37%) it reduces $CMRO_2$ (Alexander et al., 1968a,1970).

Previous investigations into the effect on ICP of enflurane have given conflicting results. In dogs 3% enflurane caused increases in ICP which were greater when ICP was increased experimentally (Boop and Knight, 1978). These increases were less than those caused by equipotent concentrations of halothane (Hans et al., 1980). However, in two-thirds of a group of dogs with cerebral oedema, enflurane caused a reduction of ICP because of its hypotensive effect in the presence of defective autoregulation, which caused a reduction in hydrostatic pressure in the dilated cerebral vascular bed (Hans et al., 1980; Stevenaert et al., 1980). In rats Mann et al. (1980) showed an increase in CSF formation rate and an increased resistance to CSF reabsorption during enflurane anaesthesia, when compared with pentobarbitone anaesthesia. In man, Zattoni et al. (1974) reported that 1 to 2% enflurane caused increases in ICP of up

to 9 to 15 mm Hg in patients with intracranial lesions presenting with high ICP. These increases were not always abolished by hypocapnia, and were frequently negligible if ICP was near normal. Ewalenko-de-Toeuf (1980) showed similar increases in ICP with 2% enflurane in some neurosurgical patients, but in most patients there was no change in ICP. Cunitz et al. (1976) found that ICP was increased to a lesser extent by enflurane than by halothane at normocapnia in neurosurgical patients, but Stullken and Sokoll (1975) found that these two agents caused similar increases in ICP. In hypocapnic head-injured patients 1.5% enflurane caused a mean increase in ICP of 9.6 mm Hg (Schulte am Esche et al., 1979). Induction of anaesthesia with 3% enflurane in patients with intracranial lesions, not surprisingly, caused an increase in ICP (Tambuniello et al., 1978). With 1% enflurane, McLeskey and colleagues (1974) found a negligible change in ICP, as the author did with 2% enflurane.

Enflurane caused an increase in CBF in two investigations in dogs (Michenfelder and Cucchiara, 1974; Takasaki, 1974), but in another there was no significant change (Sakabe, 1975), possibly because of the reduction in arterial pressure associated with the administration of enflurane. Also in dogs, it caused a decrease in $CMRO_2$ which was proportional to the enflurane concentration (Michenfelder and Cucchiara, 1974; Takasaki et al., 1974; Sakabe, 1975). In patients with subacute or chronic ischaemic brain lesions 1% enflurane caused a reduction in CBF (Reinhold et al., 1974, /1976), and in patients with head injury, in whom the MAP was maintained with phenylephrine, 1% enflurane had no effect on CBF or the distribution of rCBF (De Rood et al., 1980a, 1980b). In normal

patients 2% enflurane has no effect on CBF (Van Aken et al., 1977; Rolly and Van Aken,1979). $CMRO_2$ is reduced by about 28% during the administration of 1% enflurane in man (De Rood et al., 1980a). Thus in man enflurane appears to have little effect on CBF but reduces $CMRO_2$.

In this investigation 2% enflurane caused no significant change in ICP in patients with cerebral tumours, 60% of whom had significant intracranial compression. MAP was significantly reduced causing CPP to be reduced to less than 50 mm Hg, which is at the lower end of the range of autoregulation (Olesen, 1973), in 5 patients, and to values approaching this in another 4 patients before the enflurane was stopped. This confirms the results of other workers who found that enflurane reduced CPP (Zattoni et al., 1974; Cunitz et al., 1976; Schulte am Esch et al., 1979). The change in ICP during the administration of enflurane ranged from -18.5 to 5.5mm Hg, and the patient who showed the greatest increase in ICP had an increase in $PaCO_2$ of 0.4 KPa during the period of administration of enflurane. Although it was intended to study the patients at normocapnia, in 3 patients the $PaCO_2$ differed widely from the normocapnic range. From the results obtained in these patients, there was no evidence that alteration in $PaCO_2$ influenced the response of ICP to enflurane. The blood enflurane concentrations tended to plateau by the 10 minute epoch, thus the maximum effect on ICP of enflurane should be seen within 10 minutes of its administration, and the maximum ICP response should have been evident even when the administration of enflurane was stopped prematurely.

From the literature there is a consensus that

halothane causes the greatest increase in ICP of all the volatile agents. The majority of investigations show that enflurane has less effect on CBF and ICP than does halothane. Although enflurane causes significant increases in CBF and ICP in dogs, the majority of studies in man indicate that it has little effect on CBF and ICP. Increases in ICP of up to 15 mm Hg have been reported, but usually the increases are small or non-existent. The largest reported increases in ICP with enflurane are less than those reported with halothane. This study in patients with cerebral tumours, many of whom had reduced compliance of the intracranial contents, confirmed that changes in ICP were small and could be in either direction. The magnitude of these changes was similar to that observed with fentanyl 0.2 mg (see Chapter 7). There was a considerable reduction in CPP, but the concentration of enflurane was greater than that which would normally be used to supplement nitrous oxide-relaxant anaesthesia in the clinical situation. Enflurane may cause a small degree of cerebral vasodilatation (McKay et al., 1976) and the reduction in MAP may help to prevent the consequent increase in CBF and ICP with enflurane, although the work of De Rood and colleagues (1980b), in which CBF was unchanged when the arterial pressure was kept constant during enflurane administration, would appear to contradict this hypothesis.

With enflurane concentrations of greater than 2.5% high amplitude spikes and/or spike and wave complexes may appear on the EEG, and their occurrence is increased by increasing the inspired concentration of enflurane, by a reduction in $PaCO_2$, and by noise (de Jong and Heavner, 1971; Neigh et al., 1971; Michenfelder and Cucchiara, 1974). However, enflurane does not appear to exacerbate

a pre-existing susceptibility to seizure activity (Opitz and Oberwetter, 1979), so this property of the drug does not contra-indicate its use in neuroanaesthesia.

Thus, low concentrations of enflurane can safely be used during anaesthesia for intracranial operations provided that the arterial pressure is carefully monitored. Its effects on MAP could be useful in the control of arterial pressure and the induction of hypotension during neurosurgery.

SUMMARY

Ten patients with cerebral tumours were anaesthetised with thiopentone, nitrous oxide 70% in oxygen, d-tubocurarine and fentanyl. Ventilation was controlled to give a mean $PaCO_2$ of 4.8 (range 3.6 to 6.7) KPa). 2% enflurane was administered and ICP and MAP were recorded continuously for 10 to 15 minutes. The changes in ICP were not significant and ranged from -18.5 to 5 mm Hg. There were significant reductions in MAP ($P < 0.001$) and CPP ($P < 0.001$) during the administration of enflurane. In 4 patients the administration of enflurane had to be prematurely terminated because of a low CPP. Thus enflurane has very little effect on ICP in patients with cerebral tumours and low concentrations of enflurane can safely be used during anaesthesia for intracranial operations provided that the arterial pressure is carefully monitored. The literature concerning the effect of volatile anaesthetic agents on ICP and CBF is reviewed.

CHAPTER 9

INVESTIGATIONS ON THE USE OF ANAESTHETIC AGENTS IN THE INTENSIVE CARE OF HEAD INJURIES:

THE EFFECTS OF NITROUS OXIDE, ALTHESIN AND THIOPENTONE ON ICP DURING CHEST PHYSIOTHERAPY IN PATIENTS WITH SEVERE HEAD INJURY

INTRODUCTION

In the preceding chapters investigations on the effects of anaesthetic agents on ICP and CPP in patients about to undergo intracranial surgery are described. The investigations described in this chapter were designed to determine whether anaesthetic agents modify the increases in ICP which occur during chest physiotherapy in patients with severe head injury (Gibson et al., 1975). These increases are thought to be partially due to noxious stimulation and partially due to an increase in intrathoracic pressure as a result of chest compression. When the investigations were begun it was thought that the analgesic property of nitrous oxide might help to reduce these increases in ICP. Thiopentone and Althesin both reduce ICP (see Chapter 5), and would be expected to reduce ICP increases during chest physiotherapy. This chapter describes investigations of the effects of nitrous oxide, Althesin and thiopentone on ICP during chest physiotherapy in patients with head injury, and also the effect of nitrous oxide on ICP in such patients when no noxious stimulus was being applied.

METHODS

The patients had severe head injuries and were being mechanically hyperventilated ($PaCO_2$ 3.3 to 4.0 KPa) under the influence of non-depolarizing muscle relaxants, a supplementary dose of which was given before each investigation. The only sedative drugs which the patients were receiving were papaveretum and/or diazepam, and no patient received these drugs within one hour of an episode of chest physiotherapy. During chest physiotherapy the

lungs were hyperinflated by anaesthetists using a Mapleson C circuit (Mapleson, 1954) (with a fresh gas flow of greater than twice the minute volume of the patient). ICP was recorded from a subdural catheter or device, or an extradural device (Coroneos et al., 1973), using a transducer, amplifier and chart recorder. The maximum increase in mean ICP occurring during the period of chest physiotherapy was read from the chart recordings. Random number tables were used to choose the treatment for each episode of chest physiotherapy.

The initial study was to compare the effects of chest physiotherapy on ICP in the presence of 100% oxygen or 50% nitrous oxide in 50% oxygen (Entonox). This study was stopped when Entonox had been given 12 times to 3 patients, because it was found that Entonox was accentuating the ICP changes produced by chest physiotherapy.

In a second study, the effect of Entonox on ICP in a further 9 patients with severe head injury was investigated when they were not receiving chest physiotherapy. Mechanical ventilation had been established for at least 6 hours, with $PaCO_2$ values between 3.3 and 4.0 KPa, and the inspired oxygen concentration was less than 50%. ICP was recorded at a fast chart speed for 10 minutes before the administration of Entonox, for either 5 minutes (2 administrations) or 10 minutes (4 administrations) during the administration of Entonox (through the oxygen inlet of the Cape ventilator), and for 10 minutes after the discontinuation of the Entonox. During the last 6 Entonox administrations, end-tidal carbon dioxide concentration was measured by mass spectrometry (BOC). Arterial blood gas tensions were measured within 4 hours of the Entonox administration as part of the routine intensive care management.

In the third study 100% oxygen, thiopentone (3 mg/Kg) and 100% oxygen, or Althesin (0.03 ml/Kg) and 100% oxygen were given

in random order to 10 patients for chest physiotherapy. The thiopentone or Althesin was given to the patient over 30 seconds, and 30 seconds later the systolic arterial pressure was measured using a sphygmomanometer. Chest physiotherapy was then performed for 5 minutes. This study was repeated using higher doses of thiopentone (4.5 mg/Kg) and Althesin (0.045 ml/Kg) by the author's colleagues.

RESULTS

Mean ICP before chest physiotherapy was the same in the 100% oxygen group as in the Entonox group. Mean ICP increased by 22.7 mm Hg (S.D. 10.62) when physiotherapy was performed with Entonox compared with 10.5 mm Hg (S.D. 10.41) during physiotherapy using 100% oxygen (Table 25). This difference between the two groups was statistically significant ($0.02 > P > 0.01$). In two patients A-waves (Lundberg, 1960) were precipitated by Entonox and physiotherapy, but this also occurred in one patient when physiotherapy was being carried out with oxygen alone.

When Entonox was administered to patients not undergoing chest physiotherapy there was a mean increase in ICP of 3.8 mm Hg (S.D. 2.4) (range 0 to 8.5 mm Hg) ($P < 0.001$). There was a mean decrease in ICP of 4.6 mm Hg (S.D. 2.8) after the withdrawal of nitrous oxide ($P < 0.001$) (Table 26).

There was a mean fall in end-tidal carbon dioxide concentration of less than 0.1% (range 0 to 0.1%) during the period of nitrous oxide administration.

Mean ICP before chest physiotherapy was the same in the

TABLE 25

Comparison of increases in ICP produced by chest physiotherapy during 100% oxygen and during Entonox administration. Control values are those of mean ICP before physiotherapy

OXYGEN		ENTONOX	
Control mm Hg	Change from control mm Hg	Control mm Hg	Change from control mm Hg
7	+10	19	+16
15	+4.0	15	+4.0
26	+15	16	+4.0
18	+3	7	+6
9	+4	10	+11
13	+4	8	+23
14	+10	10	+23
7	+5	12	+19
13	+9	10	+22
9	+7	13	+33
10	+8	12	+15
		14	+24
n = 11		12	
$\bar{x}$ 12.8	+10.5 *	12.2	+22.7 *
S.D.5.6	10.4	3.5	10.6

* 0.02>P>0.01

TABLE 26

ICP (mm Hg) before, during and after Entonox. The peak values reached during Entonox administration were used in calculating the changes

Patient	Control	Change after N_2O administration	Change after N_2O withdrawal
A	4	+1	-2
	13	+5	-1
	6.5	+4.5	-5
B	13.5	+2	-3.5
C	6	+1	-1
D	16	+2	-4
E	3	+7	-4
	3	+2	-4
	1	+6	-6
F	22	+4	-11
G	1	+6	-6
	6	+5	-8
H	5	0	-0.5
I	25.5	+8.5	-8
	21	+3	-5
	23	+3	-5
n = 16			
$\bar{x}$ =	10.6	$\bar{d}$ = +3.8	$\bar{d}$ = -4.6
S.D.	8.53	2.40	2.83
P		<0.001	<0.001

TABLE 27

Peak change from control of mean intracranial pressure (mm Hg) during chest physiotherapy. (Significance values are for the comparison of the thiopentone and Althesin groups with the control group.)

Patient	OXYGEN ALONE (Control)		THIOPENTONE/OXYGEN (3 mg/Kg)		ALTHESIN/OXYGEN (0.03 ml/Kg)	
	Before physio-therapy	Peak change	Before physio-therapy	Peak change	Before physio-therapy	Peak change
A	25	+7	30	0	20	+9
	19	+8	16	+3	18	+15
B	13.5	+13	12	+10	16.5	+12
	4	+7	2	0	4	+3
C	12	+9	15	+5	11.5	+2
	13	+16	-	-	-	-
D	13.5	+4	7.5	+7	15	+5
	10	+5	9	+7	7.5	+5
E	25	-1	16	+2	21	-3
	16.5	+5.5	15.5	+4	21	0
F	3	+4	5	+2	-1	+1
	3	+9	-1	+5	5	+6
G	16	+5	25	+1	25	+1
	20	+3	17	+1	22	+1
H	2	+5	2	+8	2	+3
	10	+20	16	+2.5	20	+5
I	2	+10	6	+3	4	+5
	0	+9	9	+7	6	+9
J	9	+5	5	+4	5	+2
	6	+9	10	+2	4	0
n	20	20	19	19	19	19
$\bar{x}$	11.6	7.6	11.4	3.9	11.9	4.3
S.E.M.	1.66	1.05	1.81	0.66	1.90	1.03
P				0.01>P >0.001		0.05>P >0.02

TABLE 28

Peak change from control of mean intracranial pressure (mm Hg) during chest physiotherapy

	OXYGEN ALONE (Control)		THIOPENTONE/OXYGEN (4.5 mg/Kg)		ALTHESIN/OXYGEN (0.045 ml/Kg)	
	Before physio-therapy	Peak change	Before physio-therapy	Peak change	Before physio-therapy	Peak change
n	21	21	19	19	18	18
$\bar{x}$	6.38	7.14	7.37	5.97	5.47	4.92
S.E.M.	1.06	0.93	1.10	0.71	1.27	0.55

oxygen alone, the thiopentone and oxygen, and the Althesin and oxygen groups. Mean ICP increased by 3.9 mm Hg (S.D. 2.86), when physiotherapy was performed with thiopentone, by 4.3 mm Hg (S.D. 4.47) with Althesin, and by 7.6 mm Hg (S.D. 4.70) with oxygen alone (Table 27). The change in ICP during chest physiotherapy was significantly less with thiopentone and oxygen ($0.01 > P > 0.001$) and with Althesin and oxygen ($0.05 > P > 0.02$) than with oxygen alone. The scatter diagram (Fig.2) shows that there is considerable variability in the ICP response to physiotherapy in all three groups. The systolic arterial pressure 30 seconds after the administration of thiopentone or Althesin was 110 mm Hg or more in all except one patient, in whom the pressure was 100 mm Hg on 2 occasions following the administration of Althesin.

A subsequent study, in which higher doses of thiopentone (4.5 mg/Kg) and Althesin (0.045 ml/Kg) were used but which followed the same protocol in all other respects, showed no significant differences between the test groups and the control group (Table 28). The full results of the latter study are not included because the author was not directly involved in this investigation.

DISCUSSION

Reports on the effect of nitrous oxide on ICP are contradictory. Increases in ICP have been reported during the induction of anaesthesia in patients with intracranial tumours and aneurysms (Sondergard, 1961; Laitinen et al., 1967; Hulme and Cooper, 1972; Henriksen and Jorgensen, 1973; Cold, 1975; Greenbaum et al.,1975; Phirman and Shapiro, 1977), and smaller increases have been

described during established anaesthesia with hypocapnia in patients with cerebral tumours (Misfeldt et al., 1974). However, Gordon and Greitz (1970) found no increase in lumbar CSF pressure when nitrous oxide was administered with the anaesthetic gases to patients with normal ICP. Nitrous oxide may also increase ICP after air encephalography by diffusion into the intracranial air space at a faster rate than nitrogen diffuses out (Saidman and Eger, 1965; Gordon and Greitz, 1970; Campkin and Turner, 1972). CPP is significantly reduced during induction of anaesthesia with nitrous oxide (Hulme and Cooper, 1972; Henriksen and Jorgensen, 1973).

Increases in CBF occur when nitrous oxide is administered to dogs (McDowall and Harper, 1965; Theye and Michenfelder, 1968; Sakabe et al., 1978; Oshita et al., 1979), but the reports on the effect of nitrous oxide on CBF in man are conflicting. Wollman and colleagues (1965) reported no change in CBF when 70% nitrous oxide was given to healthy male volunteers, whereas Sakabe and colleagues (1976) found an increase in CBF equivalent (which is the ratio of CBF to $CMRO_2$) during the administration of 60% nitrous oxide to human volunteers. There has been no report of the effect of nitrous oxide on ICP or CBF in patients with severe head injuries, although it has been suggested that increases in ICP may occur (Henriksen and Jorgensen, 1973). $CMRO_2$ is increased by nitrous oxide in dogs (Theye and Michenfelder, 1968), but is decreased by it in man (Wollman et al., 1965). On balance it appears that nitrous oxide increases CBF and ICP in man, and that the greatest increases in ICP occur when nitrous oxide is used for induction of anaesthesia in patients with initially raised ICP.

Gibson and colleagues (1975) reported increases in ICP

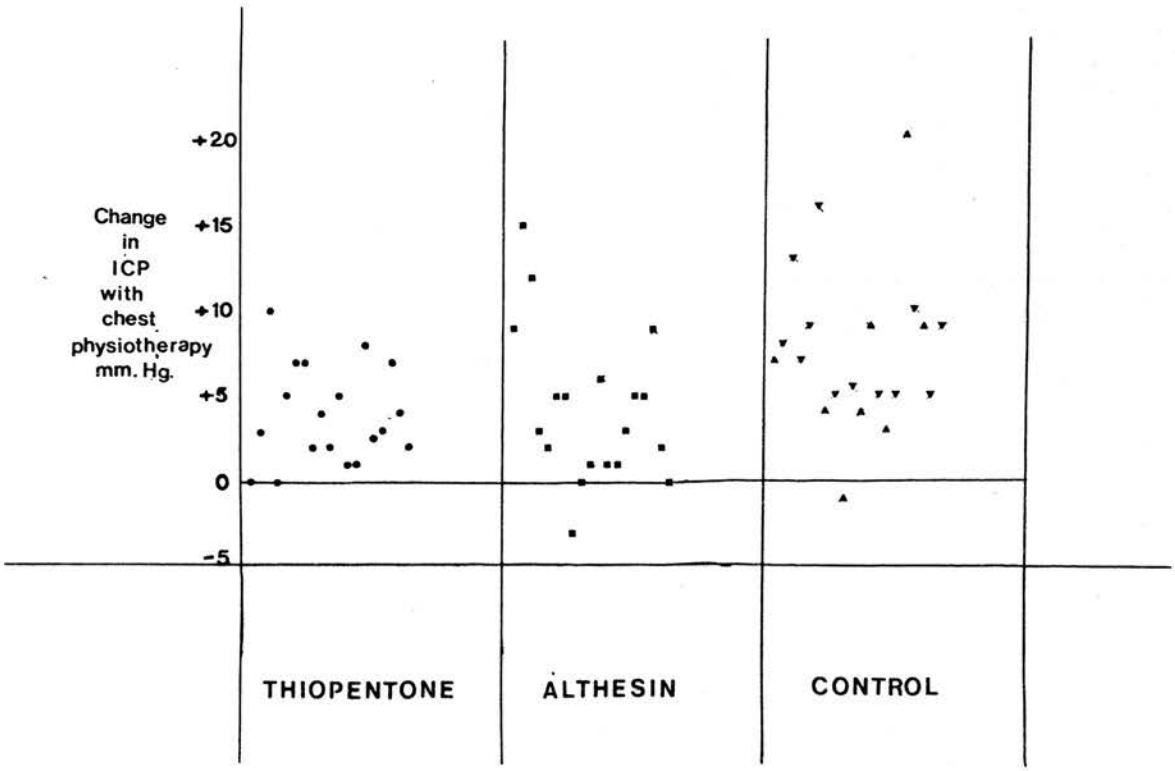

Figure 2. Scatter diagram of the maximum change in mean ICP during chest physiotherapy (mm Hg) following the administration of thiopentone, Althesin or no drug (control).

during chest physiotherapy in patients with severe head injuries which were thought to be partly a result of an increase in intra-thoracic pressure due to chest compression, and partly a result of cerebral activation produced by noxious stimulation. Although it has never been demonstrated that short-lived increases in ICP associated with chest physiotherapy are harmful, it is reasonable to assume that in certain circumstances they could be detrimental to the patient with a head injury. The large increases, which sometimes occur, could cause or accentuate brain shift and may cause cerebral ischaemia by reducing CPP. Even small increases in ICP may lead to cerebral ischaemia in focal areas of damaged brain because small increases in local tissue pressure, which reduce local perfusion pressure, may seriously impair an already compromised local circulation. As Entonox is an analgesic it might be expected to decrease such increases in ICP. However, after Entonox had been given on 12 occasions during chest physiotherapy it was clear that the increases in ICP were exacerbated. The inspired oxygen concentration was different in the two study groups and this could have had a small influence on the ICP values obtained, but this study was designed to determine what happened when the use of Entonox was compared with the method normally used in clinical practice.

The increase in ICP during the administration of Entonox in the absence of chest physiotherapy is almost certainly due to a cerebral vasodilatory action of the drug. An increase in end-tidal carbon dioxide concentration, which was expected because of the initial rapid uptake of nitrous oxide, was not seen and therefore an increase in $PaCO_2$ cannot account for the increase in ICP. In the absence of chest physiotherapy the increases in ICP were small, but

they might be greater in patients with severe head injury breathing spontaneously, especially when the volume of the intracranial contents is on the steep part of the pressure/volume curve.

The results of these investigations indicate that Entonox should be avoided in spontaneously breathing head-injured patients during transport and admission to hospital. However, the use of nitrous oxide during general anaesthesia in patients with head injuries is not contra-indicated by these results, but it should not be used for the induction of anaesthesia and should not be introduced until after intubation has been performed and hyperventilation with 100% oxygen has been established (Henriksen and Jorgensen, 1973; Phirman and Shapiro, 1977). Misfeldt and colleagues (1974) showed that prior hyperventilation for 10 minutes or more with 100% oxygen prevented any marked increase in ICP during the administration of nitrous oxide, and Jorgensen and Henriksen (1973) demonstrated that any increase in ICP associated with the administration of nitrous oxide could be effectively counteracted by hyperventilation. However, when controlled hyperventilation has been in use for several hours, as in the management of severe head injury, any protective effect of hypocapnia against the increases in ICP induced by nitrous oxide may be lost because of the adaptation of CBF and ICP to the lower $PaCO_2$ values. The increase in ICP induced by nitrous oxide can be prevented or reduced by the administration of thiopentone (Phirman and Shapiro, 1977; Schulte am Esch et al., 1980).

Thiopentone and Althesin cause reductions of ICP and CBF (see Chapter 5). Intravenous bolus doses of thiopentone have been used to reduce elevated ICP rapidly, but the effect is short-lived and continuous infusion is required to maintain the reduction of ICP

(Shapiro et al., 1973; Levin et al., 1979). Shapiro and colleagues (1974) have demonstrated reductions in ICP and increases in CPP with the administration of thiopentone and pentobarbitone in patients with persistent intracranial hypertension, and good results have been reported from the use of thiopentone and pentobarbitone infusions in patients with head injury in whom raised ICP could not be reduced by conventional treatment (Levin et al., 1979; Marshall et al., 1979). Althesin (1 to 2 ml) has also been given in bolus doses to reduce ICP in patients with severe head injury (Versari et al., 1980; Moss et al., 1980), and Bedford and co-workers (1980) reported that lignocaine 1.5 to 2 mg/Kg often controlled increased ICP in patients with head trauma.

Before this investigation there were no reports on how thiopentone or Althesin affected the response of ICP to chest physiotherapy. The results of this study show that pre-treatment with thiopentone 3 mg/Kg or Althesin 0.03 ml/Kg intravenously significantly reduce the increase in ICP caused by chest physiotherapy in patients with head injury without causing large reductions in arterial pressure. However, there was still considerable variability in the ICP response to physiotherapy when thiopentone or Althesin were administered (Fig. 2). Surprisingly, higher doses of these drugs did not significantly reduce this increase in ICP, although the result with Althesin was almost significant. The mean ICP before physiotherapy was much lower in the patients receiving the higher doses, and this may explain the difference in results. Therefore the drugs may be ineffective when the ICP is low.

It must be pointed out that this was a clinical study and thus it was impossible to standardise the inflation pressures and

$PaCO_2$ values during chest physiotherapy. However, any changes in these parameters which occurred during the investigations would be similar to those which normally occur during chest physiotherapy, so that the results are applicable to the clinical situation.

These results suggest that the main mechanism of the increases in ICP associated with chest physiotherapy is likely to be the increase in intrathoracic pressure, leading to increases in CVP and spinal CSF pressure, which in turn causes an increase in ICP. If these increases had been largely due to noxious stimulation one would have expected thiopentone or Althesin, by counteracting such stimulation, to reduce them to a much greater extent, although combination of thiopentone or Althesin with a potent analgesic may have had more effect in reducing the increases, because thiopentone and Althesin have no analgesic properties. The thiopentone and Althesin probably reduced the magnitude of the increases in ICP by reducing ICP before physiotherapy was begun, so that ICP effectively started at a lower level in the thiopentone and Althesin groups. At lower values of ICP the decrease caused by the thiopentone and Althesin would be expected to be less because the intracranial compliance would be greater, and thus these drugs would be expected to have less effect on the changes in ICP occurring during chest physiotherapy.

Although thiopentone and Althesin will cause some reduction in ICP changes during chest physiotherapy, they do not abolish these changes and the ICP display should therefore be observed carefully during chest physiotherapy. Thus the duration and aggressiveness of the physiotherapy can be adjusted to avoid increases in ICP of more than 5 mm Hg. In patients with increased ICP before physio-

therapy the administration of thiopentone or Althesin will probably help to reduce these increases in ICP.

In the investigations reported in this chapter ICP was measured from the subdural or extradural spaces. In Chapter 3 I have pointed out that values of ICP measured from these sites do not correspond exactly with those obtained from a ventricular catheter. However, in the investigations reported here it is the changes in ICP which are important and these can be measured reliably from the subdural or extradural sites.

From the results described in this chapter the following conclusions can be drawn. Chest physiotherapy can cause marked increases in ICP in patients with severe head injury. 50% Nitrous oxide in oxygen worsens these increases in ICP and thus should not be used in head injured patients. Thiopentone and Althesin can reduce the ICP increases but neither drug prevents them. During chest physiotherapy ICP should be carefully monitored and the intensity of the physiotherapy adjusted according to the ICP response. 50% Nitrous oxide in oxygen causes ICP to increase in patients with head injury and thus should be used in such patients only when controlled hyperventilation has been commenced.

SUMMARY

Three separate investigations were performed on patients with severe head injuries who were being mechanically hyperventilated ($PaCO_2$ 3.3 to 4.0 KPa). During chest physiotherapy the lungs were manually hyperinflated with 100% oxygen or 50% nitrous oxide in oxygen (Entonox) using a Mapleson C circuit. In a randomised trial Entonox accentuated the ICP changes produced by chest physiotherapy, the average maximum increase in ICP during chest physiotherapy with Entonox was 22.7 mm Hg (S.D. 10.62) compared with 10.5 mm Hg (S.D. 10.41) when 100% oxygen was given. This difference was statistically significant ($0.02 > P > 0.01$). When Entonox was given to 9 patients with severe head injury who were not receiving chest physiotherapy there was a mean increase in ICP of 3.8 mm Hg (S.D. 2.4), and a mean decrease of 4.6 mm Hg (S.D. 2.8) after the withdrawal of nitrous oxide. Both these changes were statistically significant ($P < 0.001$). When thiopentone (3 mg/Kg) or Althesin (0.03ml/Kg) or no drug at all were given at random to 10 patients who were being manually ventilated with 100% oxygen during chest physiotherapy, the average maximum increases in ICP during physiotherapy were 3.9 mm Hg (S.D. 2.86), 4.3 mm Hg (S.D. 4.47) and 7.6 mm Hg (S.D. 4.70) respectively. These average changes in ICP were significantly less in both the thiopentone group ($0.01 > P > 0.001$) and the Althesin group ($0.05 > P > 0.02$) than in the oxygen only group. In a subsequent study both thiopentone 4.5 mg/Kg and Althesin 0.045 ml/Kg caused a reduction in the average maximum ICP increases during chest physiotherapy when compared with the oxygen only group, but this reduction was not statistically significant. In this latter study the average ICP immediately before physiotherapy was lower than in

the previous study. Thus Entonox increases ICP in patients with head injury and exacerbates the increases in ICP associated with chest physiotherapy. Thiopentone and Althesin reduce the increases in ICP associated with chest physiotherapy, but do not prevent them. The literature concerning the effect of nitrous oxide on ICP, CBF and $CMRO_2$ is reviewed.

CHAPTER 10

FINAL DISCUSSION

In order to decide which anaesthetic agents can safely be used during intracranial operations, and how to produce the best possible operating conditions without causing damage to the brain, the neuroanaesthetist needs a detailed knowledge of the physiology and pathophysiology of the cranial contents, and of how anaesthetic drugs and manoeuvres alter ICP, CBF and $CMRO_2$. Similar considerations apply to the intensive care of patients with head injury.

In Chapter 2 I have already discussed the possible mechanisms by which anaesthetic agents could influence ICP and concluded that, in the absence of $PaCO_2$ changes which themselves influence ICP, the most likely mechanism is a change in CBF caused either by a direct effect of the agent on the cerebral vessels or by its influence on cerebral metabolic rate, which in turn causes a reduction in CBF. A change in metabolic rate could only be the mechanism of the change in CBF with agents, such as the intravenous induction agents, which reduce both CBF and $CMRO_2$ in parallel. This mechanism would not be valid for the volatile agents in which the relationship between $CMRO_2$ and CBF is uncoupled. The change in CBF leads to a change in CBV which in turn alters ICP. Thus ICP measurements during drug administration could be regarded as a continuous assessment of CBV. ICP measurements have the advantage that they are continuous whereas CBF measurements are intermittent, and any variations which occurred in between measurements would be missed.

Cerebral pathology can alter the normal physiological responses of the brain, and cause changes in ICP and the distribution of CBF. It can also influence the way in which anaesthetic agents affect CBF and ICP. When there is significant intracranial space occupation, any agent which causes cerebral vasodilatation will cause a much

greater increase in ICP than it would if there was no space occupation. This effect has been demonstrated with volatile anaesthetic agents (Jennett et al., 1969). Such vasodilator stimuli might be expected to precipitate plateau waves but these have not been demonstrated during anaesthesia with volatile agents. However, in the author's investigations in patients with severe head injuries, they did occur during chest physiotherapy whilst 50% nitrous oxide in oxygen was being administered (Chapter 9). Conversely, any agent which causes cerebral vasoconstriction would be expected to cause a greater reduction in ICP in patients with initially raised ICP than in patients with normal ICP. This effect has been demonstrated with Althesin (Turner et al., 1973), but not with etomidate although there was a trend in that direction (Chapter 5).

Cerebral autoregulation and carbon dioxide reactivity are important mechanisms for control of CBF, which may be disturbed in various disease processes (see Chapter 1). Autoregulation is usually lost first. Autoregulation may also be disturbed by deep general anaesthesia with cyclopropane or halothane and following induced hypotension (Chapter 2). In contrast, cerebrovascular reactivity to carbon dioxide is usually maintained during general anaesthesia (Chapter 2), so that hyperventilation will still influence ICP during general anaesthesia. However, according to Adams and colleagues (1972) hypocapnia must be established 10 minutes before the halothane is introduced if it is to influence the ICP changes with this agent. When cerebral autoregulation and cerebrovascular reactivity to carbon dioxide are disturbed and the luxury perfusion syndrome exists, intracerebral steal and inverse intracerebral steal can occur. If intracerebral steal is due to the diversion of

blood flow because of a change in the diameter and thus the resistance of vessels which are still reactive, then anaesthetic agents may cause steal effects through their effect on CBF. However, if steal effects are due to 'intracerebral squeeze', through changes in local tissue pressure influencing the resistance to flow within non-reactive vessels, then anaesthetic drugs which increase ICP would be expected to cause intracerebral steal by increasing local tissue pressure, and those which reduce ICP would cause inverse intracerebral steal by reducing local tissue pressure. There is some evidence that intracerebral steal and inverse intracerebral steal occur with halothane and Althesin anaesthesia respectively (Chapter 1).

When autoregulation is lost on a focal or global basis, marked changes in CBF and ICP may occur due to hypertension or hypotension caused by the administered drug, because the CBF is pressure passive. Under these circumstances hypotension is more likely to cause cerebral ischaemia, and hypertension may lead to the formation of cerebral oedema, because the increase in arterial pressure is transmitted through the dilated arterioles to the capillaries in which the hydrostatic pressure is increased. Such an increase in hydrostatic pressure favours the formation of oedema. Thus under these conditions it is important to keep the arterial pressure stable. Anaesthetic agents which have a marked effect on arterial pressure in either direction should be used with care, and the choice of a suitable combination of anaesthetic drugs may reduce the formation and spread of cerebral oedema fluid.

From the above discussion, it is clear that the ideal anaesthetic agents for use during intracranial surgery should reduce CBF and ICP and should not cause excessive

changes in arterial pressure. However, a reduction in CBF without a parallel reduction in cerebral oxygen consumption could impair cerebral oxygenation. Thus information on the effects of anaesthetic agents on $CMRO_2$ is important also in choosing suitable drugs for use in neuroanaesthesia. With the exception of ketamine, the intravenous induction agents and the volatile anaesthetic agents reduce $CMRO_2$ and thus do not interfere with the oxygen supply to demand ratio for the brain.

The pathological influences on CBF and ICP must be taken into account not only in deciding upon anaesthetic techniques, but also in the design and interpretation of investigations of drug effects on these parameters. In this context it is also important to consider physiological influences on CBF and ICP. Because of the influence of the arterial blood gases on CBF and ICP, it is obvious that these should be kept within fairly narrow limits during such investigations in order to avoid changes which are not due to the drugs administered. It is more important that the $PaCO_2$ is kept within narrow limits than the PaO_2, because ICP is much more sensitive to changes in $PaCO_2$. CBF is unaffected by a reduction of PaO_2 until this is less than 6.7 KPa, and an increase in F_IO_2 from 0.21 to 1 only causes a 10% decrease in CBF (see Chapter 1). Changes in body temperature also alter ICP, and it is important to keep the temperature constant during investigations on this parameter. In addition, when testing the effects of anaesthetic agents on ICP, it is important to avoid any factors which may cause an increase in cerebral metabolism, such as arousal due to surgical stimulation. With the exception of enflurane (Mann et al., 1980), which increases the rate of formation of CSF, anaesthetic agents have not been shown to influence the rate

of CSF production, but the respiratory alkalosis which is deliberately induced during anaesthesia for intracranial operations can be expected to reduce CSF production by about 40% (Oppelt et al., 1963). Both ketamine and enflurane cause an increased resistance to CSF reabsorption (Mann et al., 1980). The other parameter which may influence ICP is the central venous pressure. Increases in central venous pressure may lead to an increase in cerebral venous pressure which will cause ICP to increase. Thus, during investigations on the effects of anaesthetic agents on ICP, the pulmonary inflation pressure should be constant and straining against the ventilator should be avoided by the use of adequate doses of muscle relaxants. Any increase in CVP caused by the myocardial depressant effect of the anaesthetic agents must be taken into account in the interpretation of the results.

In the original work described in this thesis, $PaCO_2$, PaO_2 and ventilator inflation pressures were kept constant and surgical or other stimulation was avoided during measurements of ICP (except in some of the studies described in Chapter 9). The investigations were short so that temperature changes would have little effect on the ICP values recorded. These investigations were performed on patients with intracranial disorders because it is in such patients that ICP changes are most important. The effect of drugs on ICP is clinically insignificant in patients without brain pathology. Therefore, the information obtained from these investigations is directly relevant to clinical neuroanaesthesia in which the anaesthetist is managing patients with intracranial pathology.

In the original work described in Chapters 4 to 8, ICP was measured from a ventricular catheter and arterial pressure from an

intra-arterial cannula. These are the most direct methods of measurement of ICP and arterial pressure. In one patient in the enflurane study a **subarachnoid bolt** was used for ICP measurement because the ventricles were seen to be collapsed on the CAT scan, and in the investigations in patients with head injuries a subdural catheter or a Leeds device placed in the subdural or extradural space was used. In Chapter 3 I have discussed the discrepancies between ICP values obtained from the extradural or subdural spaces and those obtained using a ventricular catheter. The correlation of the measurements is not perfect for either site when compared with those from the ventricular site, but in those investigations in which the subdural and extradural sites were used the changes in ICP rather than its absolute value were important. Changes in ventricular fluid pressure are generally reflected well in the pressure changes recorded from the subdural and extradural spaces, and in the different study groups in Chapter 9 the method of measurement was comparable, therefore when the groups were compared any error in the recorded values caused by the site of measurement should have been eliminated.

During the investigations on patients who were about to undergo intracranial surgery the anaesthetic technique was the standard method which was normally employed in the author's hospital for such operations. The same technique is routinely used in many other neurosurgical centres. Three points should be made about the anaesthetic management. Firstly, if premedication was required diazepam was administered either intramuscularly or orally. This agent reduces CBF and $CMRO_2$ in man and in dogs (Cotev and Shalit, 1975; Sari et al., 1975), but has no effect on ICP in dogs (Campan and Lazorthes, 1976), and in the dose used for premedication, does

not depress respiration significantly. Therefore, it will not interfere with the ICP response to the agent under investigation. Secondly, nitrous oxide, the maintenance anaesthetic agent used in all the investigations, may show a drug interaction with some sedative drugs regarding their effect on CBF and $CMRO_2$, and this has been demonstrated with diazepam in rats (Carlsson et al., 1976). However, even if such drug interactions occur with the agents studied by the author, they would also occur when the drugs were used in clinical practice, because nitrous oxide is very commonly employed as a maintenance agent in neuroanaesthesia. Thirdly, fentanyl is used frequently during anaesthetic maintenance for intracranial operations. No drug interactionsbetween this drug and other anaesthetic agents regarding their effect on CBF, ICP or $CMRO_2$ have been reported, but if an interaction occurs between this agent and enflurane (see Chapter 8) this would also occur when the drugs were used in clinical neuroanaesthetic practice. Thus the information obtained from these investigations is directly relevant to practical neuroanaesthesia.

The study, described in Chapter 4, on induction of anaesthesia in patients about to undergo intracranial operations, confirms that ICP is decreased following induction of anaesthesia with both thiopentone and Althesin (provided that $PaCO_2$ is not allowed to increase) and shows that the two agents have similar effects on ICP during the induction of anaesthesia. It also demonstrates that the ICP response during laryngoscopy and intubation is similar when either of these two agents is given with d-tubocurarine to allow intubation. Large increases in ICP could still occur in some patients using this combination of drugs for intubation, but it appears that these increases are smaller if non-depolarising relaxants are used for

intubation than if suxamethonium is used (see Chapter 4). When suxamethonium is the relaxant used, pretreatment with small doses of a non-depolarising muscle relaxant may reduce the increases in ICP during intubation by abolishing the muscle fasciculations, because the limited data obtained by the author and described in Chapter 6 indicates that the effect of suxamethonium on ICP is very small when muscle fasciculations are abolished. The study on induction of anaesthesia also confirms the dramatic reduction of MAP and CPP which occurs when thiopentone or Althesin is given in combination with d-tubocurarine in the dose required for intubation. This arterial pressure reduction may help in reducing the response of ICP to intubation which is probably partially caused by an increase in arterial pressure due to catecholamine release (De Vault et al.,1960; Reves et al., 1981), but in many patients the CPP was reduced below the lower limit of the autoregulatory range which could lead to cerebral ischaemia. Fortunately the reduction of MAP and CPP was short-lived and did not appear to affect the patients adversely. Several methods have been suggested for reducing the ICP response to intubation, and these are discussed in Chapter 3. The most useful seem to be the use of thiopentone (or other intravenous anaesthetic agent) or fentanyl to deepen anaesthesia before intubation, and the administration of lignocaine intravenously which probably works by deepening anaesthesia as well as by suppressing the cough reflex.

The results on the effect of etomidate on ICP indicate that it would be a suitable alternative to thiopentone, Althesin or methohexitone for induction of anaesthesia for intracranial surgery. One problem with this agent is that the involuntary movements which are often associated with its administration may cause ICP to increase

(Patel, 1980). However, if it is given by infusion, as described in the multicentre study on etomidate infusion (Boyes et al., 1981), the incidence of involuntary movements is low. So, used in this way, etomidate could be a useful agent for induction and maintenance of anaesthesia for intracranial surgery. In addition to etomidate, thiopentone, methohexitone and Althesin have been shown to decrease ICP and CBF (see Chapter 5), and thus an infusion containing any one of these agents would decrease CBV and ICP and consequently be useful in patients in whom a decrease in brain bulk and ICP was considered necessary. Hunter (1972a, 1972b) has described the use of both thiopentone and methohexitone infusions for supplementing nitrous oxide/relaxant anaesthesia, and the use of Althesin in similar circumstances is common practise in parts of Great Britain. However, when these agents are used analgesic supplementation is required because they do not have analgesic properties of their own. Etomidate infusions may prove useful also in reducing elevated ICP in patients with severe head injury.

Until the report by Tarkkanen and colleagues (1974) it was believed that non-depolarising muscle relaxants had no effect on the cerebral circulation or ICP except by their indirect effects, which reduced straining against the ventilator or coughing on an endotracheal tube. The literature on the effect of the muscle relaxants on ICP and CBF is reviewed in Chapter 6. The author's data on the effects of d-tubocurarine on ICP indicate that even in large doses it has little or no effect on ICP. In small doses (15 to 20 mg) it definitely does not increase ICP; it causes a small reduction in ICP. If larger doses do cause sufficient release of histamine to cause cerebral vasodilatation, the hypotension induced when given with thiopentone or

Althesin would appear to prevent any associated increase in CBF. Thus d-tubocurarine is not contra-indicated in patients with intracranial lesions, but care should be taken to avoid excessive decreases in MAP because of the danger of causing cerebral ischaemia. This may be achieved by using another relaxant for intubation, for example alcuronium or suxamethonium (the latter agent should be preceded by a small dose of non-depolarising agent), and then giving the d-tubocurarine in smaller incremental doses. Although the reduction of CPP is usually short-lived, it can last for several minutes in old or dehydrated patients, so care must be taken when administering d-tubocurarine to such patients. Tubocurarine has useful properties for neuroanaesthesia because its hypotensive effect helps in the control of arterial pressure and it is long-acting. Alcuronium is fairly short-acting so that there is a greater risk of the patient coughing or straining against the ventilator, although careful monitoring of neuromuscular blockade using a nerve stimulator will prevent this. Pancuronium, although long-acting, has the disadvantage of causing arterial hypertension (Kelman and Kennedy, 1971; Gordon, 1975) which can cause problems during some intracranial operations. Tubocurarine should be avoided in patients who are subject to bronchospasm because it can cause severe bronchoconstriction.

Nitrous oxide causes an increase in ICP in patients with intracranial space-occupying lesions, especially during induction of anaesthesia (see Chapter 9), but it is generally accepted that it is safe to use it for maintenance of anaesthesia during intracranial operations. However, in patients with high ICP due to cerebral tumours it is recommended that nitrous oxide is not introduced until intubation has been performed and hyperventilation is established

(Henriksen and Jorgensen, 1973; Phirman and Shapiro, 1977). The author's results show that nitrous oxide also increases ICP in patients with head injury, and it would seem wise to avoid it in patients with significant head injuries until hypocapnia is established and intubation is completed.

Fentanyl is commonly used to supplement nitrous oxide for maintenance of anaesthesia during intracranial operations. The results given in Chapter 7 show that during hypocapnia fentanyl has very little effect on ICP and that changes can occur in either direction. These results are similar to those of other authors at normocapnia (Misfeldt et al., 1976; Cunitz and Gaab, 1980), and are supported by reports on the effect of fentanyl on CBF (De Rood et al., 1974; Vernhiet et al., 1977). It appears that other narcotic agents similarly do not affect CBF or ICP provided that the $PaCO_2$ is not allowed to increase. This is true for morphine, pentazocine and phenoperidine (when given in combination with droperidol), but if $PaCO_2$ is allowed to increase ICP will increase. Thus fentanyl should only be given if the patient's ventilation is, or will be, controlled before this agent can significantly increase $PaCO_2$ by causing respiratory depression. Fentanyl should also be avoided if the patient is hypotensive (see Chapter 7).

Most volatile anaesthetic agents increase CBF and ICP whilst decreasing $CMRO_2$; this is true for diethyl ether, trichloroethylene, methoxyflurane, halothane and isoflurane (see Chapter 8). If such agents are administered during spontaneous respiration, the resultant respiratory depression will magnify the increase in CBF and ICP caused by the volatile agent. The author's results indicate that during normocapnia and hypocapnia enflurane appears to have very

little effect on ICP. These results are in agreement with those in most of the reported studies of the effect of enflurane on ICP in humans, although in some of these studies some patients showed fairly substantial increases in ICP (see Chapter 8). Thus enflurane appears to have the least effect on ICP of the commonly used volatile agents. Studies on CBF in man also support the view that the effect of enflurane on the cerebral vessels and ICP is minimal (see Chapter 8). However, enflurane does cause a marked decrease in MAP and CPP so that the arterial pressure must be carefully observed during its administration. The author's results in patients with cerebral tumours confirm that enflurane is a suitable agent for use in neuroanaesthesia. It could be used to control arterial pressure whilst causing very little change in brain bulk. Despite its effect on the electroencephalograph it seems unlikely that it will precipitate convulsions in patients with cerebral lesions.

The changes in ICP associated with the administration of enflurane are very similar to those caused by fentanyl, and thus enflurane should be as useful a supplement to nitrous oxide/oxygen/relaxant anaesthesia as fentanyl, particularly when its hypotensive effect would be beneficial.

During intracranial surgery, ventilation is usually controlled so that the $PaCO_2$ is in the hypocapnic range. There are two conflicting points of view with regard to the use of volatile anaesthetic agents or neuroleptanalgesic agents for the supplementation of nitrous oxide anaesthesia during hypocapnia. The first point of view is that previous hypocapnia renders increases in ICP with volatile anaesthetic agents, particularly halothane, so small as to be clinically unimportant (Adams et al., 1972).

In the investigation of Adams and colleagues (1972) ICP increased in 10 out of 17 cases with the administration of 0.5 to 1% halothane at a mean $PaCO_2$ of 3.5 KPa, but only one patient showed an increase greater than 4 mm Hg. The second point of view holds that although hypocapnia reduces the changes in ICP produced by volatile anaesthetics, major changes in ICP still occur in patients whose intracranial compression is advanced (Jennett et al., 1969; Gordon, 1970). If the second view is correct, then neuroleptanalgesic supplementation may be preferable. However, the author's work, and that of others, shows that both at hypocapnia and normocapnia enflurane has effects on ICP which are very similar to those of fentanyl, so that this agent should be equally useful as a supplement to anaesthesia in neurosurgery (see Chapter 8). The marked reduction in CPP seen with enflurane does not occur with fentanyl unless it is given when the arterial pressure is already reduced (see Chapter 7), so that fentanyl will be the agent of choice if hypotension is not wanted. If the mechanism for CSF absorption is disturbed the increased production of CSF during enflurane anaesthesia demonstrated by Mann and coworkers (1980) may contraindicate the use of this agent.

Chest physiotherapy performed during the intensive care of patients with head injury causes increases in ICP (Gibson et al.,1975) which may on occasions be considerable in magnitude. There have been no reports on the effect of anaesthetic drugs on these increases in ICP. It is clear from the results presented in Chapter 9 that the analgesic effect of 50% nitrous oxide in oxygen is overridden by its cerebral vasodilatory effect, and that this agent could be positively harmful if used during chest physiotherapy in patients with head injury. This argument can be taken a stage further by suggesting

that Entonox should not be used as an analgesic in patients with head injury during transport or admission to hospital, because of its potential harmful effects on ICP. Thiopentone and Althesin in small anaesthetic doses did significantly reduce the changes in ICP which occurred during chest physiotherapy in patients with head injury, but the scatter of ICP changes was considerable. Larger doses of thiopentone and Althesin did not significantly reduce the ICP changes. The initial ICP was lower in the second study investigating the larger doses, and this may explain why the increases in ICP were not significantly reduced. Thus thiopentone and Althesin appear to be of use in reducing the ICP changes due to chest physiotherapy only when the initial ICP is raised, and they are not effective in abolishing these changes.

Before concluding that knowledge of the effects of anaesthetic agents on ICP should influence the neuroanaesthetist's choice of agents, one has to consider at what value of ICP harmful effects will be produced when the cranium is intact, and how much the increase in brain bulk caused by agents which increase ICP interferes with surgical access when the cranium is open. The problem of deciding when to treat increased ICP when the cranium is intact has been discussed in Chapter 1. When the ICP and the compliance of the intracranial contents are normal, increases in ICP are probably not significant, but in the presence of raised ICP and reduced compliance of the intracranial contents, a small increase in CBV may cause substantial increases in ICP, which could lead to cerebral damage either through shift causing distortion of the brain, or reduction in CPP causing ischaemia. Thus in some patients with considerable intracranial compression, even a small increase in CBV may compromise brain function.

In such patients, great care should be taken to minimise changes in CBV and ICP. Once the cranium is open the ICP falls to zero, but the restraints on brain bulk are removed, so that there is a danger of herniation of the brain through the craniotomy site if ICP was high before decompression. The same process, but in a lesser degree, can cause difficulties with surgical retraction and access to the site of operation. Thus the greater the brain bulk the greater the pressure that will have to be applied with the brain retractor in order to obtain the same degree of surgical access. Therefore, even if a small increase in ICP will not cause harm in most patients, during intracranial surgery it will be advantageous to keep CBV to a minimum, in order to reduce retraction pressures which in turn will diminish the amount of ischaemia caused by retraction both under the retractor and on the surface of the contralateral hemisphere. As anaesthetic agents increase ICP by increasing CBV, it is clearly advantageous to use agents which either do not affect ICP or, preferably, reduce it, so that brain retraction pressures are reduced to a minimum. It is therefore the author's belief that knowledge of the effects of anaesthetic agents on ICP is important in deciding which are the best anaesthetic agents to use during intracranial operations, and that optimum operating conditions are produced by anaesthetic agents which reduce ICP. The other important factor in the choice of anaesthetic agents is the maintenance of an adequate CBF. Anaesthetic agents can reduce CBF by decreasing CPP through an increase in ICP or a decrease in MAP or both.

Several conclusions can thus be made regarding the agents investigated in the original work described in this thesis. Etomidate, Althesin and thiopentone reduce ICP and will therefore produce safe

anaesthesia in patients with raised ICP, and if given by infusion should produce good operating conditions. Tubocurarine has no effect on ICP and does not alter CBV and operating conditions. Fentanyl and enflurane cause no significant change in ICP although in individual patients changes in either direction can occur. The changes are so small, however, that they will not have detrimental effects on the brain tissue or significantly interfere with surgical access. The increase in ICP caused by nitrous oxide administration during controlled hyperventilation is small and probably clinically insignificant except when ICP is already very high. All these agents therefore are suitable for use during intracranial surgery. Of these agents, fentanyl can cause a significant reduction in CPP when the patient is hypotensive at the time of its administration, and enflurane in a concentration of 2% can cause reduction of CPP to levels which are associated with cerebral ischaemia. So, in addition to their effect on ICP and thus operating conditions, the effect of anaesthetic agents on CPP must be taken into account and measures taken to avoid dangerous reductions in this pressure. Short-lived large reductions in CPP, as when tubocurarine is given with thiopentone or Althesin during the induction of anaesthesia, do not appear to be detrimental to the patient (see Chapter 4) but are probably best avoided.

When considering the effects of anaesthetic agents on the response of ICP to manoeuvres such as endotracheal intubation and chest physiotherapy, one must decide again whether these responses, which are generally short-lived, are in any way detrimental to the patient. There is no evidence that these increases in ICP do cause harm, although it is reasonable to assume that even short-lived large increases in ICP can accentuate brain shift and may compromise the

circulation to damaged regions of the brain. The increase in ICP associated with endotracheal intubation is usually secondary to an increase in MAP, and that associated with chest physiotherapy is secondary to an increase in cerebral venous pressure, both of which will increase the hydrostatic pressure in the cerebral capillaries and promote cerebral oedema formation. Even if these increases in ICP were not detrimental it would be unwise to exaggerate them, so it can be concluded from the results reported in Chapter 9 that 50% nitrous oxide in oxygen should not be used for analgesia during chest physiotherapy in patients with head injury. Thiopentone and Althesin may help to avoid further brain damage during chest physiotherapy, particularly in patients with high ICP, but there is no direct evidence to confirm this. The mean increase in ICP associated with endotracheal intubation was small when thiopentone and Althesin were given together with tubocurarine for intubation, and the MAP did not increase above the control value. Therefore this combination of agents may help to prevent the potentially harmful consequences of endotracheal intubation in patients with raised ICP.

The pressures measured in these studies were global pressures, and it would be interesting to know how anaesthetic agents affected local tissue pressures, for example under the blade of the brain retractor. Such measurements would give additional help in determining which techniques of anaesthesia were best employed for intracranial surgery.

However, the investigations described in this thesis

have provided information which, when added to that obtained by other workers, allows rational decisions to be made on the choice of anaesthetic agents for use during intracranial surgery and the intensive care of patients with head injury.

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A P P E N D I X

REPRINTS OF PUBLICATIONS

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The use of anesthetic drugs to reduce ICP changes in head-injured patients

by E. MOSS, M.B., Ch.B., F.F.A.R.C.S.*
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SUMMARY

Chest physiotherapy causes increases in intracranial pressure (ICP) in patients with severe head injuries. In mechanically hyperventilated severe head injuries ($Paco_2$ 3.3 - 4 kPa) 50 % nitrous oxide in 50 % oxygen exacerbated ICP increases associated with chest physiotherapy, while thiopentone and Althesin reduced these changes in ICP. (Acta anaesth. belg., *1980*, 31, *suppl.*, 43-48).

Key words : Nitrous oxide, thiopentone, Althesin, chest physiotherapy, intracranial pressure.

Changes in intracranial pressure (I.C.P.) are common in patients with severe head injuries, and increases in I.C.P. may be detrimental to the patient in that they may cause brain shifts and reduce cerebral perfusion pressure. Intravenous anesthetic induction agents such as thiopentone, methohexitone, propanidid, Althesin and etomidate have all been shown to reduce cerebral blood flow (C.B.F.) (4, 11, 12, 15), and thus cerebral blood volume and I.C.P. (2, 5, 6, 10, 16, 19). So in patients with head injury these agents can be used to reduce I.C.P. rapidly whilst one is waiting for a dehydrating agent such as mannitol to take effect. They can also be used by continuous infusion to control I.C.P., although systemic hypotension often limits their use. This paper describes the effects of 50 % nitrous oxide in 50 % oxygen, thiopentone and Althesin on the I.C.P. rises known to occur during chest physiotherapy in head-injured patients (3). These increases in I.C.P. are thought

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to be due partially to noxious stimulation and partially to the increase in central venous pressure caused by chest hyperinflation and compression.

Method

Two separate studies were performed. In both studies the patients had severe head injuries and were being mechanically hyperventilated to Pa_{CO_2} values of 3.3 to 4.0 kPa. During chest physiotherapy the patients were ventilated manually by anesthetists, and before any study was performed the patient received a further dose of muscle relaxant. I.C.P. was recorded from a subdural catheter or device or an extradural device (1), using a transducer, amplifier and chart recorder. The maximum rise in mean I.C.P. during the period of chest physiotherapy was read from the chart recordings.

In the first study patients were given, in random order, either 100 % oxygen or 50 % nitrous oxide in 50 % oxygen during chest physiotherapy. This study was stopped when nitrous oxide had been given 12 times to 3 patients.

In the second study, 100 % oxygen, thiopentone (3 mg/kg) and 100 % oxygen, or Althesin (0.03 ml/kg) and 100 % oxygen were given at random to 10 patients for chest physiotherapy. Each patient received each treatment twice. The thiopentone or Althesin was given to the patient over a 30-second period, and 30 seconds later the systolic arterial pressure was measured. Chest physiotherapy was then performed for 5 minutes.

Results

There was a greater increase in I.C.P. when nitrous oxide was used during chest physiotherapy than when 100 % oxygen alone was used ($0.02 > P > 0.01$) (fig. 1) (9).

In 2 patients A-waves (7) occurred during physiotherapy with nitrous oxide, but an A-wave also occurred in one patient given physiotherapy with 100 % oxygen.

There was a statistically-significant reduction in the I.C.P. increase associated with the chest physiotherapy when thiopentone and Althesin were used, compared with 100 % oxygen alone. This reduction in I.C.P. change was achieved without significant arterial hypotension.

Discussion

Noscious stimulation causes an increase in I.C.P. in patients with head injury by causing a reflex increase in CBF and cerebral blood volume. Chest physiotherapy also causes I.C.P. increases in patients with head injury (3). These could be due partially to noxious stimulation causing systemic hypertension and cerebral activation, and partially to the increase in

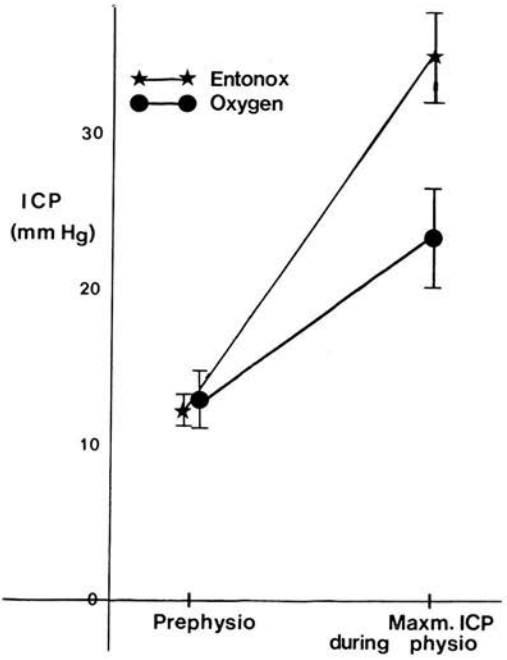

FIG. 1. — Comparison of the increases in ICP with chest physiotherapy during Entonox (50 % nitrous oxide in 50 % oxygen) and 100 % oxygen administration in patients with severe head injuries. The bars represent the standard errors of the means. (Reproduced from : Moss E., McDowall D.G. ICP increases with 50 % nitrous oxide in oxygen in severe head injuries during controlled ventilation. *Brit. J. Anaesth., 51,* 757-761, 1979, by kind permission of the Editor and publishers.)

central venous pressure caused by chest hyperinflation and compression. Such increases in I.C.P. could be detrimental in that they may cause or worsen brain shifts, or reduce cerebral perfusion pressure.

Anesthetic agents might be expected to reduce the increases in I.C.P. associated with chest physiotherapy, either by an analgesic effect, as in the case of nitrous oxide, or by reducing I.C.P. as do thiopentone (5) and Althesin (19). We have shown that 50 % nitrous oxide in 50 % oxygen exacerbates the increases in I.C.P. associated with chest physio-

therapy (9). This can be explained by the I.C.P. increase which nitrous oxide causes in patients with head injury (9, 17), which is probably caused by cerebral vasodilation (8, 13, 14, 18). Schulte am Esch and his colleagues (17) showed an average increase in I.C.P. of 15 mm Hg with 66.6 % nitrous oxide and Moss and McDowall (9), using 50 % nitrous oxide, showed an average increase of 4 mm Hg. This I.C.P. increase more than offsets any benefit gained from the analgesic action of nitrous oxide during chest physiotherapy.

Thiopentone and Althesin were effective in reducing the I.C.P. changes with chest physiotherapy in these patients with severe head injuries, but there were still some unacceptably large increases in I.C.P. during chest physiotherapy using both agents, particularly Althesin. This is possibly because the doses used were too small, and we are at present conducting a further study using thiopentone (4.5 mg/kg) and Althesin (0.045 ml/kg). With the smaller doses of these agents, the changes in arterial pressure and cerebral perfusion pressure were not clinically significant. With the larger doses significant hypotension may be caused, and this possibility is the subject of further investigation.

Thus, the rapid reduction in I.C.P. caused by thiopentone and Althesin is useful in reducing the I.C.P. changes during chest physiotherapy in head-injured patients, and can also be used to reduce high I.C.P. rapidly. Nitrous oxide exacerbates the I.C.P. increases which occur during chest physiotherapy in head-injured patients, and this would suggest that nitrous oxide should not be used for analgesia in head-injured patients.

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* *

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RESUME

E. MOSS, J.S. GIBSON et D.G. McDOWALL. — *Emploi de drogues anesthésiques pour réduire les changements de pression intracrânienne chez des traumatisés crâniens.*

La physiothérapie de la cage thoracique occasionne des augmentations de la pression intracrânienne chez des patients avec des traumatismes crâniens sévères. Chez des traumatisés crâniens sévères hyperventilés artificiellement ($Paco_2$ 3,3 - 4 kPa), 50 % de protoxyde d'azote et 50 % d'oxygène potentialisent les augmentations de la pression intracrânienne associée avec la physiothérapie de la cage thoracique, tandis que le thiopentone et l'Althésine réduisent ces changements de pression intracrânienne.

SAMENVATTING

E. MOSS, J.S. GIBSON en D.G. McDOWALL. — *Gebruik van anesthetische stoffen om de intracraniële drukveranderingen te verminderen bij hersengetraumatiseerde patiënten.*

Borstkasfysiotherapie veroorzaakt stijgingen van de intracraniële druk bij patiënten met hersentraumata. Bij mechanisch gehyperventileerde ($Paco_2$ 3,3 - 4 kPa) zware hersentraumata patiënten, deed 50 % lachgas met 50 % zuurstof de intracraniële druk toename geassocieerd met borstkasfysiotherapie verergeren, dan wanneer thiopentone en Althesine deze intracraniële druk veranderingen verminderden.

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EFFECTS OF TRACHEAL INTUBATION ON INTRACRANIAL PRESSURE FOLLOWING INDUCTION OF ANAESTHESIA WITH THIOPENTONE OR ALTHESIN IN PATIENTS UNDERGOING NEUROSURGERY

E. Moss, D. Powell, R. M. Gibson and D. G. McDowall

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SUMMARY

Intracranial pressure (i.c.p.) and mean arterial pressure (m.a.p.) were studied in 20 patients during the induction of anaesthesia for craniotomy. Tubocurarine was administered as the muscle relaxant and either thiopentone or Althesin for the induction of anaesthesia. No significant differences were found in the i.c.p. changes with induction, intubation or pharyngeal packing, between the thiopentone and the Althesin groups. Except for two patients (one in each group) the increases in i.c.p. associated with intubation were small. In these two patients moderate increases from normal values to 28 and 37 mm Hg were recorded, but in one of these patients coughing and straining followed intubation. Marked decreases in m.a.p. were noted in both groups, but the recovery of m.a.p. was significantly more rapid in the Althesin group. Only two patients had i.c.p. values greater than 20 mm Hg before operation and in neither did i.c.p. increase above control values during induction and intubation. Packing the pharynx produced minimal changes in i.c.p. in all patients.

Increases in intracranial pressure (i.c.p.) and mean arterial pressure (m.a.p.) occurring at the time of laryngoscopy and intubation were described first by Stephen and colleagues (1954). Such changes in i.c.p. are likely to be more marked in neurosurgical patients especially those with increased i.c.p. caused by tumour or other intracranial space-occupying lesion (Shapiro et al., 1972b). In addition it has been suggested that these increases in i.c.p. may lead to transcompartmental herniation of brain tissue (Shapiro et al., 1972a). An increase in m.a.p. is a well-recognized response to intubation (King et al., 1951; DeVault, Greifenstein and Harris, 1960) which may accentuate cerebral oedema in patients with intracranial pathology. Thiopentone and Althesin have been shown to decrease i.c.p. (Horsley, 1937; Turner et al., 1973), presumably by decreasing cerebral blood flow (Pierce et al., 1962; Sari et al., 1976). Thus both these agents might mitigate the above i.c.p. changes. This paper describes a randomized trial comparing the effects of thiopentone with those of Althesin on i.c.p. and m.a.p. during the induction of anaesthesia.

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METHOD

Twenty patients undergoing craniotomy were studied. All gave their informed consent for the study. Each patient was premedicated with diazepam 10 mg i.m., except for one patient who received papaveretum 10 mg and hyoscine 0.2 mg. Anaesthesia was induced in 10 patients with thiopentone and in 10 with Althesin, the choice of agent being randomized. After a preliminary Allen test, a cannula was placed in one radial artery following infiltration of local analgesic. I.v. lines were inserted subsequently. A burr hole was made under local analgesia, and a catheter was inserted into a lateral ventricle. The arterial cannula and the ventricular catheter were connected to pressure transducers and the pressures were displayed on a chart recorder. The zero for the arterial pressure was at heart level and the reference point for i.c.p. was the external auditory meatus.

Once m.a.p. and i.c.p. were stable, tubocurarine 45 mg was given (40 mg in one frail woman). This was followed immediately by an induction dose of thiopentone (range 250–400 mg) or Althesin (range 3–5 ml), the drug being given until there was loss of the eyelash reflex. The patients were then hyperventilated moderately with nitrous oxide and oxygen for 2 min, via a face mask, by hand compression of the reservoir bag. Exactly 2 min after the completion of the thiopentone or Althesin injection, laryngoscopy and intubation were performed. After intubation the

patient was ventilated mechanically and a pharyngeal pack was inserted. Ventilation was adjusted to produce moderate hypocapnia by reference to an infra-red carbon dioxide analyser. In all patients arterial blood-gas tensions were estimated once the patient was established on the ventilator. However, in addition, in the last six patients in the series the arterial blood-gas tensions were estimated immediately before the induction of anaesthesia and immediately before intubation. From the chart records the following measurements were made: (1) m.a.p. and i.c.p. in the 5 min immediately before induction of anaesthesia (hereafter described as control m.a.p. and i.c.p.) and at 1, 2, 3, 4 and 5 min after induction; (2) m.a.p. and i.c.p. immediately before laryngoscopy and (3) at the point of maximum i.c.p. in the first 60 s after intubation. From these measurements cerebral perfusion pressure (c.p.p.) was calculated by subtracting the values of i.c.p. from the corresponding values of m.a.p.

RESULTS

The indications for craniotomy and the i.c.p. values in the individual patients are presented in table I. There was no significant difference in control mean i.c.p. between the two groups. However, two patients (one in each group) were noted to have control i.c.p. values of greater than 20 mm Hg; these results have been excluded from the statistical analysis and are discussed separately later. The two groups were similar with regard to age and sex distribution. The thiopentone group had an average age of 51.1 yr (range 33–66 yr), the Althesin group 55.1 yr (range 43–71 yr).

The values of m.a.p. obtained in the individual patients are displayed in table II. The difference

TABLE I. *Intracranial pathology and mean intracranial pressure (mm Hg)*

Patient (age, yr)	Pathology		Control (pre-induction)	1 min	2 min	Max. i.c.p. in 1st min after intubation	3 min	4 min	5 min
Thiopentone									
A (59)‡	Glioblastoma†		22.5	8.5	9	13	15	16	12
B (47)	Metastatic carcinoma†*		13	11	11	14	14	14	13
C (46)	Pituitary tumour*		3	2.5	4	9	8	8	7
D (41)	Dural repair		15	13	15	28	28	19	16.5
E (61)	Pituitary tumour		9	11	8	10	10	9	9.5
F (66)	Metastatic carcinoma†?		10	9.5	9	12	10	10	15
G (49)	Meningioma		9	15	15	16	13	13	13.5
H (63)	Metastatic carcinoma		5	4	3	4.5	4	4	3.5
I (33)	Aneurysm		15.5	8.5	9.5	17	15.5	19	28
J (46)	Aneurysm†*		12.5	9	8.5	8	7.5	9.5	9.5
		Mean	10.2						
		SD	4.27						
		SEM	1.42						
Althesin									
K (60)‡	Glioblastoma		30	10	9	15	12	14	13
L (59)	Meningioma		18	12	12	15	12	10	11
M (47)	Aneurysm		14	11	12	15	12	10	10
N (56)	Pituitary tumour		9	9	8	10	9	8	9
O (57)	Aneurysm		6.5	5	5	6	5	5	2
P (45)	Pituitary tumour		6	5.5	2	4.5	3.5	2	4.5
Q (43)	Meningioma*		16	17	14	15.5	15.5	15	15
R (54)	Aneurysm		11.5	8.5	6	13	11	12.5	14.5
S (59)	Meningioma†		12.5	14	9.5	11.5	10.5	10	9
T (71)	Meningioma		9.5	9	12.5	37	34.5	27.5	13
		Mean	11.4						
		SD	4.11						
		SEM	1.37						

* Papilloedema before operation; † Dexamethasone before operation; ‡ patients A and K were excluded from the statistical analysis (see text); ?—fundus could not be visualized.

TABLE II. *Mean arterial pressure (mm Hg)*

Patient	Control (pre-induction)	1 min	2 min	Max. m.a.p. in 1st min after intubation	3 min	4 min	5 min
Thiopentone							
A†‡	95	65	55	68	70	73	70
B†*	123	110	107	112	112	110	103
C*	120	67	63	100	87	95	130
D	107	38	48	87	87	100	90
E	90	58	53	57	57	57	55
F†?	103	53	52	31	48	53	67
G	97	43	48	48	43	42	40
H	107	73	53	52	63	95	108
I	83	25	13	25	22	28	35
J†*	127	105	65	73	63	73	77
Mean	106.3						
SD	15.01						
SEM	5.00						
Althesin							
K‡	103	88	70	110	113	113	98
L	112	55	70	93	93	105	103
M	135	73	88	93	102	112	117
N	98	35	30	33	31	28	27
O	100	70	40	70	80	100	—
P	113	107	93	133	133	120	123
Q*	77	77	63	113	113	92	87
R	148	113	107	200	200	170	200
S†	110	96	57	88	93	120	123
T	117	92	63	117	117	132	127
Mean	112.2						
SD	20.67						
SEM	6.89						

* Papilloedema before operation; † dexamethasone before operation; ‡ patients A and K were excluded from the statistical analysis (see text); ?—fundus could not be visualized.

between the two control m.a.p. (106 mm Hg (SD 15) and 112 mm Hg (SD 21)) was not statistically significant. In five of the 20 patients, m.a.p. decreased to less than 50 mm Hg following induction of anaesthesia, in one patient to less than 20 mm Hg. At 5 min after induction m.a.p. was greater than 50 mm Hg in all except three patients.

Table III depicts the changes in i.c.p. with intubation related to the control value and to the value obtained immediately before laryngoscopy. In each group mean i.c.p. decreased following the induction of anaesthesia and increased slightly following laryngoscopy and intubation. There was no significant difference between the two groups except at 5 min after induction, when mean i.c.p. was significantly less in the Althesin group ($0.05 > P > 0.02$). There was no significant difference between the groups in the response of i.c.p. to intubation. There was a significant correlation between the pre-induction i.c.p. and the increase in i.c.p. associated with intubation in the thiopentone group ($0.05 > P > 0.02$), but there was no such correlation in the Althesin group.

Table IV shows the changes of m.a.p. from control in the first 5 min following induction. In the last column the changes in m.a.p. produced by laryngoscopy and intubation are presented. As already stated, the control m.a.p. was very similar but the m.a.p. after induction of anaesthesia with tubocurarine and thiopentone was at each stage lower than those obtained following tubocurarine and Althesin. This difference reached significance ($0.05 > P > 0.02$) at approximately 3 min after the induction of anaesthesia which, incidentally, was the time at which the maximum m.a.p. was reached after intubation, and remained significant ($0.02 > P > 0.01$) at 4 min, but

TABLE III. *I.c.p.—changes from control and changes following intubation compared with prelaryngoscopy value (mm Hg)*

Patient	1 min	2 min	Max. change from control in 1st min after intubation	3 min	4 min	5 min§	Changes from pre-laryngoscopy value following intubation
Thiopentone							
A†‡	−14	−13.5	−9.5	−7.5	−6.5	−10.5	+12
B†*	−2	−2	+1	+1	+1	0	+3
C*	−0.5	+1	+6	+5	+5	+4	+5
D	−2	0	+13	+13	+4	+1.5	+13
E	+2	−1	+1	+1	0	+0.5	+2
F†?	−0.5	−1	+2	0	0	+5	+3
G	+6	+6	+7	+4	+4	+4.5	+1
H	−1	−2	−0.5	−1	−1	−1.5	+1.5
I	−7	−6	+1.5	0	+3.5	+12.5	+7.5
J†*	−3.5	−4	−4.5	−5	−3	−3	−0.5
Mean	−0.9	−1	+2.9	+2.0	+1.5	+2.6	+3.9
SD	3.58	3.35	5.06	5.02	2.74	4.61	4.12
SEM	1.19	1.12	1.69	1.68	0.91	1.54	1.37
Althesin							
K‡	−20	−21	−15	−18	−16	−17	+6
L	−6	−6	−3	−6	−8	−7	+3
M	−3	−2	+1	−2	−4	−4	+3
N	0	−1	+1	0	−1	0	+2
O	−1.5	−1.5	−0.5	−1.5	−1.5	−4.5	+1
P	−0.5	−4	−1.5	−2.5	−4	−1.5	+2.5
Q*	+1	−2	−0.5	−0.5	−1	−1	+1.5
R	−3	−5.5	+1.5	−0.5	+1	+3	+7
S†	+1.5	−3	−1	−2	−2.5	−3.5	+2
T	−0.5	+3	+27.5	+25	+18	+3.5	+25
Mean	−1.3	−2.4	+2.7	+1.1	−0.3	−1.7	+5.2
SD	2.35	2.69	9.40	9.13	7.34	3.48	7.6
SEM	0.78	0.90	3.03	3.04	2.45	1.16	2.53

* Papilloedema before operation; † dexamethasone before operation; ‡ patients A and K were excluded from the statistical analysis (see text); ?—fundus could not be visualized; § significance between thiopentone and Althesin groups: $0.05 > P > 0.02$.

not at 5 min. The increase in arterial pressure which followed within 60 s of intubation was significantly greater in the Althesin group ($0.02 > P > 0.01$).

There were no significant differences between the two groups in mean Pa_{CO_2} at the time of intubation (thiopentone 4.0 ± 1.2 kPa, Althesin 4.5 ± 1.1 kPa) or at 5 min after induction (thiopentone 3.8 ± 0.9 kPa, Althesin 4.2 ± 0.8 kPa).

The changes in m.a.p. and i.c.p. caused by packing the pharynx were minimal and there was no statistically significant difference between the two groups (table V).

In the two patients with values of i.c.p. greater than 20 mm Hg the changes in m.a.p. were similar to those noted in patients with i.c.p. less than 20 mm Hg. In these two patients i.c.p. decreased markedly following the administration of the induction agent and tubocurarine (by 14 mm Hg and 20 mm Hg; see table III) and did not increase above the control value with intubation.

DISCUSSION

In this study, in which anaesthesia was induced with either thiopentone or Althesin, and muscular relaxation was produced with tubocurarine, the increases in i.c.p. which resulted from intubation were small. Thus, of the 18 patients with a control mean i.c.p. of less than 20 mm Hg, the mean change from control with intubation was 2.8 mm Hg (range −4.5 to 27.5 mm Hg) and the mean change from the immediate

TABLE IV. *Arterial pressure—changes from control and changes following intubation compared with prelaryngoscopy value (mm Hg)*

Patient	1 min	2 min	Max. change from control in 1st min after intubation	3 min	4 min	5 min	Changes from pre-laryngoscopy value following intubation
Thiopentone							
A†‡	−30	−40	−27	−25	−22	−25	+15
B†*	−13	−16	−11	−11	−13	−20	+20
C*	−53	−57	−20	−33	−25	+10	+37
D	−69	−59	−20	−20	−7	−17	+32
E	−32	−37	−33	−33	−33	−35	+12
F†?	−50	−51	−72	−55	−50	−36	+4
G	−54	−49	−49	−54	−55	−57	0
H	−34	−54	−55	−44	−12	+1	+10
I	−58	−70	−58	−61	−55	−48	+12
J†*	−22	−62	−54	−64	−54	−50	+8
Mean	−42.8	−50.6	−41.3	−40.2	−33.8	−28.0	15.0
SD	18.42	15.87	20.99	19.82	20.23	23.21	12.43
SEM	6.14	5.29	6.99	6.61	6.74	7.74	4.14
Althesin							
K‡	−15	−33	+7	+10	+10	−5	+40
L	−57	−42	−19	−19	−7	−9	+30
M	−62	−47	−42	−33	−23	−18	+20
N	−63	−68	−65	−67	−70	−71	+3
O	−30	−60	−30	−20	0	—	+30
P	−6	−20	+20	+20	+7	+10	+40
Q*	0	−14	+36	+36	+15	+10	+45
R	−35	−41	+52	+52	+22	+52	+93
S†	−14	−53	−22	−17	+10	+13	+36
T	−25	−54	0	0	+15	+10	+55
Mean	−32.4	−44.3	−7.8	−5.3	−3.4	−0.4	39.1
SD	23.90	17.71	38.06	36.70	28.40	35.09	25.09
SEM	7.97	5.90	12.69	12.23	9.47	12.41	8.36
P§			$0.05 > P > 0.02$	$0.05 > P > 0.02$	$0.02 > P > 0.01$		$0.02 > P > 0.01$

* Papilloedema before operation; † dexamethasone before operation; ‡ patients A and K were excluded from the statistical analysis (see text); ?—fundus could not be visualized; § significance between thiopentone and Althesin groups.

pre-laryngoscopy value was 4.6 mm Hg (range −0.5 to 25 mm Hg). Of the four patients with papilloedema, none showed an increase of more than 6 mm Hg from control i.c.p. at intubation. Except for two patients, all the increases in i.c.p., as a result of intubation, were 7 mm Hg or less. One patient showed an increase of 13 mm Hg from the control value. This was related to coughing and straining on the endotracheal tube. In the other patient an increase of 27.5 mm Hg was noted. This patient had a large meningioma but no papilloedema or symptoms of increased i.c.p. before operation. However, during cannulation of the ventricle a substantial quantity of cerebrospinal fluid was lost, so this patient may have had a higher i.c.p. before operation than that recorded after cannulation of the ventricle. Also, in this particular patient, Pa_{CO_2} increased by 1.1 kPa between induction of anaesthesia and laryngoscopy, Pa_{CO_2} being 5.2 kPa at the time of intubation. This may have been the reason for the marked increase in i.c.p., as this was the only patient in the series who showed an increase in Pa_{CO_2} between induction of anaesthesia and intubation.

There have been several previous studies of changes in i.c.p. occurring with intubation. Shapiro and his colleagues (1972b) found, in patients intubated under suxamethonium, that the increases were greater in those patients who had symptoms or signs of

TABLE V. *Changes in i.c.p. and m.a.p. related to packing the pharynx (mm Hg)*

Patient	I.c.p. before pack	Change in i.c.p.	M.a.p. before pack	Change in m.a.p.
Thiopentone				
A†‡	14	0	112	+15
B†*	8	+0.5	97	+23
C*	24.5	−1	100	0
D	9.5	0	57	0
E	10.5	0	55	+5
F†?	13	0	45	−5
G	4	0	68	+20
H	17	+3	25	+5
I	7.5	+1.5	63	+5
J†*	15	+2	72	−5
Mean		+0.6		+6.3
SD		1.20		9.90
SEM		0.54		4.43
Althesin				
K‡	11.5	0	97	+16
L	12.5	−0.5	110	+8
M	10	0	30	−3
N	5	0	80	+10
O	5.5	+1.5	113	+12
P	10	0	92	+11
Q*	12.5	+2	175	+25
R	10	−0.5	95	+23
S†	27.5	+2	118	+19
T	15	−2.5	110	0
Mean		+0.2		+12.1
SD		1.36		9.10
SEM		0.61		4.07

* Papilloedema before operation; † dexamethasone before operation; ?—fundus could not be visualized.

increased i.c.p. before operation. They found increases in i.c.p. from the pre-induction value averaging 22 mm Hg (range 19–30 mm Hg) and from the pre-laryngoscopy value averaging 27 mm Hg (range 20–34 mm Hg) in their "increased i.c.p. group". The increases in their "normal i.c.p. group" averaged 1.5 mm Hg (range −7 to +5 mm Hg) and 6 mm Hg (range 4–7 mm Hg) respectively. The changes did not, however, relate to the measured i.c.p. values immediately before induction of anaesthesia. Burney and Winn (1975), who also used suxamethonium, showed increases in i.c.p. similar to those of Shapiro and colleagues, and in our opinion their data, like Shapiro's, showed no correlation between the initial values of i.c.p. and the increase associated with intubation. This discrepancy between clinical signs of i.c.p. and the pre-induction value of measured i.c.p. is probably explained by the pressure/volume relationship of the intracranial space. Thus, considerable intracranial compression can be present when i.c.p. is either normal or increased only slightly. In these circumstances the varying degrees of intracranial compression result in different i.c.p. changes with such stimulation as intubation.

The reports in the literature which showed the greatest increases in i.c.p. with intubation were those of Greenbaum and colleagues (1975) who described increases of as much as 80 mm Hg with peaks of 100 mm Hg, and Misfeldt, Jörgensen and Rishöj (1974) who described increases of up to 50 mm Hg with peaks of more than 80 mm Hg. These workers used suxamethonium for intubation.

McLeskey and colleagues (1974) and Lewelt, Moszynski and Kozniewska (1976) used pancuronium to produce muscular relaxation for intubation while measuring i.c.p. McLeskey and colleagues found much smaller increases in i.c.p. when pancuronium was used, as compared with suxamethonium. None the less, despite using very large doses of thiopentone they had marked increases in m.a.p. in some patients in their pancuronium group. Lewelt and his co-workers found no significant increase in mean i.c.p. at intubation, provided that adequate time was allowed for the relaxant to act. They did not induce anaesthesia until pancuronium had produced a full muscular relaxation, and they did not record arterial pressure during induction. In terms of the magnitude of i.c.p. changes observed, the results of Lewelt, Moszynski and Kozniewska (1976) and McLeskey and colleagues (1974) are closest to those described here, probably because in all three studies a competitive muscle relaxant was used. Suxamethonium may increase the i.c.p. change with intubation because of the muscle fasciculations, or the direct action of the drug, or because the duration of hyperventilation before intubation is likely to be shorter than that which exists when a long-acting muscle relaxant is used. The longer period of hyperventilation in patients receiving a long-acting muscle relaxant produces hypocapnia which may partially restore defective autoregulation (Paulson, Olesen and Christensen, 1972) and thus protect the cerebral circulation against any sudden increase in m.a.p.

We believe that large changes in i.c.p. associated with intubation are important in neurosurgery because they may cause transcompartmental pressure gradients and so induce brain shifts, may precipitate cerebral oedema if secondary to an acute episode of systemic hypertension or may result in an inadequate c.p.p. In stating that increases in i.c.p. associated

with intubation are harmless, Misfeldt, Jörgensen and Rishöj (1974) have concentrated only on c.p.p. and did not consider the other factors discussed above, which are probably of greater importance in this context.

Tubocurarine was chosen for this study, since it is commonly used in neurosurgery, partly because the hypotension produced (Thomas, 1957) may reduce bleeding during reflection of skin and muscle. In this respect it may have an advantage over pancuronium which does not produce hypotension and may, indeed, produce increases in arterial pressure (Kelman and Kennedy, 1971; Gordon, 1975). In this study tubocurarine and an i.v. induction agent produced significant decreases in m.a.p., an effect which lasted for a few minutes only. M.a.p. decreased to a similar degree with Althesin and thiopentone, but recovery was more rapid and complete in the Althesin group. Mean c.p.p. was reduced to less than 60 mm Hg in 75% of the patients and to less than 40 mm Hg in 20% of the patients. A mean c.p.p. of 50 mm Hg is at the lower end of the autoregulation range (Olesen, 1973; Lassen, 1974). However, there was no clinical evidence in the period after operation that this decrease in c.p.p. affected the recovery of the patient in any way, and indeed it may have been a factor in avoiding large increases in i.c.p. on intubation. The wide inter-patient variation in m.a.p. response to tubocurarine is in keeping with the observations of Thomas (1957). Unlike Tarkkanen, Laitinen and Johansson (1974), we saw no increases in i.c.p. which could be attributed to tubocurarine. The fact that we ventilated our patients immediately after the administration of the tubocurarine may explain this difference in results.

Four of the patients were receiving dexamethasone before operation, but their i.c.p. response to intubation did not appear to differ from the other patients.

There has been no previous reported comparison between thiopentone and Althesin for the induction of anaesthesia for craniotomy. Our results show that there was no significant difference between these two agents in their effects on i.c.p. when combined with tubocurarine, and that there was no difference between the two groups with regard to change in i.c.p. following intubation or packing the pharynx.

The positive correlation between pre-induction i.c.p. and the increase in i.c.p. associated with intubation in the thiopentone group only just reaches statistical significance, and the i.c.p. increases with intubation in this series were small. We conclude, therefore, that the changes in i.c.p. at intubation are similar with thiopentone and Althesin even in patients with increased i.c.p.

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EFFETS DE L'INTUBATION TRACHEALE SUR LA PRESSION INTRACRANIENNE APRES INDUCTION DE L'ANESTHESIE A L'AIDE DE THIOPENTONE OU D'ALTHESINE SUR DES MALADES SUBISSANT UNE INTERVENTION NEUROCHIRURGICALE

RESUME

On a étudié sur 20 malades la pression intracranienne (ICP) et la tension artérielle moyenne (m.a.p.) pendant l'induction de l'anesthésie pour une craniotomie. On a administré de la tubocurarine en tant que décontracturant musculaire, et soit du thiopentone, soit de l'althésine pour l'induction de l'anesthésie. On n'a trouvé aucune différence importante dans les variations de l'ICP, lors de l'induction, de l'intubation ou du bourrage pharyngien entre le groupe soumis au thiopentone et celui soumis à l'althésine. A l'exception de deux malades (un dans chaque groupe), les augmentations de l'ICP associées à l'intubation ont été faibles. On a enregistré sur ces deux malades, des augmentations modérées allant des valeurs normales à 28 et 37 mm Hg, mais sur l'un de ces deux malades l'intubation a été suivie de toux et de fatigue. On a noté sur les deux groupes une diminution marquée de la m.a.p., mais la récupération de la m.a.p. a été beaucoup plus rapide dans le groupe anesthésié à l'althésine. Seuls deux malades ont eu des valeurs ICP supérieures à 20 mm Hg avant l'opération et sur aucun d'eux l'ICP n'a augmentée au-delà des valeurs témoins pendant l'induction et l'intubation. Le bourrage du pharynx n'a produit que des variations minimales dans l'ICP de tous les malades.

WIRKUNGEN TRACHEALER INTUBATION AUF DEN INTERKRANIELLEN DRUCK NACH NARKOSEEINLEITUNG MIT THIOPENTON ODER ALTHESIN VOR NEUROCHIRURGISCHEN EINGRIFFEN

ZUSAMMENFASSUNG

Der interkranielle Druck (i.c.p.) und der mittlere arterielle Druck (m.a.p.) wurden an 20 Patienten während Narkoseeinleitung für eine Kraniotomie gemessen. Zur Muskelentspannung wurde Tubocurarin, für die Narkose entweder Thiopenton oder Althesin verabreicht. Zwischen diesen beiden Gruppen ergaben sich keine wesentlichen Unterschiede, was Veränderungen des i.c.p. bei Einleitung, Intubation oder pharingealer Packung betrifft. Abgesehen von zwei Patienten (einer pro Gruppe) waren die mit Intubation verbundenen Anstiege von i.c.p. gering. Bei diesen beiden Patienten wurden mässige Anstiege von den Normalwerten auf 28, bezw. auf 37 mm Hg berichtet, doch bei einem dieser Patienten kam es nach der Intubation zu Husten und Anspannung. Deutlich Verringerungen von m.a.p. wurden in beiden Gruppen festgestellt, aber die Wiederherstellung dieser Werte ging in der Althesin-Gruppe wesentlich schneller vor sich. Nur zwei Patienten hatten vor der Operation höhere i.c.p.-Werte als 20 mm Hg, und bei keinem der beiden stieg dieser Wert während Einleitung und Intubation über den Kontrollwert. Die pharingeale Packung führte bei allen Patienten nur zu minimalen Änderungen des i.c.p.

EFECTOS QUE EJERCE LA INTUBACION TRAQUEAL SOBRE LA PRESION INTRACRANEAL SIGUIENDO LA INDUCCION DE ANESTESIA CON TIOPENTONA O ALTESINA EN PACIENTES SOMETIDOS A NEUROCIRUGIA

SUMARIO

Se estudiaron la presión intracraneal (i.c.p.) y la presión arterial media (m.a.p.) en 20 pacientes durante la inducción de anestesia para craneotomía. Se administró tubocurarina como relajante muscular y tiopentona o Altesina para la inducción de anestesia. No se descubrieron diferencias significativas en los cambios de la i.c.p. mediante inducción, intubación y taponamiento faringeal entre los grupos de tiopentona y Altesina. Exceptuando dos pacientes (uno en cada grupo), los aumentos en la i.c.p. asociada con intubación fueron de escasa magnitud. En estos dos pacientes se registraron aumentos moderados de los valores normales a 28 y 37 mm Hg, pero uno de estos pacientes sufrió tos y esfuerzo después de la intubación. Se notaron marcadas disminuciones en la m.a.p. en ambos grupos, pero la recuperación de la m.a.p. fue significativamente más rápida en el grupo de Altesina. En solo dos pacientes se presentaron valores de i.c.p. superiores a 20 mm Hg antes de la operación y en ninguno de ellos aumentó el i.c.p. en más de los valores de control durante la inducción e intubación. El taponamiento de la faringe produjo cambios mínimos en la i.c.p. de todos los pacientes.

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SUMMARY

Ten patients with intracranial lesions, anaesthetized with thiopentone and nitrous oxide (70%) in oxygen (30%) received etomidate 0.2 mg kg^{-1} i.v. Ventilation was controlled in each patient. Intracranial pressure (i.c.p.) and mean arterial pressure (m.a.p.) were recorded. I.c.p. decreased significantly in all patients ($0.01 > P > 0.001$). Although Pa_{CO_2} decreased during the period of measurement, the extent and time-course of this change suggested that it was not mainly responsible for changes in i.c.p. M.a.p. decreased in most patients, but the decrease was statistically significant only at 3 and 4 min after the administration of etomidate ($0.05 > P > 0.02$). The changes in cerebral perfusion pressure (c.p.p.) and heart rate were not clinically or statistically significant. We conclude that etomidate can be used for the induction of anaesthesia in patients with intracranial space-occupying lesions without increasing i.c.p. or seriously reducing c.p.p.

All the agents used commonly i.v. to induce anaesthesia have been shown to decrease intracranial pressure (i.c.p.) (Horsley, 1937; Hunter, 1972; Turner et al., 1973) and cerebral blood flow (c.b.f.) (Pierce et al., 1962; Herrschaft et al., 1975; Sari et al., 1976), with the sole exception of ketamine, which increases both i.c.p. (Evans et al., 1971; Gardner, Olson and Lichtiger, 1971; Takeshita, Okuda and Sari, 1972) and c.b.f. (Dawson, Michenfelder and Theye, 1971; Takeshita, Okuda and Sari, 1972). Etomidate, an i.v. agent, has been introduced recently for induction of anaesthesia and has the advantages of cardiovascular stability (Doenicke, 1974; Morgan, Lumley and Whitwam, 1975; Holdcroft et al., 1976; Rifat, Gamulin and Gemperle, 1976; Famewo and Odugbesan, 1977; Ghoneim and Yamada, 1977; Lees and Hendry, 1977; Patschke et al., 1977), freedom from marked respiratory depression (Doenicke, 1974; Morgan, Lumley and Whitwam, 1975, 1977; Famewo and Odugbesan, 1977, 1978; Ghoneim and Yamada, 1977), and rapid inactivation (Kay, 1976; Lees and Hendry, 1977). It has been shown by Herrschaft and his co-workers (1975) that etomidate decreases c.b.f. in normal man, and thus it would be expected to reduce i.c.p. also. This study was undertaken to determine the effect of etomidate on i.c.p. in patients with intracranial pathology who were about to undergo craniotomy, and thus to determine its suitability for use in patients with intracranial space-occupying lesions.

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METHODS

Ten patients with intracranial lesions requiring craniotomy were investigated. All gave their informed consent for the study. If considered necessary, the patients were premedicated with diazepam 10 mg i.m. Anaesthesia was induced with thiopentone, which was given until the eyelash reflex was obtunded, and was maintained with nitrous oxide 70% in oxygen. Ventilation was controlled using a Manley Pulmovent ventilator and tubocurarine 45 mg was administered to produce neuromuscular blockade. The volume of ventilation was adjusted to produce normocapnia and this was maintained constant throughout the period of the study. Allen's test was performed on all the patients and, if there was adequate ulnar collateral circulation, a radial artery cannula was inserted. After infiltration of the scalp with local analgesic a burr hole was made, through which a catheter was inserted into a lateral ventricle. The radial artery and ventricular cannulae were connected to suitably calibrated transducers, the signals from which were amplified and recorded on chart recorders. The zero reference for the arterial transducer was the mid-axillary line (with the patient supine, tilted 10° head-up), and for the ventricular transducer was the external auditory meatus. The arterial pressure and intracranial pressure traces were observed for 5 min before the injection of etomidate 0.2 mg kg^{-1} body

weight given i.v. over a period of 10 s. The arterial pressure and i.c.p. were recorded for 10 min after the administration of the etomidate and before surgery was continued. Cerebral perfusion pressure (c.p.p.) was calculated by subtracting mean i.c.p. from the mean arterial pressure (m.a.p.). From the recordings, the following measurements were made: (i) m.a.p., mean i.c.p. and c.p.p. in the 5 min before the injection of etomidate (control values for m.a.p., mean i.c.p. and c.p.p.); (ii) m.a.p., mean i.c.p. and c.p.p. at 1-min intervals for 10 min after the administration of the etomidate. (Only the results obtained at 2-min intervals are tabulated.)

Samples were taken for measurement of arterial blood-gas tensions just before the administration of the etomidate (initial Pa_{CO_2}) and at 10 min after the administration of etomidate (final Pa_{CO_2}). During the period of measurement the end-tidal carbon dioxide concentration was monitored continuously with an infra-red gas analyser.

RESULTS

The ages and diagnoses of all the patients and their mean i.c.p. during the control period, and at 2-min intervals after the administration of etomidate are in table I. It was found that i.c.p. decreased initially in all the patients and then started to increase, but in only two patients, it returned to control values within the 10 min (fig. 1). This decrease from control was statistically significant ($0.01 > P > 0.001$) at the 1st min after injection, and remained significant at the 1% level or greater for the 10 min of measurement.

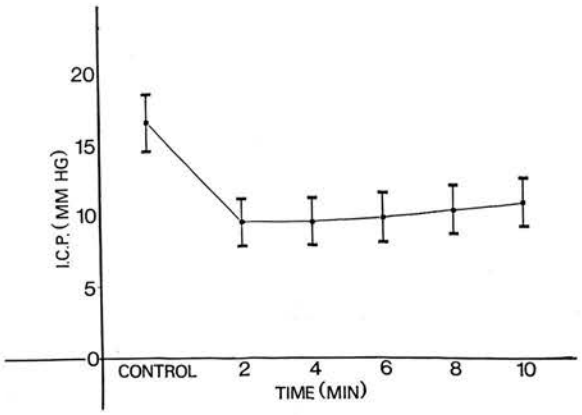

FIG. 1. The average i.c.p. (±SEM) (mm Hg) for the 10 patients before (control) and after the administration of etomidate 0.2 mg kg^{-1}.

There was a small decrease in m.a.p. in eight patients which was significant statistically at 3 and 4 min after the administration of etomidate ($0.05 > P > 0.02$) (table II). The heart rate decreased slightly in eight patients but did not differ significantly from the control value at any time.

On average c.p.p. decreased slightly, but this decrease never reached statistical significance (table III, fig. 2). In only one patient did the c.p.p. decrease to less than 60 mm Hg (patient B, minimum c.p.p. = 54 mm Hg).

TABLE I. *The mean intracranial pressure (mm Hg), diagnoses and ages (yr) of the 10 patients. Control indicates the mean pressure in the 5 min before administration of etomidate. The probability values represent the significance of the changes in i.c.p. from the control value*

Patient and age (yr)	Diagnosis	Control i.c.p.	2 min	4 min	6 min	8 min	10 min
A (51)	Aneurysm	14	9	9	6	8	8
B (46)	Pituitary tumour	28	22	22	23	23	23
C (35)	Glioblastoma	16	10	11	12	14	16
D (22)	Glioblastoma	16	11	11	11	12	13
E (66)	Pituitary tumour	9	4	4	4	5	6
F (71)	Pituitary tumour	9	6	5	6	6	6
G (70)	Pituitary tumour	13	6	6	6	6	6
H (33)	Pituitary tumour	26	11	11	12	11	13
I (61)	Glioblastoma	21	8	7	8	8	9
J (51)	Meningioma	12	9	10	10	11	11
$\bar{x}$		16.4	9.6	9.6	9.8	10.4	11.1
SD		6.62	4.93	5.08	5.43	5.32	5.43
SEM		2.09	1.56	1.61	1.72	1.68	1.72
P			0.001	<0.001	<0.001	0.01>*P*>0.001	0.01>*P*>0.001

TABLE II. *The mean arterial pressure (mm Hg) of the 10 patients. "Control" indicates the mean pressure in the 5 min before the administration of etomidate. The probability value represents the significance of the change in m.a.p. from the control value*

Patient	Control	2 min	4 min	6 min	8 min	10 min
A	183	185	175	180	180	180
B	102	87	78	77	83	90
C	123	123	122	128	133	135
D	108	108	108	108	108	103
E	87	83	78	83	85	85
F	115	107	107	122	125	120
G	102	93	95	95	90	90
H	133	128	130	140	133	137
I	107	107	105	105	100	100
J	143	112	105	98	103	103
$\bar{x}$	120.3	113.3	110.3	113.6	114.0	114.3
SD	27.39	29.03	28.10	30.47	29.68	29.42
SEM	8.66	9.18	8.89	9.64	9.39	9.30
P			$0.05 > P > 0.02$			

TABLE III. *The cerebral perfusion pressure (mm Hg) of the 10 patients. "Control" indicates the mean cerebral perfusion pressure in the 5 min before the administration of etomidate*

Patient	Control	2 min	4 min	6 min	8 min	10 min
A	169	176	166	174	172	172
B	74	65	56	54	60	67
C	107	113	111	116	119	119
D	92	97	97	97	96	90
E	78	79	74	79	80	79
F	106	101	102	116	119	114
G	89	87	89	89	84	84
H	107	117	119	128	122	124
I	86	99	98	97	92	91
J	131	103	95	88	92	92
$\bar{x}$	103.9	103.7	100.7	103.8	103.6	103.2
SD	28.37	29.72	29.07	32.43	31.02	30.27
SEM	8.97	9.40	9.19	10.26	9.81	9.57

It can be seen (table IV) that in five patients Pa_{CO_2} was in the lower part of the normal range, and in four patients just below the lower limit of normal. One patient was markedly hypocapnic. In most patients there was a slight decrease in Pa_{CO_2} over the 10-min period of measurement, so that mean Pa_{CO_2} decreased by 0.23 kPa (statistically significant: $0.01 > P > 0.001$). The decrease in the end-tidal carbon dioxide concentration occurred usually at between 2 and 7 min after the administration of etomidate.

Figure 3 shows the scatter diagram and regression line for the decrease in i.c.p. after the administration of etomidate plotted against the initial i.c.p. value. The correlation ($r = 0.624$) between decrease in i.c.p. and initial i.c.p. was not significant statistically.

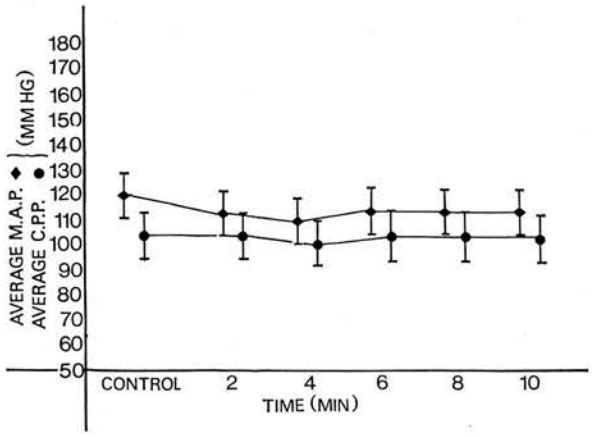

FIG. 2. The average m.a.p., average c.p.p. (±SEM) (mm Hg) for the 10 patients before (control) and after the administration of etomidate 0.2 mg kg^{-1}.

TABLE IV. Pa_{CO_2} *values (kPa) of the 10 patients immediately before the administration of etomidate (initial* Pa_{CO_2}*) and at 10 min after administration of etomidate (final* Pa_{CO_2}*). The probability value refers to the significance of the change in* Pa_{CO_2} *during the period of measurement*

Patient	Initial Pa_{CO_2}	Final Pa_{CO_2}
A	4.67	4.13
B	4.80	4.80
C	4.40	4.40
D	4.13	4.0
E	4.53	4.27
F	4.93	4.67
G	4.53	4.27
H	4.80	4.67
I	5.60	5.33
J	3.07	2.67
$\bar{x}$	4.55	4.32
SD	0.65	0.70
SEM	0.21	0.22
P	$0.01 > P > 0.001$	

DISCUSSION

It is known that thiopentone, methohexitone and Althesin reduce i.c.p. (Horsley, 1937; Hunter, 1972; Turner et al., 1973) and c.b.f. (Pierce et al., 1962; Herrschaft et al., 1975; Sari et al., 1976), but that ketamine increases i.c.p. (Evans et al., 1971; Gardner,

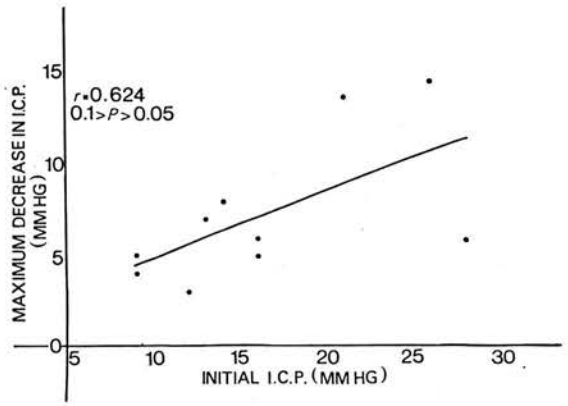

FIG. 3. Comparison of the maximum decrease in i.c.p. produced by etomidate with the initial i.c.p. value.

Olson and Lichtiger, 1971; Wyte et al., 1972) and c.b.f. (Dawson, Michenfelder and Theye, 1971; Takeshita, Okuda and Sari, 1972). In the presence of intracranial space-occupying lesions, it is preferable to use agents which either do not affect i.c.p. or which decrease it. Thus, it is important to determine the effect on i.c.p. of any new anaesthetic agent, such as etomidate, to ascertain its suitability for use in patients with increased i.c.p.

In this study there was a decrease in i.c.p. in all 10 patients following the administration of etomidate i.v. This reduction can be explained almost certainly by the rapid decrease in c.b.f., and thus cerebral blood volume, which is known to occur after the administration of etomidate (Herrschaft et al., 1975). Herrschaft's studies were in normal patients anaesthetized with propanidid, suxamethonium, nitrous oxide, oxygen and halothane 0.1–0.4 vol%. The use of halothane may explain the more short-lived reduction in c.b.f. that they observed (less than 5 min) as compared with the duration of the decrease in i.c.p. that we observed (more than 10 min). The duration of the decrease in i.c.p. seen in our study is more in keeping with the duration of action of etomidate reported in the literature both by Doenicke (1974), who reported that the time to complete recovery after the administration of etomidate 0.3 mg kg^{-1} was approximately 12 min, and by Lewi and Heykants (1978) who found that the plasma concentration decreased by approximately 90% in 16 min after a dose of 0.21 mg kg^{-1}. The numbers in this present series were inadequate to show whether there was a greater decrease in i.c.p. if the i.c.p. was high initially.

The small decrease in Pa_{CO_2} (average 0.23 kPa), noted in most of the patients during the period of measurement, occurred during constant ventilation which had been established for at least 30 min before the administration of etomidate. It may have been a result of a reduction in metabolic rate, and thus a reduction in carbon dioxide production. With one exception this decrease in Pa_{CO_2} occurred between 2 and 7 min after the administration of etomidate, whereas the maximum change in i.c.p. occurred within 90 s, and by 7 min i.c.p. was beginning to increase again. Thus, the influence on i.c.p. of this small change in Pa_{CO_2} was probably minimal.

Although the m.a.p. decreased in all but two patients, the lowest m.a.p. recorded was 77 mm Hg which was above the value at which the autoregulation of c.b.f. ceases and c.b.f. becomes pressure-dependent. The c.p.p. increased in 50% of the patients and decreased in 50%, remaining adequate in all. The heart rate decreased slightly in most of the patients, but the change was not significant statistically. These findings confirm the cardiovascular stability found with etomidate (Doenicke, 1974; Morgan, Lumley and Whitwam, 1975; Holdcroft et al., 1976; Rifat, Gamulin and Gemperle, 1976; Famewo and Odugbesan, 1977; Ghoneim and Yamada, 1977; Lees and Hendry, 1977; Patschke et al., 1977).

There are other possible advantages of etomidate which were not assessed in this study. Plasma histamine concentration does not increase after its administration (Doenicke et al., 1973) (whereas it does after Althesin and propanidid), and as yet there is no reported case of allergic reaction to the drug. In the dose required for anaesthesia, respiratory depression is not a problem (Doenicke, 1974; Morgan, Lumley and Whitwam, 1975, 1977; Famewo and Odugbesan, 1977, 1978; Ghoneim and Yamada, 1977), although this is not so important in neuroanaesthesia as ventilation is usually controlled. Etomidate is metabolized quickly and, judged on clinical grounds in man, is not cumulative (Kay, 1976; Lees and Hendry, 1977). Thus, its use by continuous i.v. infusion may have a place, as an alternative to methohexitone (Hunter, 1972) or Althesin, in maintaining anaesthesia in patients with intracranial space-occupying lesions. The rapid metabolism of the drug and its ability to reduce i.c.p. suggest that it would be suitable for the rapid reduction of i.c.p. in patients with head injuries, or for prophylactic use before chest physiotherapy or other procedures known to increase i.c.p. in this group of patients.

On the basis of this study, we conclude that etomidate would be a useful addition to the drugs

available to the neuroanaesthetist for the induction of anaesthesia, a conclusion which is supported by recent reports by Cunitz, Danhauser and Wickbold (1978) and Schulte am Esch, Pfeifer and Thiemig (1978). In addition, it could be used as an agent for the rapid reduction of i.c.p. and possibly for maintenance of anaesthesia by continuous infusion.

Note added in proof: Since this manuscript was prepared, Renou and colleagues (1978) have published work showing a reduction in c.b.f. following etomidate in patients with intracranial pathology.

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EFFET DE L'ETOMIDATE SUR LA PRESSION INTERCRANIENNE ET SUR LA PRESSION DE PERFUSION CEREBRALE

RESUME

Dix malades ayant des lésions intracrâniennes, anesthésiés au thiopentone et au protoxyde d'azote (70%) dans l'oxygène (30%), ont reçu de l'étomidate par voie intraveineuse à raison de 0,2 mg kg^{-1}. La ventilation a été contrôlée sur

chaque patient. La pression intracrânienne (ICP) et la pression artérielle moyenne (MAP) ont été enregistrées. L'ICP a diminué d'une manière significative chez tous les malades ($0{,}01 > P > 0{,}001$). Bien que la Pa_{CO_2} ait diminué pendant la période ou l'on a pris les mesures, l'importance et le temps de ce changement laissent penser que celle-ci n'a pas été essentiellement responsable des variations de l'ICP. La MAP a diminué chez la plupart des patients, mais cette diminution n'a eu d'importance statistique que 3 et 4 min après l'administration d'étomidate ($0{,}05 > P > 0{,}02$). Les variations de la pression de la perfusion cérébrale (CPP) et de la fréquence cardiaque n'ont eu aucune importance clinique ou statistique. Nous en concluons que l'étomidate peut être utilisé pour l'induction de l'anesthésie sur les malades ayant des lésions intracrâniennes envahissantes et qu'il ne fait pas augmenter l'ICP ou diminuer sérieusement la CPP.

DIE WIRKUNG VON ETOMIDAT AUF INTRAKRANIELLEN UND ZEREBRALEN PERFUSIONSDRUCK

ZUSAMMENFASSUNG

Zehn Patienten mit intrakraniellen Verletzungen erhielten intravenös 0,2 mg kg^{-1} Etomidat, während sie mit Thiopenton und Stickoxyd (70%) in Sauerstoff (30%) narkotisiert waren. Die Beatmung wurde bei allen Patienten kontrolliert. Der intrakranielle Druck (I.C.P.) und der mittlere arterielle Druck (M.A.P.) wurden aufgezeichnet. I.C.P. sank wesentlich bei allen Patienten ($0{,}01 > P > 0{,}001$). Obwohl Pa_{CO_2} während der Messungsperiode sank, deuteten Ausmass und Zeitablauf dieser Veränderung darauf hin, dass sie nicht in erster Linie für die Anderungen von I.C.P. verantwortlich war. M.A.P. sank bei den meisten Patienten, doch war diese Verringerung nur bei 3 und 4 Minuten nach der Verabreichung von Etomidat ($0{,}05 > P > 0{,}02$) statistisch von Bedeutung. Die Veränderungen des zerebralen Perfusionsdruckes (C.P.P.) und die Herztätigkeit waren klinisch oder statistisch unbedeutend. Wir schliessen daraus, dass Etomidat für die Einleitung von Narkose bei Patienten mit intrakraniellen grösseren Verletzungen verwendet werden kann, ohne I.C.P. zu erhöhen oder C.P.P. ernsthaft zu verringern.

EFECTO EJERCIDO POR ETOMIDATA SOBRE LA PRESION INTRACRANEAL Y PRESION DE PERFUSION CEREBRAL

SUMARIO

Diez pacientes con lesiones intracraneales, anestesiados con tiopentona y oxido nitroso (70%) en oxígeno (30%), recibieron etomidata 0,2 mg kg^{-1} intravenosamente. La ventilación fue controlada en todos los pacientes. Se registró la presión intracraneal (I.C.P.) y presión arterial media (M.A.P.). La I.C.P. disminuyó significativamente en todos los pacientes ($0{,}01 > P > 0{,}001$). Aunque el Pa_{CO_2} disminuyó durante el período de medición, la magnitud y el transcurso de tiempo de este cambio sugirieron que no era principalmente responsable de los cambios en la I.C.P. La M.A.P. disminuyó en la mayoría de los pacientes, pero la disminución fue estadísticamente significativa solamente después de 3 y 4 min de administrarse etomidata ($0{,}05 > P > 0{,}02$). Los cambios en la presión de perfusión cerebral (C.P.P.) y en los latidos del corazón no fueron clínica ni estadísticamente significativos. Concluimos que la etomidata puede emplearse para la inducción de anestesia en pacientes con lesiones intracraneales que ocupan espacio, sin aumentar la I.C.P. ni reducir seriamente la C.P.P.

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EFFECTS OF FENTANYL ON INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION PRESSURE DURING HYPOCAPNIA

E. Moss, D. Powell, R. M. Gibson and D. G. McDowall

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SUMMARY

Ten patients presenting for craniotomy were studied. Each was anaesthetized with thiopentone or Althesin followed by tubocurarine and the lungs were hyperventilated with nitrous oxide in oxygen. Fentanyl 0.2 mg was administered i.v. and the intracranial pressure (i.c.p.) and mean arterial pressure were recorded continuously for 10 min. At the time of administration of fentanyl nine of the 10 patients were hypocapnic (Pa_{CO_2} less than 4 kPa). The changes in i.c.p. were small. Cerebral perfusion pressures less than 50 mm Hg were observed in two patients who had moderate hypotension before the drug was given. We conclude that fentanyl is a valuable agent in the hyperventilation technique in patients with intracranial space-occupying lesions, provided that hypotension is absent.

Fitch and colleagues (1969a) reported first that the administration of fentanyl and droperidol either did not alter, or decreased slightly, the intracranial pressure (i.c.p.) in patients with intracranial space-occupying lesions during controlled ventilation, and Sari, Okuda and Takeshita (1972) found that Thalamonal had no effect on cerebral blood flow (c.b.f.) or the cerebral metabolic rate for oxygen. Because fentanyl is short-acting, and as a result of these studies, it has been used widely, sometimes with droperidol, to supplement nitrous oxide/oxygen/relaxant anaesthesia for neurosurgery. However, when Misfeldt and colleagues (1976) used droperidol and fentanyl for the induction of anaesthesia, they observed a marked increase in i.c.p. Following these observations they studied systematically the effects of droperidol and fentanyl on i.c.p. during controlled ventilation at normocapnia, and concluded that these drugs were contraindicated in neurosurgery, unless hypocapnia was established and the arterial pressure was normal or increased. Because this latter communication appears superficially to contradict earlier work, this study was conducted on the effect of fentanyl on i.c.p. in neurosurgical patients during controlled ventilation.

METHODS

Ten patients with intracranial lesions presenting for craniotomy were studied. If indicated, diazepam 10 mg i.m. was administered, otherwise no premedication was given. Following the induction of anaesthesia with thiopentone (five patients) or Althesin (five patients), which were given until the eyelash reflex was lost, tubocurarine 45 mg was administered. Anaesthesia was maintained subsequently with nitrous oxide in oxygen. The ventilation was adjusted to maintain the Pa_{CO_2} at between 2.7 and 4.0 kPa. As all the craniotomies were being performed for major intracranial procedures during which induced hypotension could be required, after Allen's test had been performed, a cannula was inserted into a radial artery and connected to a pressure transducer. If there was no ventricular catheter *in situ* already, one was inserted through a burr hole into a lateral ventricle. In this way cerebrospinal fluid could be withdrawn and the surgical access improved. The ventricular catheter was connected also to a pressure transducer and i.c.p. and arterial pressure were recorded continuously on a chart recorder. The zero level for the arterial pressure was heart level and the zero for the i.c.p. was the external auditory meatus, the operating table being tilted 10° head-up. Once the i.c.p. and arterial pressure had remained stable for 5 min fentanyl 0.2 mg was given i.v. The i.c.p. and arterial pressure recordings were followed for 10 min. Pco_2 was maintained constant during the measurements by observing the end-tidal carbon dioxide concentration on an infra-red carbon dioxide analyser and Pa_{CO_2} was measured at the beginning and end of the 10-min period.

The following measurements were obtained from the chart recordings:

(1) The mean arterial pressure (m.a.p.) and mean i.c.p. in the 5 min before the injection of fentanyl (termed control m.a.p. and control i.c.p.);

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TABLE I. *Diagnosis and mean i.c.p. (mm Hg) before (control) and after the administration of fentanyl 0.2 mg*

Patient (age, yr)	Diagnosis	Control (value before induction, if known)	Time after fentanyl (min)				
			2	4	6	8	10
A (42)	Pituitary tumour	12	10	8	7	8	7
B (71)	Meningioma	15 (10)	13	10	14	10	10
C (59)	Meningioma	10 (13)	8	9*	11	11	12
D (59)	Glioblastoma	10 (23)	11	10	16	15	15
E (47)	Aneurysm	20 (17)	—	—	19	20	19
F (59)	Meningioma	9 (17)	8	9	10	10	11
G (33)	Aneurysm	11 (15)	10	9	9	8	8
H (62)	Glioblastoma	16	16	19	19	19	19
I (50)	Acoustic neuroma	9	9	9	9	8	8
J (64)	Spontaneous intracerebral haemorrhage	9	8	8	8	8	8
Mean		12.1	10.3	10.1	12.2	11.7	11.7
SEM		1.2	0.9	1.1	1.4	1.5	1.4

* Head turned at this time.

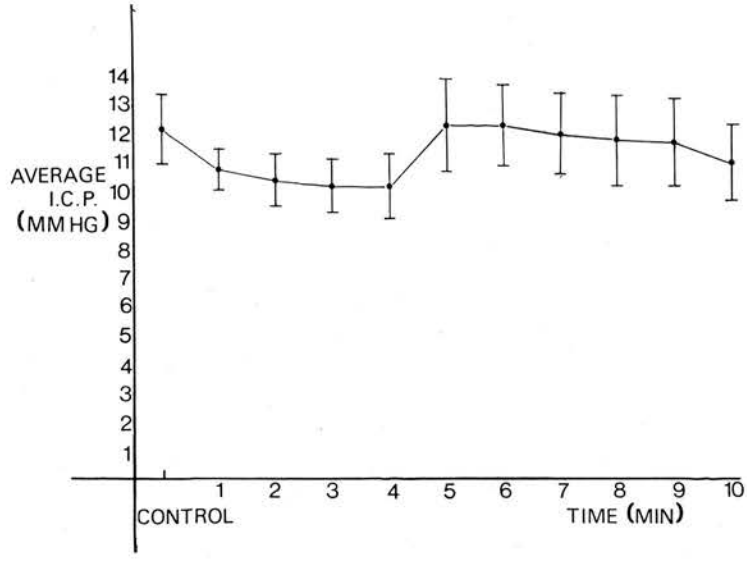

FIG. 1. The average i.c.p. (mean) and SEM before (control) and after the administration of fentanyl 0.2 mg i.v. The changes from control i.c.p. were not significant statistically.

(2) M.a.p. and mean i.c.p. at 1-min intervals for the first 10 min after the administration of the fentanyl; (3) The cerebral perfusion pressure (c.p.p.) (m.a.p.—mean i.c.p.) at 1-min intervals for 10 min after the administration of the fentanyl.

RESULTS

The ages of the patients, their intracranial pathology and the effects of fentanyl on mean i.c.p. are presented in table I. The average i.c.p. for the group decreased initially from the control value after the administration of fentanyl (fig. 1). I.c.p. decreased in six patients (−5, −5, −1, −3, −1 and −1 mm Hg), increased in three patients (+2, +6 and +3) and remained constant in one patient until the patient's head was turned, whereupon it increased (+2 mm Hg).

The maximum increase recorded in i.c.p. was

TABLE II. *Mean arterial pressure (mm Hg) before (control) and after the administration of fentanyl 0.2 mg*

Patient	Control	Time after fentanyl (min) 2	4	6	8	10
A	113	93	83	70	70	75
B	105	98	98	—	83	85
C	127	102	88	82	80	82
D	73	55	65	55	58	65
E	113	115	105	105	98	98
F	100	80	70	65	72	75
G	63	53	60	57	63	63
H	83	72	70	70	70	70
I	115	95	85	80	90	95
J	107	97	92	90	90	88
Mean	99.9	86.0	81.6	74.9	77.4	79.6
SEM	6.5	6.5	4.7	5.4	4.1	3.8

6 mm Hg, and in three of the four patients showing an increase in i.c.p. after fentanyl, the i.c.p. did not reach the pre-induction value; the fourth patient had no pre-induction measurement for comparison. The changes in i.c.p. from control were not significant statistically for the group. In all 10 patients m.a.p. decreased after the administration of fentanyl (table II, fig. 2) and was less than 60 mm Hg in two patients (55 and 53 mm Hg). These decreases in m.a.p. were significant statistically from 2 min after the administration of fentanyl until the end of the period of measurement ($0.01 > P > 0.001$). C.p.p. was less than 60 mm Hg in four patients (55, 51, 43 and 39 mm Hg), and less than 40 mm Hg in only one patient (table III), and this for less than 1 min. The changes in c.p.p. from control were significant statistically at 1 min after the administration of fentanyl ($0.02 > P > 0.01$) but from 2 min onwards were of greater significance ($0.01 > P > 0.001$). For brevity the measurements in the tables are presented at 2-min intervals, because there was no additional information in the readings at 1-min intervals.

TABLE III. *Cerebral perfusion pressure (mm Hg) before (control) and after the administration of fentanyl 0.2 mg*

Patient	Control	Time after fentanyl (min) 2	4	6	8	10
A	101	83	75	63	62	68
B	90	85	88	—	73	75
C	120	94	79	71	69	70
D	63	44	55	39	43	50
E	93	—	—	86	78	79
F	91	72	61	55	62	64
G	52	43	51	48	55	55
H	67	56	51	51	51	51
I	106	86	76	71	82	87
J	98	89	84	82	82	80
Mean	88.1	72.4	68.9	62.9	65.7	67.9
SEM	6.7	6.6	4.8	5.3	4.2	4.1

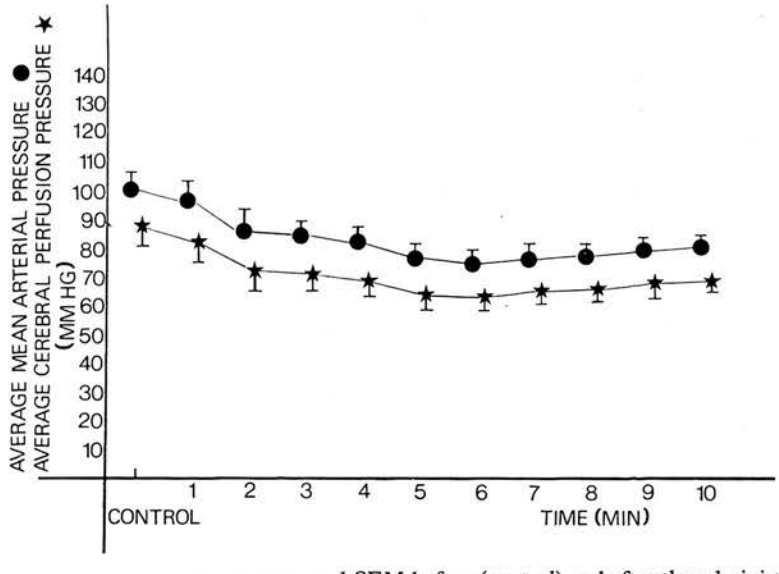

FIG. 2. The average m.a.p., average c.p.p. and SEM before (control) and after the administration of fentanyl 0.2 mg i.v. The changes from control m.a.p. and c.p.p. were significant statistically (see text).

However, the small differences between the figures quoted above and those in the tables are caused by this point.

Table IV shows the Pa_{CO_2} measurements obtained at the time of the injection of fentanyl and 10 min after the injection. These values showed little change during the period of measurement. Although most of the Pa_{CO_2} values were between 2.7 and 4.0 kPa (the range aimed for), one was 5.5 kPa and another 2.5 kPa. In each patient the end-tidal carbon dioxide concentration remained constant during the period of the study.

TABLE IV. *Pa_{CO_2} values at the time of injection of fentanyl 0.2 mg and 10 min after injection*

Patient	Initial Pa_{CO_2} (kPa)	Final Pa_{CO_2} (kPa)
A	2.7	2.8
B	3.7	3.7
C	2.9	2.9
D	3.3	2.9
E	4.0	4.0
F	5.2	5.5
G	2.8	2.8
H	3.2	3.2
I	3.1	3.1
J	2.5	2.5

DISCUSSION

The original report of the effects of neuroleptanalgesic drugs on i.c.p. was that of Fitch and colleagues (1969a), who reported that, in patients with space-occupying lesions ventilated with nitrous oxide and oxygen at normocapnia, the i.v. administration of droperidol 5 mg and fentanyl 0.1 mg led to small decreases in i.c.p. in eight out of nine patients. The effect of these drugs on i.c.p. was re-assessed by Misfeldt and colleagues (1976) who also studied patients with space-occupying lesions at normocapnia and reported that fentanyl 0.2 mg given after droperidol 7.5–12.5 mg resulted in increases in i.c.p. in five patients and decreases in three. These latter authors concluded that they could not explain the lack of agreement between their results and those of Fitch and colleagues. However, the disagreements do not seem large to us since, of the five patients with increases in i.c.p. reported by Misfeldt and colleagues, three had very small increases indeed (1, 2 and 3 mm Hg). In the other two patients the increases were greater (8 and 9 mm Hg), but the methodology employed by these workers would bias the results towards the finding of increases in i.c.p., since they measured the highest i.c.p. achieved at an undefined time more than 10 min after the administration of the drugs. Patients with space-occupying pathology show "spontaneous" variations in i.c.p., so that in any group of such patients a method which selects the highest i.c.p. value reached will include increases in i.c.p. which are not a result of the previous drug administration, and the effect will increase the longer the post-administration period of observation. This consideration is reinforced by the fact that, in five of Misfeldt's patients, plateau waves were recorded before the induction of anaesthesia, and these five patients included the two with the greatest increases in i.c.p. following the injection of fentanyl. Therefore i.c.p. in these patients was unstable before the administration of fentanyl.

To conclude this discussion of the i.c.p. changes during controlled ventilation *at normocapnia*, it is worth emphasizing that supplementation of nitrous oxide/oxygen anaesthesia with neuroleptanalgesic drugs produces small changes in i.c.p., while the administration of volatile anaesthetics produces large and consistent increases in i.c.p. (Jennett et al., 1969; Adams et al., 1972).

However, most neurosurgical operations are conducted during hypocapnia and not normocapnia, and the present study extends the information available on neuroleptanalgesic drugs by reporting measurements made at hypocapnia. Furthermore, since fentanyl is a short-acting drug with a serum half-life of 2 min (Schleimer et al., 1978), the measurements were made during the first 10 min after drug administration at a time when the maximum effect of the drug is seen clinically, although of course some lesser effect persists for a longer time. Under hypocapnic conditions fentanyl 0.2 mg produced small changes in i.c.p. which could be in either direction. The mean i.c.p. decreased for 4 min after the administration of fentanyl, but this decrease did not reach statistical significance.

By comparison, in the study of Adams and colleagues (1972), in which the i.c.p. response to 0.5–1% halothane was measured during hypocapnia at a mean Pa_{CO_2} of 3.5 kPa, i.c.p. increased in 10 out of 17 patients, but only one patient showed an increase greater than 4 mm Hg. In the studies of Fitch and colleagues, no deliberate attempt to hyperventilate was made, but inadvertent hypocapnia occurred in some patients in their series. They noted that large increases in i.c.p. were produced by volatile anaesthetics in patients with space-occupying

lesions, despite Pa_{CO_2} values of about 4.5 kPa (Fitch et al., 1969b).

The clinical question about the choice between NLA supplementation and supplementation with volatile anaesthetics *during hypocapnia* remains unresolved, for there are two conflicting points of view: (i) that previous hypocapnia renders increases in i.c.p. with volatile anaesthetics so small as to be clinically unimportant (Adams et al., 1972); or (ii) that, although hypocapnia reduces the changes in i.c.p. produced by volatile anaesthetics, major changes in i.c.p. occur still in patients whose intracranial compression is advanced (Jennett et al., 1969; Gordon, 1970). If the second view is correct, then NLA supplementation may be preferable.

Another method of supplementing nitrous oxide relaxant anaesthesia for neurosurgery employs infusions of thiopentone or methohexitone, as described by Hunter (1972a, b). Thiopentone, methohexitone, Althesin and etomidate have all been shown to decrease i.c.p. (Horsley,1937; Hunter, 1972b; Turner et al., 1973; E. Moss and colleagues, 1978, unpublished observations) and cerebral blood flow (Pierce et al., 1962; Herrschaft et al., 1975; Sari et al., 1976) and thus an infusion containing any one of these agents would decrease i.c.p. and consequently be useful in patients in whom a decrease in i.c.p. is considered necessary.

The present results on the effect of fentanyl on m.a.p. and c.p.p. are in complete agreement with those of Misfeldt and colleagues (1976) and we wish to emphasize the point made by these authors, that fentanyl should not be given to patients who are hypotensive already, otherwise low cerebral perfusion pressures may result. In the present study, cerebral perfusion pressures of less than 50 mm Hg were observed in two patients, both of whom were moderately hypotensive when the drug was given (m.a.p. = 73 and 63 mm Hg).

Therefore we would conclude that:

(1) In hypocapnic patients with intracranial space-occupying lesions, changes in i.c.p. following fentanyl are small and may be in either direction.

(2) Fentanyl causes decreases in m.a.p. and in c.p.p., but unless the patient is already hypotensive the changes are small.

(3) The establishment of hypocapnia before the administration of fentanyl does not provide complete protection against a decrease in c.p.p. to less than 50 mm Hg if the patient is already hypotensive (see patients D and G).

(4) In our view fentanyl continues to be a valuable adjunct to nitrous oxide oxygen relaxant anaesthesia in patients with intracranial space-occupying lesions, provided that it is not used in patients who are hypotensive. Its effect on i.c.p. in hypocapnic patients is small and, both clinically and statistically, insignificant.

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EFFETS DU FENTANYL SUR LA PRESSION INTRACRANIENNE ET LA PRESSION DE PERFUSION CEREBRALE PENDANT L'HYPOCAPNIE

RESUME

On a examiné 10 malades se présentant pour une craniotomie. Chacun avait été anesthésié à l'aide de thiopentone ou d'althésine puis tubocurarine, et leurs poumons étaient hyperventilés par du protoxyde d'azote dans de l'oxygène. Le fentanyl a été administré par voie intraveineuse à raison de 0,2 mg et on a enregistré par la suite, pendant 10 min et d'une manière continue l'I.C.P. (pression intracranienne) ainsi que la tension artérielle moyenne. Au moment où l'on a administré le fentanyl, neuf malades sur 10 étaient en état d'hypocapnie (Pa_{CO_2} inférieure à 4 kPa). Les variations de l'I.C.P. ont été faibles. On a observé sur deux malades que les pressions de perfusion cérébrale étaient inférieures à 50 mm Hg, ces malades ayant tous deux une hypotension modérée avant l'injection du médicament. Nous en concluons que le fentanyl est un agent utile pour la technique d'hyperventilation pour les malades ayant des lésions intracraniennes envahissantes, à la condition toutefois que ceux-ci ne soient pas hypotendus.

AUSWIRKUNGEN VON FENTANYL AUF INTRAKRANIELLEN UND ZEREBRALEN DURCHBLUTUNGSDRUCK WÄHREND HYPOKAPNIE

ZUSAMMENFASSUNG

Studiert wurden 10 Patienten für Gehirnchirurgie. Alle waren entweder mit Thiopenton oder mit Althesin, dann mit Tubocurarin narkotisiert und mit Stickoxyd in Sauerstoff hyperventiliert. Dann wurden 0,2 mg Fentanyl intravenös verabreicht, worauf der intrakranielle und der mittlere arterielle Druck 10 min lang kontinuierlich gemessen wurden. Bei der Verabreichung von Fentanyl waren neun der 10 Patienten hypokapnisch (Pa_{CO_2} unter 4 kPa). Die Veränderung des intrakraniellen Drucks waren gering. Zerebraler Durchblutungsdruck von unter 50 mm Hg wurde bei zwei Patienten beobachtet, bei denen vor Verabreichung von Fentanyl eine mässige Hypotension bestand. Wir schliessen daraus, dass Fentanyl für die Hyperventilationstechnik sehr wertvoll bei Patienten ist, bei denen intrakranielle Verletzungen bestehen—vorausgesetzt, dass bei diesen Patienten keine Hypotension vorhanden ist.

LOS EFECTOS QUE EJERCE FENTANIL SOBRE LA PRESION INTRACRANEAL Y LA PRESION DE PERFUSION CEREBRAL DURANTE HIPOCAPNIA

SUMARIO

Se estudiaron 10 pacientes que sufrían de craneotomía. Cada uno fue anestesiado con tiopentona o Altesina pues tubocurarin y sus pulmones fueron hiperventilados con oxido nitroso en oxígeno. El fentanil 0,2 mg fue administrado intravenosamente y posteriormente se anotó continuamente durante 10 min la presión intracraneal (i.c.p.) y la presión arterial media. En el momento de la administración de fentanil, nueve de los 10 pacientes fueron hipocápnicos (Pa_{CO_2} inferior a 4 kPa). Los cambios en la i.c.p. fueron escasos. Se observaron presiones de perfusión cerebral inferiores a 50 mm Hg en dos pacientes quienes sufrían de una hipotensión moderada antes de suministrarse la droga. Concluimos que el fentanil es un valioso agente en la técnica de hiperventilación en pacientes con lesiones intracraneales que ocupan espacio, siempre que esté ausente la hipotensión.

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I.C.P. INCREASES WITH 50% NITROUS OXIDE IN OXYGEN IN SEVERE HEAD INJURIES DURING CONTROLLED VENTILATION

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SUMMARY

In a randomized trial nitrous oxide 50% in oxygen (Entonox) or oxygen 100% was given during chest physiotherapy on 23 occasions to three mechanically ventilated patients with severe head injuries. Intracranial pressure (i.c.p.) increased by 22.7 mm Hg (SD 10.62) during chest physiotherapy with Entonox, compared with 10.5 mm Hg (SD 10.4) with oxygen 100% ($P > 0.02$). A further nine mechanically ventilated patients with severe head injuries were given Entonox without chest physiotherapy. There was a mean increase in i.c.p. of 3.8 mm Hg (SD 2.4) ($P < 0.001$) when Entonox was given, and a mean decrease of 4.6 mm Hg (SD 2.8) when the nitrous oxide was withdrawn. End-tidal carbon dioxide concentration showed almost no change during nitrous oxide administration (decrease of 0–0.1%). We conclude that nitrous oxide causes an increase in i.c.p. in patients with severe head injuries and exacerbates the increases in i.c.p. occurring during chest physiotherapy.

Nitrous oxide is used widely in intensive care units as a 50% mixture with oxygen (Entonox) to produce analgesia during chest physiotherapy and other painful procedures. The aim of this study was to determine whether the administration of nitrous oxide 50% in oxygen would prevent or decrease the increases in intracranial pressure (i.c.p.) which occur normally during chest physiotherapy in patients with severe head injuries (Gibson et al., 1975). The results obtained prompted a second investigation into the effects of nitrous oxide in oxygen on i.c.p. in the absence of chest physiotherapy.

METHODS

The changes in i.c.p. which occurred during chest physiotherapy were compared during administration of either oxygen 100% or nitrous oxide 50% in oxygen (Entonox).

Random number tables were used to determine the treatment for each episode of chest physiotherapy. There were three patients in the trial, all of whom had severe head injury and whose lungs were being ventilated mechanically. During chest physiotherapy the lungs were "bagged" by an anaesthetist, using a Mapleson C system (Mapleson, 1954) (fresh gas flow of greater than twice the minute volume of the patient). I.c.p. was recorded continuously from a subdural catheter or device, or an extradural device (Coroneos et al., 1973) connected to a transducer, the signal from which was amplified and recorded on a Devices chart recorder. The maximum increase in mean i.c.p. occurring during the period of chest physiotherapy was obtained from the chart recordings. This trial was terminated prematurely when it was found that the administration of Entonox was accentuating the changes in i.c.p. produced by chest physiotherapy.

In a second study, the effect of Entonox on i.c.p. was studied in a further nine patients with severe head injury during mechanical ventilation. However, in these patients physiotherapy was not undertaken. In these patients IPPV had been established for at least 6 h with Pa_{CO_2} values between 3.3 and 4.0 kPa. No patient was included who required an inspired oxygen concentration greater than 50%. I.c.p. was measured as described above, and was recorded at a fast chart speed for 10 min before the administration of Entonox, for either 5 min (two administrations) or 10 min (14 administrations) during the administration of Entonox (through the oxygen inlet of the Cape ventilator), and for 10 min after the discontinuation of the Entonox. During the last six administrations of Entonox, end-tidal carbon dioxide concentration was measured by mass spectrometry (Medishield). Arterial blood-gas tensions were measured within 4 h of the administration of the Entonox as part of the routine management of the patient in the intensive care ward.

RESULTS

Mean i.c.p. before chest physiotherapy was the same in the 100% oxygen group as in the Entonox group.

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I.c.p. increased by 22.7 mm Hg (SD 10.6) when physiotherapy was performed with Entonox compared with 10.5 mm Hg (SD 10.4) during the administration of oxygen ($0.02 > P > 0.01$) (table I and fig. 1). In two patients A-waves (Lundberg, 1960) were precipitated by Entonox and physiotherapy, but this occurred also in one patient when physiotherapy was being carried out with oxygen alone.

TABLE I. *Comparison of increases in i.c.p. produced by chest physiotherapy during 100% oxygen and during Entonox administration. Control values are those of mean i.c.p. before physiotherapy.* *$0.02 > P > 0.01$

Oxygen		Entonox	
Control (mm Hg)	Change from control (mm Hg)	Control (mm Hg)	Change from control (mm Hg)
7	+10	19	+16
15	+40	15	+40
26	+15	16	+40
18	+3	7	+6
9	+4	10	+11
13	+4	8	+23
14	+10	10	+23
7	+5	12	+19
13	+9	10	+22
9	+7	13	+33
10	+8	12	+15
		14	+24
n 11		12	
$\bar{x}$ 12.8	+10.5*	12.2	+22.7*
SD 5.6	10.4	3.5	10.6

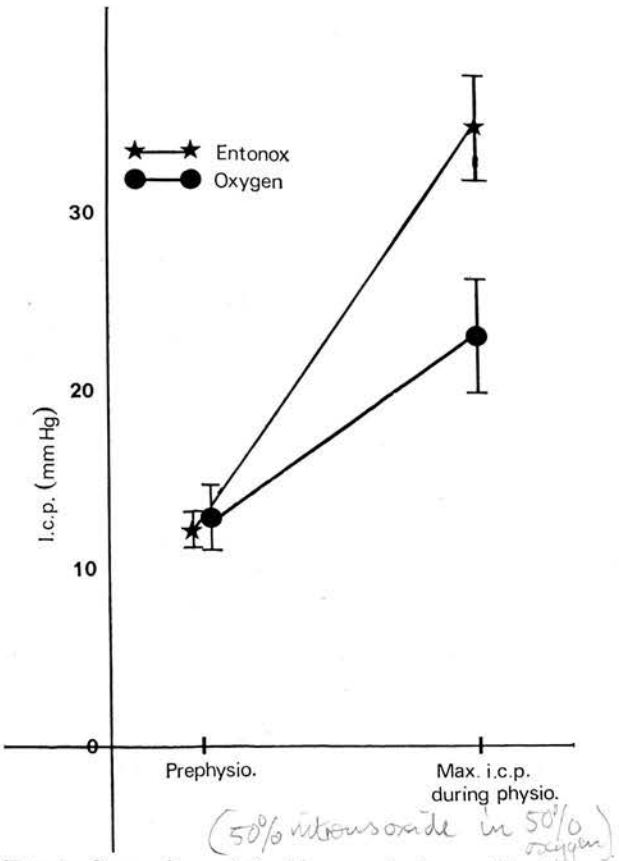

FIG. 1. Comparison of the increases in i.c.p. with chest physiotherapy during Entonox and 100% oxygen administration in patients with severe head injuries. The bars represent the standard errors of the means.

When Entonox was administered to patients not undergoing chest physiotherapy there was a mean increase in i.c.p. of 3.8. mm Hg (SD 2.4) (range 0–8.5 mm Hg) ($P < 0.001$). After the withdrawal of nitrous oxide there was a mean decrease in i.c.p. of 4.6 mm Hg (SD 2.8) ($P < 0.001$) (table II and fig. 2).

There was a mean decrease in end-tidal carbon dioxide concentration of less than 0.1% (range 0–0.1%) when nitrous oxide was given.

DISCUSSION

Reports on the effect of nitrous oxide on i.c.p. are contradictory. In dogs, Saidman and Eger (1965) showed no change in i.c.p. with 70–75% nitrous oxide, whereas Sakabe and colleagues (1978) found an increase in i.c.p. In man, increases in i.c.p. have been reported during the induction of anaesthesia in patients with intracranial tumours and aneurysms (Sondergard, 1961; Hulme and Cooper, 1972; Henriksen and Jorgensen, 1973; Greenbaum et al., 1975; Phirman and Shapiro, 1977), and during established anaesthesia with hypocapnia in patients with cerebral tumours (Misfeldt, Jörgensen and Rishöj, 1974). However, Gordon and Greitz (1970) found no increase in lumbar cerebrospinal fluid pressure when nitrous oxide was administered with the anaesthetic gases to patients with normal i.c.p.

Increases in cerebral blood flow (c.b.f.) occur on the administration of nitrous oxide to dogs (McDowall and Harper, 1965; Theye and Michenfelder, 1968; Sakabe et al., 1978), but the reports in man are conflicting. Wollman and others (1965) reported no change in c.b.f. when 70% nitrous oxide was given to healthy male volunteers, whereas Sakabe and others (1976) found an increase in c.b.f. with 60% nitrous oxide in human volunteers. There has been no report

TABLE II. *I.c.p. (mm Hg) before, during and after Entonox. The peak values reached during Entonox administration were used in calculating the changes*

Patient	Control	Change after N_2O administration	Change after N_2O withdrawal
A	4	+1	−2
	13	+5	−1
	6.5	+4.5	−5
B	13.5	+2	−3.5
C	6	+1	−1
D	16	+2	−4
E	3	+7	−4
	3	+2	−4
	1	+6	−6
F	22	+4	−11
G	1	+6	−6
	6	+5	−8
H	5	0	−0.5
I	25.5	+8.5	−8
	21	+3	−5
	23	+3	−5
($n = 16$)			
$\bar{x}$	10.6	$\bar{d} = +3.8$	$\bar{d} = -4.6$
SD	8.53	2.40	2.83
		$P < 0.001$	$P < 0.001$

of the effect of nitrous oxide on i.c.p. or c.b.f. in patients with severe head injury, although it has been suggested that increases may occur (Henriksen and Jorgensen, 1973).

Gibson and co-workers (1975) reported increases in i.c.p. during chest physiotherapy in patients with severe head injuries, which were thought to be partly a result of systemic hypertension and partly a result of cerebral activation produced by noxious stimulation. As Entonox is an analgesic, it might be expected to decrease such increases in i.c.p. However, after Entonox had been given on 12 occasions during chest physiotherapy, it was clear that the increases in i.c.p. were exacerbated.

The increase in i.c.p. with Entonox in the absence of chest physiotherapy is almost certainly a result of a cerebral vasodilatory action of the drug. An increase in end-tidal carbon dioxide concentration, which was expected because of the initial rapid uptake of nitrous oxide, was not seen and therefore cannot account for the increase in i.c.p. The increases in i.c.p. recorded here, in the absence of chest physiotherapy, were small but might be greater in patients with severe head injury breathing spontaneously, especially when the volume of the intracranial contents is on the steep part of the pressure–volume curve.

The use of nitrous oxide for general anaesthesia in head injuries is not contraindicated by our results, but

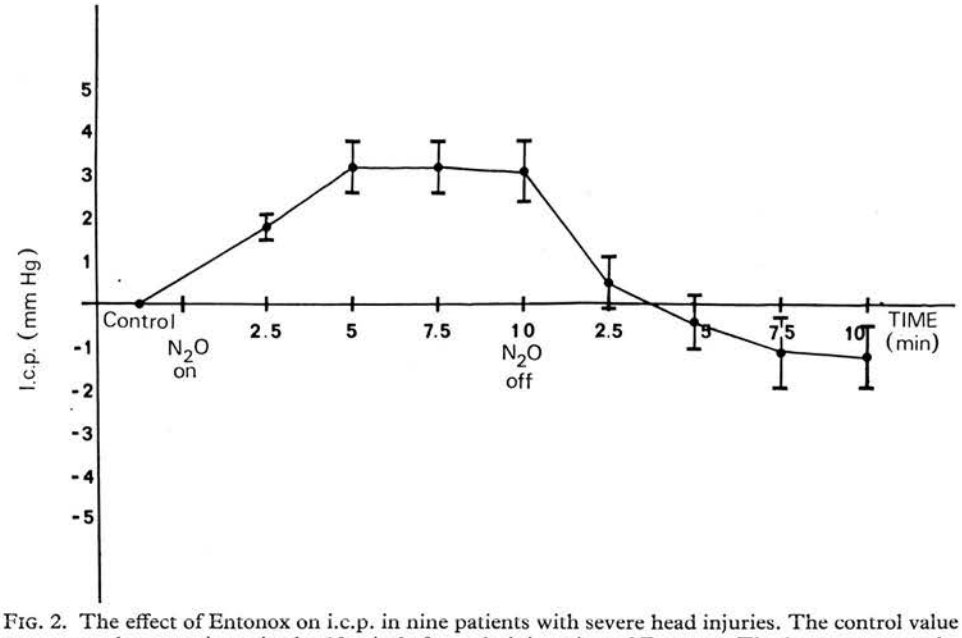

FIG. 2. The effect of Entonox on i.c.p. in nine patients with severe head injuries. The control value represents the mean i.c.p. in the 10 min before administration of Entonox. The bars represent the standard errors of the means.

hypocapnia should probably be induced first by hyperventilation with oxygen 100%.

Misfeldt and colleagues (1974) showed that prior hyperventilation for 10 min or more with oxygen 100% prevented any marked increase in i.c.p. during the administration of nitrous oxide. However, when controlled hyperventilation has been in use for some hours, as in the management of severe head injury, any protective effect of hypocapnia against the increases in i.c.p. induced by nitrous oxide may be lost because of the adaptation of c.b.f. and i.c.p. with time to the low Pa_{CO_2} values.

Finally, the results obtained here suggest that Entonox should be avoided in spontaneously-breathing head-injured patients during transport and admission to hospital.

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AUGMENTATIONS DE LA PRESSION INTRA-CRANIENNE AVEC 50% DE PROTOXYDE D'AZOTE DANS L'OXYGENE DANS LES CAS DE BLESSURES GRAVES A LA TETE PENDANT UNE VENTILATION CONTROLEE

RESUME

Au cours d'essais effectués au hasard, on a administré soit 50% de protoxyde d'azote dans l'oxygène (Entonox), soit 100% d'oxygène pendant une physiothérapie de la poitrine et ce à 23 reprises à trois patients ventilés mécaniquement et souffrant de blessures graves à la tête. La pression intracranienne (i.c.p.) a augmenté de 22,5 mm Hg (écart type 10,62) pendant la physiothérapie de la poitrine à l'aide d'Entonox, par rapport à 10,5 mm Hg (écart type 10,4) lorsqu'on a utilisé de l'oxygène à 100% ($P > 0,02$). Neuf autres malades ventilés mécaniquement et souffrant également de blessures graves à la tête se sont vus administrer de l'Entonox sans physiothérapie de la poitrine. Il s'est produit une augmentation moyenne de l'i.c.p. de 3,8 mm Hg (écart type 2,4) ($P < 0,001$) lorsque l'Entonox a été administré et une diminution moyenne de 4,6 mm Hg (écart type 2,8) lorsque le protoxyde d'azote a été arrêté. La concentration d'acide carbonique en fin d'expiration n'a virtuellement accusé aucun changement pendant l'administration de protoxyde d'azote (diminution de 0–0, 1%). Nous en concluons que le protoxyde d'azote provoque une augmentation de l'i.c.p. chez les malades souffrant de blessures graves à la tête et aggrave l'augmentation de l'i.c.p. qui se produit pendant la physiothérapie de la poitrine.

INTRAKRANIELLER DRUCK (I.C.P.) STEIG BEI KONTROLLIERTER BELÜFTUNG VON PATIENTEN MIT SCHWEREN KOPFVERLETZUNGEN BEI VERABREICHUNG VON 50% STICKOXYD IN SAUERSTOFF

ZUSAMMENFASSUNG

Bei einem wahllos durchgeführten Versuch wurden 50% Stickoxyd in Sauerstoff (Entonox) oder 100% Sauerstoff bei 23 Gelegenheiten während Brust-Physiotherapie an drei mechanisch belüftete Patienten mit schweren Kopfverletzungen verabreicht. I.c.p. stieg um 22,7 mm Hg (SD 10,62) während der Brust-Physiotherapie mit Entonox, verglichen mit 10,5 mm Hg (SD 10,4) mit 100% Sauerstoff ($P < 0{,}02$). Weiter neun mechanisch belüftete Patienten mit schweren Kopfverletzungen erhielten Entonox ohne Brust-Physiotherapie. Es kam zu einem mittleren Anstieg von i.c.p. von 3,8 mm Hg (SD 2,4) ($P < 0{,}001$), wenn Entonox verabreicht wurde, und zu einem mittleren Abstieg von 4,6 mm Hg (SD 2,8) bei Entzug von Stickoxyd. Die Endausatmungskonzentration von Kohlendioxyd zeigte fast keine Veränderung während der Verabreichung von Stickoxyd (Abstieg von 0–0,1%). Wir schliessen daraus, dass Stickoxyd einen Anstieg von i.c.p. bei Patienten mit schweren Kopfverletzungen bewirkt, und den Anstieg von i.c.p., zu dem es während Brust-Physiotherapie kommt, verschlechtert.

AUMENTOS EN LA PRESION INTRACRANEAL CON 50% DE OXIDO NITROSO EN OXIGENO PARA SERIAS LESIONES A LA CABEZA DURANTE VENTILACION CONTROLADA

SUMARIO

En una prueba aleatoria, se administró óxido nitroso 50% en oxígeno (Entonox) u oxígeno 100% durante la fisioterapia del pecho, en 23 ocasiones, a tres pacientes ventilados mecánicamente que habían sufrido serias lesiones a la cabeza. La presión intracraneal (p.i.c.) aumentó en un 22,7 mm Hg (SD 10,62) durante la fisioterapia del pecho con Entronox, en comparación con 10,5 mm Hg (SD 10,4) con oxígeno 100% ($P < 0{,}02$). Otros nueve pacientes mecánicamente ventilados con lesiones severas a la cabeza recibieron Entonox sin fisioterapia del pecho. Se produjo una p.i.c. media de 3,8 mm Hg (SD 2,4) ($P < 0{,}001$) cuando se administró Entonox, y una disminución media de 4,6 mm Hg (SD 2,8) cuando se suspendió la administración de óxido nitroso. La concentración de dióxido de carbono al fin mareal prácticamente no acusó cambio alguno durante la administración de óxido nitroso (disminución de 0–0,1%). Concluímos que el óxido nitroso produce un aumento en la p.i.c. en aquellos pacientes con serias lesiones a la cabeza y exacerba los aumentos de p.i.c. que se producen durante la fisioterapia del pecho.