PHYSOSTIGMINE AND NITROUS OXIDE IN ANAESTHESIA

Fysostigmine en lachgas in anesthesie

PROEFSCHRIFT

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PROMOTOREN	:	Prof. Dr. I.L. Bonta Prof. Dr. W. Erdmann
OVERIGE LEDEN	:	Prof. Dr. M.W. van Hof Prof. Dr. J. Jeekel

Anaesthesia is more than applied physiology. Its good results depend on applying physiologic thinking to the clinical setting in terms of maintaining body homeostasis.

Carlos Parsloe, Survey, 28: 193-193, 1984.

This Thesis is based on clinical observations of patients during anaesthesia and recovery from anaesthesia at the University Hospital Dijkzigt, Rotterdam and on experiments performed at the Department of Pharmacology of the Medical Faculty, Erasmus University, Rotterdam under the guidance of Dr. M.R. Dzoljic.

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PREFACE

"....sine ulla hypothesi et fallaci auxilio librorum rerum proprietates propriis oculis ita quaeruntur, ac si de illis nemo hominum scripsisset unquam".

(Johannes Antonius Scopoli, 1771)*

Recovery from anaesthesia may be smooth and uneventful or disturbed. Disturbed recovery reflects derangements of motor or psychic functions, on their own or in combination.

The central anticholinergic syndrome is frequently the cause of disturbed recovery from anaesthesia. The syndrome consists of many signs and symptoms, all of them caused by drugs capable of central anticholinergic activity. These drugs include atropine-like substances, antidepressants, antihistamines, anti-Parkinsonian drugs, general anaesthetic agents, antiemetics and antipsychotics, opiates, tranquillizers and several others. The patient with the central anticholinergic syndrome may be clinically either excited or depressed and sometimes appears quite normal but with superimposed amnesia. The syndrome consists of confusion, agitation, restlessness, hallucinations, dysarthria, delirium, amnesia, speech disturbances, somnolence, stupor or coma. Central hyperpyrexia may be observed and there may be va-

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* Johannes Antonius Scopoli deliberately, broke with the old habit of copying unproved facts from one book to the other (1). Scopoli was a famous botanist and C. von Linné made him immortal by naming a solanaceous plant Solanum somniferum alterum after him: Hyosciamus scopolii (2). The substance scopolamine, deriving from this plant, now called Scopolia carniolica Jacq., is still widely used and is one of the most potent agents to produce the central anticholinergic syndrome.

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rious peripheral signs of anticholinergic action. These signs may be present in any given combination or degree. As a rule, the central anticholinergic syndrome is diagnosed when two peripheral and one central anticholinergic signs are present. The peripheral signs confirm the etiology of the central sign.

Physostigmine is the drug of choice for the treatment of the central anticholinergic syndrome. It was established that 0.04 mg kg^{-1} is the optimal and maximal initial dose of physostigmine in anaesthetic practice. However, in the treatment of intoxicated patients, a higher initial dose may be necessary. Although various side effects of physostigmine have been described, the drug proved to be very safe when used properly. There are now only a few well-known contraindications to its use.

In patients treated with physostigmine during recovery from anaesthesia, the analgesia-preserving property of the drug was observed. The somnolent but not the analgesic effects of opiates were reversed by physostigmine. Several experimental studies, ours included, indicate that physostigmine itself is capable of producing analgesia. The present data indicate a possible interaction of physostigmine with the 5-HT transmission system (see pp 36 and 82-91).

The use of physostigmine during recovery from anaesthesia shortened the stay in the recovery room. Patients who regain all their capacities after physostigmine do not need intensive care which can thus be reserved for others who do. Understanding of the central anticholinergic syndrome made preventive measures possible. The replacement of the centrally active atropine sulphate by its exclusively peripherally active methyl-congener resulted in a decreased incidence of the central anticholinergic syndrome in our hospital.

In some patients, disturbed recovery from anaesthesia was marked, with intermittently-occurring rhythmical convulsive rest-

lessness, piloerection and, in conscious patients, with a varying degree of apprehension. This clinical picture did not fit well into any of the previously known disturbances of recovery, being also distinct from the central anticholinergic syndrome. It was postulated that withdrawal of the patient from prolonged exposure to nitrous oxide could produce this specific clinical picture. Physostigmine only partly ameliorated this type of unrest. Thus, a predominantly anticholinergic aetiology was excluded. Readministration of subanaesthetic concentrations of nitrous oxide or of pethidine, however, promptly abolished the rhythmic convulsant behaviour. It was hypothesised that tolerance to some effects of nitrous oxide may develop in the patient during exposure, resulting in nitrous oxide withdrawal signs. Tolerance to the effects of nitrous oxide was studied in an experimental model, using rats. It was established that individual effects of nitrous oxide follow an independent course during exposure, each requiring a different length of exposure before the animal becomes tolerant. Our interest was subsequently directed towards the study of tolerance to the nitrous oxide analgesic effect in rats. It was established that enkephalinase inhibition prevents the development of this tolerance in these animals.

Alongside the study of tolerance to nitrous oxide on an experimental model, we investigated the existence of, and time needed for development of tolerance to the anaesthetic and analgesic effects of nitrous oxide in volunteers. The results indicate that tolerance may develop to both the analgesic and anaesthetic effects of anaesthetic concentrations of nitrous oxide. The old clinical impression that a patient may regain consciousness during a prolonged nitrous oxide anaesthesia has thus been proved right. Observant analgesic supplementation during prolonged nitrous oxide anaesthesia also appears mandatory in order to compensate for the development of tolerance. In the future, however, the intra-anaesthetic use of enkephalinase inhibitors may eliminate much of the practical relevance of tolerance to nitrous oxide.

PART ONE
DISTURBED RECOVERY FROM ANAESTHESIA

CHAPTER 1.
DISTURBANCES OF RECOVERY FROM ANAESTHESIA

1.1. Some General Aspects.

The term recovery from anaesthesia will be used in this study to denote the clinical state of a patient following anaesthesia induced by the central action of pharmacological agents. Recovery from such methods as electro-anaesthesia, acupuncturial and hypnotic analgesia etc., such is not included in this context. Clinically, a patient's recovery from anaesthesia starts at the moment when anaesthetic agents are discontinued or reversed.

The aetiology of disturbed recovery from anaesthesia and the feasibility of treating it have been recognized relatively recently. Earlier authors classified postoperative behavioural changes under psychotic disorders (Cobb and McDermott, 1938). These authors concluded that routine administration of sedatives may result in postoperative delirious states. However, no therapeutic improvements occurred for years after this observation. Instead, a rather indiscriminate administration of depressant or analeptic drugs (e.g., amiphenazole, bemegride, nikethamide, micoren, picrotoxin, cardiazol, methyl-phenidate) was recommended for treatment of disturbed recovery from anaesthesia (Lee and Atkinson, 1964).

Three main features of disturbed recovery from anaesthesia are usually encountered: postanaesthetic excitement or agitation; prolonged recovery; and postanaesthetic depression. For reasons unknown, it was the postanaesthetic excitement rather than the depression, which attracted anaesthetists in the past (Eckenhoff et al., 1961; Bastron and Moyers, 1967; Heiser and Gillin, 1971). Consequently, for years the treatment of emergence delirium (Eckenhoff et al., 1961) or emergence excitement (Smiler et

al., 1973) preceded the treatment of depression or of prolonged recovery.

The essential prerequisites for the understanding of disturbed recovery were Longo's experimental findings on the behavioural and electrocorticographic effects of anticholinergic drugs (Longo, 1956; Longo, 1962; Longo, 1966). The atropine-induced dissociation between the electroencephalogram and behaviour was established. For numerous behavioural effects of anticholinergic agents, Longo coined a collective name, "the central anticholinergic syndrome". This term was soon in use to describe the disturbed recovery from anaesthesia caused by anticholinergic drugs (Duvoisin and Katz, 1968).

Besides drugs, the physiological and psychological condition of the patient, or an intercurrent disease, may also modify recovery. The anaesthetic technique may be of importance. Several syndromes and pharmacological states may mar the postanaesthetic phase. States like hypothermia, haemorrhagic conditions or changed neuromuscular function also influence recovery but should be recognized early and corrected appropriately.

1.2. Motor Disturbances

Postanaesthetic motor restlessness has been referred to as spasticity or shivering. According to Soliman and Gillies (1972), these terms may not describe the same phenomenon. Spasticity is indicative of the presence of an upper motor neurone lesion (supraspinal). Coarser shivering was explained as gross muscular activity, aimed at restoring body temperature by increasing heat production.

Heat loss during anaesthesia may delay recovery by slowing down elimination of anaesthetic agents. Such patients shiver during rewarming. However, active warming-up of patients during anaesthesia will prevent this type of shivering (Pflug et al., 1978).

A fine and a coarse type of shivering were discerned after halothane and nitrous oxide anaesthesia (Cohen, 1967). The drop in body temperature was not correlated with the incidence of shivering. Length of anaesthesia, however, was positively correlated (Cohen, 1967; Tammisto and Tigerstedt, 1979). Cohen (1967) suggested that drop of body temperature is not the mechanism by which halothane might produce shivering. He did not discuss the role of nitrous oxide in producing shivering. Holdcroft and Hall (1978) also observed that postanaesthetic motor unrest was not related to heat loss during anaesthesia. We found that shivering may cease when the patient fully regains consciousness, in spite of hypothermia (Rupreht and Dworacek, 1976). Subsequently, it has been confirmed that shivering is not solely dependent on the lowered body temperature (Tammisto and Tigerstedt, 1979; Nilsson and Himberg, 1982; Admiraal et al., 1985). It is of interest to note that meperidine (pethidine) promptly arrests shivering (Claybon and Hirsh, 1980; Roy et al., 1983). These findings may indicate that alterations in the endogenous opioid system are involved in postanaesthetic shivering, which might be a subject for further study. Other morphinomimetics than pethidine also attenuate shivering but to a lesser degree (see Chapter 11). This might imply the role of stereospecificity for this effect.

1.3. Psychological Disturbances

Adverse emotional responses are a well known problem in recovery. Personality changes following surgery were recognized early (Dupuytren, 1834). Postoperative disturbances of behaviour may occur after a lucid interval in recovery and progress to serious personality changes.

Mental disorders like fighting behaviour or depression may be a sign of a disturbed body-mind scheme. This alteration is generally associated with stress which may occur after surgery or anaesthesia. Postoperative psychological changes may convert from neu-

rotic emotional responses into true psychotic behaviour. Postoperative depression or pronounced agitation may also be a sign of pre-existent psychiatric disorders. Psychiatric attention is needed in such cases.

Hypoxia of the central nervous system has long been recognized as a cause of restlessness, delirious behaviour, loss of appropriate contact with surroundings, amnesia, confusion and irritability. During recovery, cyanosis may be present but is often undetectable (Hillary, 1983). Hypoxia of the brain may be caused by insufficient ventilation, inappropriate positioning of the head, or inadequate circulation. Ischaemic or hypoxic periods which the patient may have suffered during surgery and anaesthesia can be followed by delayed recovery or changes of behaviour. Cerebral hypoxia remains a consistent hazard, particularly where hypotensive techniques are employed to help the surgeon. Postanoxic encephalopathy may occur days or even weeks after virtual recovery of a patient who has suffered from cerebral hypoxia (Plum et al., 1962). Even mild central hypoxia may be a cause of prolonged recovery, restlessness, delirious behaviour, loss of appropriate contact with surroundings and amnesia. Cerebral hypoxia must be suspected and treated, which makes subsequent differential diagnosis of disturbed recovery easier (Rupreht and Dworacek, 1977).

Among several metabolic derangements which can mar recovery from anaesthesia is thyrotoxic crisis (Selenkow and Hollander, 1963) which is also called thyrotoxic storm (Ingbar, 1966). It is often marked by agitation, restlessness, delirium and prostration. Hypothyroidism, on the other hand, may result in prolonged recovery and unexpected depression following anaesthesia (Abbott, 1967). Adrenocortical insufficiency may be followed by prolonged postoperative unconsciousness (Morss and Baillie, 1958). While corticosteroid-insufficiency results in depression of functions, the patients to whom corticoids are administered may respond with euphoria, excitation and increased motor activity (Goodman

and Gilman, 1970). Diabetic coma, nonketotic hyperosmolar coma, but also hypoglycaemia, if not recognized early, may all not only delay, but eventually prevent, recovery from anaesthesia (Denlinger, 1983). Febrile diseases can cause narrowing of the patient's sensorium and hallucinations. In these states, anticholinergics tend further to decrease consciousness. An acute or a provoked attack of porphyria may also result in personality changes, hysteria, confusional states, coma, or epileptic seizures (Macalpine and Hunter, 1969). In systemic metabolic encephalopathy, increased permeability of the blood-brain barrier may be present. This facilitates increased penetration of drugs into the brain so that recovery from anaesthesia may be prolonged (Freeman et al., 1962).

1.4. Drug-Induced Disturbances

Acute or chronic intoxications, whether accidental, voluntary or iatrogenic, may contribute to the complexity of the differential diagnosis of disturbed recovery from anaesthesia.

Psychosomatic disorders caused by illicit drug (ab)use (opiates, barbiturates, tetrahydrocannabiol, psylocibin, mescalin, phencyclidine, cocaine, etc.) may be especially difficult to recognise and treat because the intake may not be known or admitted and, nowadays, the use of mixtures of psychoactive agents is extremely widespread (Rupreht, 1982).

Opiates, when still present after anaesthesia, may prolong recovery and cause tranquil somnolence or mild hallucinations. Their effects may correctly be diagnosed and treated by opiate antagonists or physostigmine. Inadequate analgesia, however, may also cause disturbed recovery from anaesthesia.

Barbiturates may cause restlessness although usually the plasma concentration during the period of postanaesthetic recovery is too low to influence the central nervous system (Dundee, 1955). Lemniscal pain pathways are relatively unaffected by barbiturates, which may explain cortical excitement and sensory responsi-

veness during light barbiturate narcosis. The described stimulatory effect of barbiturates on nociception may thus be due to unequal suppression by barbiturates of various ascending pathways. In rare circumstances, barbiturates may influence the patient's behaviour for hours during recovery from anaesthesia. The symptoms may vary from euphoria or drowsiness to irritability and depressivity.

Delirium from digitalis toxicity (Mariott, 1968) or the classical alcohol delirium may occasionally endanger the operated patient and complicate the picture of the central anticholinergic syndrome.

1.5. Ondine's Curse*, Pickwick's Syndrome**, Narcolepsy and a Full Bladder

Various other states may interfere with recovery from anaesthesia. For example, in Ondine's curse, the automaticity of the

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* The term "Ondine's curse" derives from a German legend, describing the beautiful water nymph, Ondine, who, having been jilted by her mortal husband, took from him all automatic functions, requiring him to remember to breathe. When he finally fell asleep he died. Opiates, e.g., in high dosages will usually produce apnoea before consciousness is lost.

** Pickwickian syndrome, a term often used rather loosely. It should be reserved for very obese patients who have an increased PCO_2 without evidence of lung disease.
The term derives from dubbing by "the Pickwickian syndrome" of some extremely obese patients, suffering from hypoventilation, obesity, somnolence, polycythaemie and excessive appetite. The first described Pickwickian, in this sense, is the fat boy, Joe, in Charles Dickens's "Pickwick Papers".
Apart from the obesity, the clinical features are similar to those in patients with idiopathic hypoventilation; in the fully developed form they include marked obesity, somnolence, twitching, cyanosis, periodic respiration, secondary polycythaemia, right ventricular hypertrophy and right-sided heart failure.
Some investigators have suggested that the Pickwickian individual is simply a patient with idiopathic hypoventilation who happens to be obese. The cause of the hypoventilation is not clear but presumably is related to the high energy cost of moving the chest wall. The association of marked somnolence and voracious appetite suggests that, in some cases, there is an abnormality in the central nervous system.

respiratory centre fails while the patient is awake (Severinghaus and Mitchell, 1962). Similarly, in rare circumstances, post-anaesthetic recovery is disturbed by a flattened ventilation response curve and periods of apnoea with disturbed consciousness. Such symptoms can be found in patients with Pickwick's syndrome, overdose of opiates or poliomyelitis (Nunn, 1981).

Sleep paralysis occurs in some narcoleptic patients and is characterized by inability to execute any voluntary activity while fully awake. The postoperative period in these patients is characterized by irregularity of respiration and an unusual glassy-eyed stare.
Incidentally, physostigmine was found to be a very efficient therapeutic agent for this affliction (Scollo-Lovizzari, 1970).

A full bladder, which may occur to anybody, may be a cause of numerous troubles during recovery. It may cause central anticholinergic syndrome-like restlessness and cardiovascular problems. In such patients, vagal tone appears to be heightened during recovery from anaesthesia, and hypotension and bradycardia may be encountered. The distended bladder is also the origin of intense pain and may result in restlessness and hypotension. On the other hand, untreated pain may lead to tachycardia or arrhythmias. We have seen restless patients, in whom acute heart decompensation was diagnosed, become perfectly calm, cooperative and healthy postoperatively when the overfilled bladder was emptied.

1.6. Central Anticholinergic Syndrome

After anaesthesia, patients may have unexpected delay in mental arousal. In many cases, where treatment of motor, psychological or drug-induced disturbances does not result in restoration of the patient's conscious and cooperative state, the disturbed recovery from anaesthesia may be due to the central anticholinergic action of drugs. Behavioural and somatic symptoms of anticholinergics are numerous and unpredictable. They have been named the "central anticholinergic syndrome".

Various terms, nowadays obsolete, have been used to describe the central anticholinergic syndrome: postanaesthetic delirium (Brebner and Hadley, 1976; Eckenhoff et al., 1961), postanaesthetic depression, emergence situation, emergence delirium (Bastron and Moyers, 1967), postoperative somnolence and adverse postanaesthetic effects (Brebner and Hadley, 1976). Nowadays the term central anticholinergic syndrome is preferred because it indicates the aetiology of the disturbed state. The term was coined by Longo (1966) when he wrote about behavioural and electroencephalographic effects of atropine and related compounds. He observed that anticholinergics may cause dissociation of behaviour from the EEG-pattern, and called this phenomenon EEG-behaviour dissociation. Longo's work, a continuation of earlier Italian studies, established that gross changes of behaviour may result from the administration of anticholinergics, without concomitant changes of the EEG (Loeb et al., 1960; Longo, 1956; Longo, 1962).

In the analysis of the postanaesthetic disturbances it was concluded that the postanaesthetic excitation is not a simple reversal of Guedel's induction stage II (Artusio, 1964). It was suspected that anticholinergics might be the causative factor (Eckenhoff, 1961).

A myriad drugs are productive of the central anticholinergic syndrome (Table 1). Most of them are given for other reasons than their anticholinergic effect. Granacher and Baldessarini (1970) reported that at least 500 drugs capable of inducing central anticholinergic effects were on sale in the USA. Such drugs may play a role in the central anticholinergic syndrome during recovery from anaesthesia (Breivik, 1975). Ketamine, benzodiazepines and nitrous oxide are nowadays thought capable of central anticholinergic effects (Rupreht, 1980a; Rupreht, 1980b). It has also been shown that psilocybin causes predominantly central anticholinergic symptoms (van Poorten et al., 1982).

Table 1. Drugs and Chemicals That May Produce the Central Anticholinergic Syndrome.

Antidepressants	(Amitriptylline, Desapiramine, Imipramine, etc.)
Antihistamines	(Phenothiazines, Butyrophenones, etc.)
Antispasmodics	(Promethazine, Orphenadrine, etc.)
Antiparkinson agents	(Propantheline, etc.)
Ophthalmic preparations	
Belladonna alkaloids	
Opioid agents	
Anaesthetic agents (including gases)	(N_2O, cyclopropane, etc.)
Warfare chemicals	(incapacitants: glycolate esters, like the psychotomimetic drug Ditran; Quinuclidinium)
Toxic plants	
Tranquillizers	(benzodiazepines)
Hypnotics	
Psylocibine	

In the presenile dementia or in Alzheimer's disease the central cholinergic system may be deranged (Peters and Levin, 1977; Thal et al., 1983) to such a degree that the symptoms of the disease resemble the anticholinergic action of drugs. In these patients even traces of anticholinergic drugs may cause complete block of central cholinergic function.

Scientific interest in the central action of anticholinergic compounds is of rather recent date, but part of this knowledge is very old. Central anticholinergic poisoning has been used in the popular drug lore of many peoples and is now becoming the study of ethnopharmacologists. The anticholinergic action of substances played an important role in states of separate reality (Castaneda, 1968), in the effects of "plants of the gods" (Schultes and Hofman, 1980) or simply "narcotic plants" (Emboden, 1979).

Signs of the Central Anticholinergic Syndrome

The popular mnestic trick for signs of a classical anticholinergic picture reads: blind as a bat, dry as a bone, mad as a hat-

ter, hot as fire, red as a beetroot. Unfortunately, there is only one central signs, "mad", included in this description and, as it happens, this madness must be further particularised in order to match the reality better. In effect, central signs actually form the bulk of an anticholinergic clinical picture. Symptoms of the central anticholinergic syndrome in recovery period are excitatory or depressive. Together with central symptoms, various peripheral signs can be observed. Longo (1966) described drowsiness, coma, nonaggressive excitement, ataxia and asynergia as the most prominent signs of the central anticholinergic syndrome. Many symptoms have been added since, both to the central symptoms (Table 2) and to peripheral ones (Table 3).

Table 2. Central Symptoms of the Central Anticholinergic Syndrome.

- disorientation
- ataxia
- asynergia, incoordinated movements
- delirium
- hallucinations
- stupor
- coma
- delay in mental arousal after anaesthesia
- thought impairment
- disturbances of short-term memory
- amnesia
- drowsiness
- non-aggressive excitement
- speech difficulties
- tremor
- crying
- logorrhoea
- weakness
- emotional instability
- motor unrest; excitation
- perseverations
- agitation
- restlessness
- headache
- convulsions
- delusions and illusions
- paranoid ideations
- toxic psychosis (in psychiatry)
- déjà vu symptom
- respiratory depression
- hyperalgesia
- central hyperpyrexia
- EEG-behaviour dissociation

Table 3. Peripheral Symptoms of Anticholinergic Poisoning

- myadriasis
- photophobia
- tachycardia
- heart arrhythmias
- dry mouth
- speech difficulties
- dry and red skin
- increased body temperature
- retention of urine
- weak or absent gastroenteral motility
- oedema of the uvula (sometimes)

1.7. Own Observations and Experience of Diagnostic Features, Incidence and Therapy of the Central Anticholinergic Syndrome

Among the diagnostic features of the central anticholinergic syndrome, drowsiness and coma, or restlessness, are most striking during the patient's recovery from anaesthesia. When it is reasonable to assume that the anaesthetic drugs have been metabolized, excreted, antagonized or pharmacologically inactivated by redistribution - and the patient is still not reacting appropriately to the surroundings - the central anticholinergic syndrome may be considered as a possible cause of the disturbed recovery. After excluding other common causes of disturbed recovery from anaesthesia, the anaesthetist may suspect the presence of the central anticholinergic syndrome on the grounds of given anticholinergics (diagnosis per exclusionem) and eventually proceed to administering a centrally active cholinergic agent (e.g., physostigmine) and waiting for the disappearance of the anticholinergic signs (diagnosis ex iuvantibus). In view of the present impossibility of diagnosing the central anticholinergic effects instrumentally, this approach has proved very practical and safe.

The spectrum of symptomatology of the central anticholinergic syndrome is wide, varying from the deeply comatose patient, through sluggish reaction to questions, to apparently normal responses but with a superimposed amnesia and disorientation. Various other symptoms may be superimposed: incoordinated movements, tremor, inadequate reactions to external stimuli, crying or logorrhoea. The delirious behaviour of patients during recovery becomes evident with the first signs of restless arousal and it demands quick intervention (Fig. 1). In this period, pain should be excluded or treated and one must also treat any existing hypoxia. Further examination of the patient in such a condition is usually of little help. Sometimes a low pulse rate may be found, but this will increase after treatment with physostigmine. The size and reaction of the pupils can be normal or changed by previously administered drugs. The pupillary signs have

become of practically no value in contemporary anaesthesia when agents with potent and possibly opposing action on the ocular signs, are often used.

Diagnostic criteria of the central anticholinergic syndrome

As a general rule, two peripheral and one central signs of anticholinergic activity (see Tables 2 and 3) are sufficient to justify the diagnosis of the syndrome.

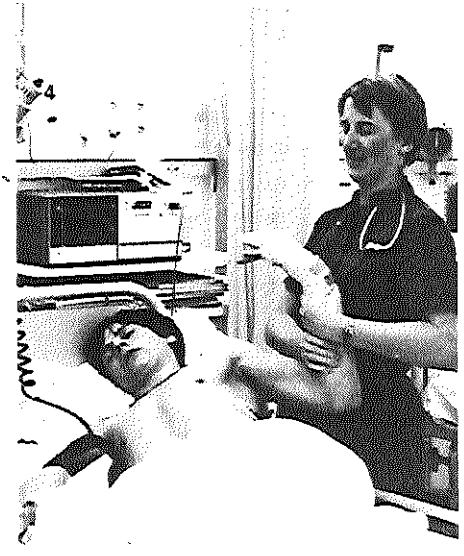


Fig. 1. Central anticholinergic syndrome in one of our patients (1979), 30 minutes after anaesthesia. Note that two persons were needed to protect the patient and the operated site. It was concluded that atropine sulphate was the main cause of the disturbed recovery. Physostigmine salicylate (2 mg) was given intravenously and the patient was awake and behaving normally within 3 minutes. At that time, no residual effects of anaesthetics or any pain were traceable.

The diagnosis of the central anticholinergic syndrome in our patients was first based on the patient's clinical state and on

the agents given before and during anaesthesia (Rupreht and Dworacek, 1976). When centrally active anticholinergics had been used, the development of the syndrome was suspected in patients who did not recover promptly and smoothly. Half an hour of recovery (mean waiting time) was allowed before considering the diagnosis of the central anticholinergic syndrome. Physostigmine (0.04 mg/kg) was then administered and the disappearance of the syndrome was required for the definite confirmation of the diagnosis.

In the group of 200 patients where the central anticholinergic syndrome was diagnosed and confirmed, six different anticholinergic drugs or combinations of drugs were discerned: atropine, atropine-promethazine, atropine-droperidol, atropine-diazepam, scopolamine, atropine-chlorpromazine. Occasionally, several symptoms were seen in one patient (Table 4).

Table 4. Symptoms of the Central Anticholinergic Syndrome in a Group of 200 Diagnosed Cases.

SYMPTOM	NUMBER
drowsiness, depression	121
restlessness	57
shivering	27
confusion	20
speech disturbance	5
central hyperpyrexia	2
ataxia	1
hallucinations	1
violence	1

We studied the incidence of the central anticholinergic syndrome in a prospective follow up of general and regional anaesthetic procedures. 3585 patients were recovered, 1720 males and 1865 females, from various types of anaesthesia (Rupreht and Dworacek, 1976).

The diagnosis of the central anticholinergic syndrome in our reasonably large amount of clinical material, was established by

the anaesthetist who was on duty in the recovery area or by the patient's own anaesthetist. The diagnosis was confirmed by the positive effect of physostigmine. Those cases of the central anticholinergic syndrome which were diagnosed but where treatment with physostigmine could not be performed (because of contraindications) were excluded from the statistics because we included only those with a double-established diagnosis of the central anticholinergic syndrome.

The central anticholinergic syndrome was diagnosed in 9.4% of the patients who were given general anaesthesia (Table 5) and in 3.3% of the patients who were operated upon under a regional block. The incidence of the central anticholinergic syndrome was not dependent on age or sex (Table 5), nor was there any difference in the frequency of the syndrome within groups of patients receiving either atropine sulphate, diazepam or enflurane (Table 6). Regional anaesthesia or block was performed on 271 patients, who were sedated with a benzodiazepine and received atropine. 9 cases of central anticholinergic syndrome were diagnosed in these patients (3.3%).

Table 5. Age Distribution of Patients and Incidence of Central Anticholinergic Syndrome after General Anaesthesia.

AGE (years)	Nr. Patients	Male	Female	Nr. CAS	%CAS	%CAS male	%CAS female
0- 5	22	14	8	1	4.5	7	-
6-15	120	59	61	11	9.6	10	8.1
16-50	2139	966	1173	221	10	10	10
> 51	1304	773	531	104	7.9	6	9.6
Total	3585	1812	1773	337	9.4	8.3	6.9

Table 6. Relation: Drugs Used and Incidence of the Central Anticholinergic Syndrome (*).

Drug	Nr. Anaesthetics	Nr. CAS	% CAS
Atropine sulph.	2763	270	9.7
Diazepam	1052	93	8.8
Enflurane	1043	98	9.3

*These anaesthesias were given in a 10-month period 1977-1978.

In a comparable review of patient material, where only "post-anaesthetic excitement" was recorded, 14.436 patients were followed. 6% males and 5% females showed "excitement" during the recovery (Eckenhoff et al., 1961). In this report no mention is made of the symptoms of depression which may be a form of the central anticholinergic action. Other reports of disturbed recovery from anaesthesia also give a varying incidence depending on the degree of agitation studied. The range was 3-20% (Smessaert et al., 1960; Artusio, 1964). Breivik (1975) found the central anticholinergic syndrome in 1% of his patients, while Holzgrafe et al. (1973) reported 11.2% of postanaesthetic "reactions to scopolamine". Several of these authors did not include all the signs of anticholinergic action in the disturbances they described. Amnesia was not considered a "disturbance" but a "normal occurrence" of the postanaesthetic state.

Treatment of the central anticholinergic syndrome requires the elevation of the acetylcholine level in the brain. This can be achieved by administration of physostigmine salicylate, galanthamine hydrobromide (Baraka and Harik, 1977), 4-aminopyridine (Rupreht, 1981) or tetrahydroaminacrine (Mendelson, 1975). All these drugs can penetrate into the brain and cause an increase of the acetylcholine level. Galanthamine hydrobromide and tetrahydroaminacrine are not readily available and no considerable knowledge has been gathered on their applicability in the treatment of the central anticholinergic syndrome (Rupreht, 1980b). 4-aminopyridine, on the other hand is so aselective in its actions (Thesleff, 1980) that the advocation of its use in this therapeutic field failed (Rupreht, 1981; see also Chapter 9).

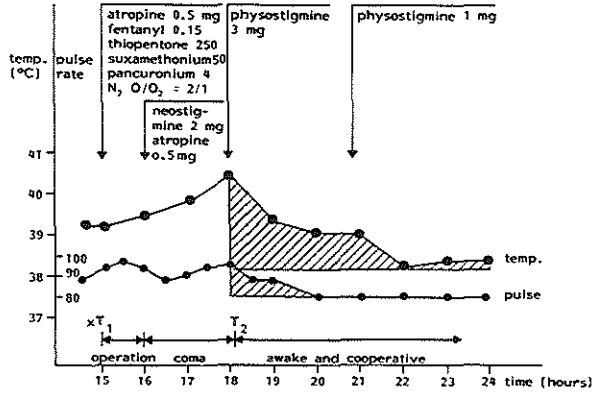
For the specific, tertiary cholinesterase inhibitor physostigmine, it was established that the optimal initial dose is 0,04 mg kg^{-1} (Rupreht and Dworacek, 1976). This dose must be given either i.m. or slowly i.v. into an open drip so that the drug is evenly flushed into the circulation. I.v. administration should not exceed 1 mg physostigmine per min. The drug in a dose of

0.04 mg kg^{-1} is inactivated within 90-120 min (Rupreht and Dworacek, 1976; Dworacek et al., 1979; Atkinson et al., 1982). This means that physostigmine injection must be repeated after 90-120 min if the signs of the anticholinergic syndrome recur.

Physostigmine acts rapidly, resolving the symptoms of the central anticholinergic syndrome within 30 sec - 10 min. In a later study (Neumark and Riegel, 1981) it was found that physostigmine was centrally active within 9 $\pm$ 4.5 min after administration. The speed and the intensity of the physostigmine-induced effect depends on the anticholinergic specificity of the CNS-active drug (the response is clear-cut in the case of pure anticholinergics), the circulatory state of the patient, and the presence of other psychoactive drugs. In patients with benzodiazepine-induced depression improvement following the administration of physostigmine is sometimes sluggish and incomplete, and may be unpredictable (Rupreht, 1980a). When there is no improvement of the psychic condition after 10 min, the diagnosis of central cholinergic block (central anticholinergic syndrome) must be dropped or one must consider whether the patient is extremely intoxicated with tricyclic antidepressants or belladonna alkaloids and therefore requires additional physostigmine. Many patients, however, are relieved from the central anticholinergic syndrome so rapidly that they wake up "on the physostigmine-needle".

In another study (Grote et al., 1981) it was found that 2 mg physostigmine shortened lormetazepam-induced sleep from 120 min to 5-12 min when given at 130 min after administration of lormetazepam. After neurolept anaesthesia, all patients were in good contact with their surroundings when given physostigmine. Those who were not given physostigmine were not able to converse until 90 min after the end of anaesthesia (Neumark and Riegel, 1981). Treatment of the central hyperpyrexia-symptom of the central anticholinergic syndrome with physostigmine in some of our patients can be illustrated by the following two Case Reports.

Case I: - A 79 year old very ill lady, body weight 80 kg, was scheduled for emergency cholecystectomy. She was febrile, rectal temperature: 39.3°C. Blood pressure was 180/100 mm Hg, pulse rate 100 per minute. She was given 0.5 mg atropine sulphate as premedication and anaesthesia was induced with 0.15 mg fentanyl and 250 mg thiopental.
Succinylcholine 50 mg was used to facilitate the intubation, 4 mg pancuronium was administered for prolonged relaxation. The patient was ventilated with nitrous oxide (60 Vol%) - oxygen mixture. The operation lasted sixty minutes, in the course of which the patient received additional 0.3 mg fentanyl and 100 mg thiopental. The residual relaxation was reversed by 2 mg neostigmine mixed with 0.5 mg atropine sulphate. The ventilatory and circulatory condition in the postoperative period was satisfactory. However, the patient did not regain consciousness for 2 hours after the operation. She did not react to pain stimuli. The rectal temperature was 40.3°C, and the hands were cold.
Physostigmine salicylate 3 mg was administered and within five minutes we could talk to the patient who appeared fully conscious and cooperative. She started to sweat profusely. Within sixty minutes the rectal temperature dropped to 39.3°C. She received additional (1 mg) physostigmine salicylate, 120 minutes after the first dose, and the rectal temperature decreased further to 38.2°C in the following two hours (Fig. 2).



♀, 79 years, ASA III, acute cholecystitis, ischaemic heart and obstructive lung disease

Fig. 2: Central hyperpyrexia complicating the anaesthetic course. It was probably caused or aggravated by atropine sulphate. The involvement of the central cholinergic transmission was established after physostigmine resulted in prompt resolution of hyperpyrexia. Note that neostigmine was administered before physostigmine but did not resolve the increase of the body temperature (detailed description in Case Report I).

Case II: - A 38 year old lady was anaesthetized for a curettage after a septic abortion. She received 0.5 mg atropine sulphate, 250 mg thiopental and 70 Vol% nitrous oxide in oxygen during induction. Rectal temperature was 38.4°C. Following the very short procedure she became very agitated while the temperature increased to 41.5°C. We carefully administered physostigmine salicylate 3 mg intravenously and within six minutes she was completely aware of her surroundings and cooperative. She started to sweat profusely, the pulse rate dropped from 120 min^{-1} to 90 min^{-1}. The blood pressure remained unchanged. The rectal temperature decreased to 39.5°C within 90 minutes. She received a further 2 mg physostigmine salicylate intravenously and thirty minutes later the temperature dropped to 38.1°C, at which level it remained for the following two days, during which time the patient was treated with antibiotics.

These two case reports are instructive because they indicate how difficult it is to differentiate between central and peripheral increase in body temperature. Neostigmine, devoid of central action, did not affect the increase in body temperature. However, administration of the tertiary anticholinesterase, physostigmine resulted in the immediate return of the temperature to normal. We concluded that a central anticholinergic effect was one of the factors causing the hyperpyrexia, which could thus be specifically treated with physostigmine. Knowledge of this possibility is important. In anaesthesia and in toxicology comatose patients may suffer from central hyperpyrexia, which is a hazardous clinical problem and may cost the patient's life. The clinical situation in this respect has now been greatly improved because doctors early suspect that changes of behaviour may be due to the central effects of anticholinergics. These effects call for the administration of physostigmine which clears the picture of the anticholinergic syndrome, including elevated body temperature of central origin.

In the thermoregulatory centre in the rostral part of the hypothalamus (Hemingway and Price, 1968) numerous cholinergic synapses have been identified (De Maar, 1956). It is probable that the blocking of muscarinic sites in the thermoregulatory center disturbs the temperature regulation, not by setting the thermostat higher (these patients do not shiver) but perhaps by block

ing incoming information from the periphery. Administration of physostigmine probably eliminates such disturbances of the central cholinergic function.

Arousal after physostigmine is usually pleasant to the patient. We have not observed psychic depression after the administration of physostigmine for the treatment of the central anticholinergic syndrome. On the contrary, patients in whom crying and unhappiness, or depressive anxiety, were a part of the central anticholinergic syndrome, calmed into a positive attitude after physostigmine had been given them. This also happened in numerous cases of tricyclic antidepressant intoxication treated with physostigmine. Although not particularly happy or grateful, such unfortunate suicidally miserable patients were obviously not more depressed on waking-up than before the ingestion of the overdose.

The analgesic state of the patient is improved after arousal from the central anticholinergic syndrome. The patient reacts appropriately to the situation and is better able to communicate his discomfort. In addition, the analgesic action of physostigmine has been documented in experimental medicine (Flodmark and Wramner, 1945). It has been suggested that this effect of physostigmine is based on its interaction with the 5-HT transmission system (Aiello-Malmberg et al., 1979). The analgesic action dependent on the 5-HT system (Yaksh, 1979) cannot be antagonized with either atropine or naloxone (Weinstock et al., 1980; Rupreht and Dzoljic, 1983).

Physostigmine can safely be given to patients with glaucoma. In a review of more than 1000 patients following anaesthesia for eye surgery, no untoward effects of physostigmine were recorded (Dworacek, 1982).

Cardiovascular activity is usually increased by physostigmine (Rupreht and Dworacek, 1976) provided that the drug is not given

to a hypercapnic or hypoxic patient. In this last respect, the same precautions are necessary as with neostigmine (Riding and Robinson, 1961). In the absence of hypercapnia and hypoxia, slowly given physostigmine causes cardiovascular stimulation. These observations are backed by experimental findings that physostigmine causes a release of adrenaline from the suprarenal gland (Schneider et al., 1980; Schneider et al., 1982). Physostigmine also causes a central pressor response (Brezenoff, 1973; Janowski et al., 1983). There is evidence that central, predominantly muscarinic acetylcholine - catecholamine linkages in the posterior hypothalamus, the brain stem, and the medial mammilary nuclei are in part responsible for the central cholinergically mediated increase in blood pressure (Brezenoff and Giuliano, 1982).

Other side effects of physostigmine during recovery from anaesthesia are: nausea, vomiting, sweating, gastrointestinal and urogenital hypermotility and diplopia. Whereas symptoms such as sweating, smooth muscle motility and diplopia are rarely of any considerable concern, the occurrence of nausea and vomiting needs close attention and preventive measures.

Factors which stimulate nausea and vomiting are: rapid injection, full stomach, concomitant drugs, hypercarbia, hypoxia and operations which stimulate the vagus.

Factors which prevent nausea and vomiting are: empty stomach, slow injection (less than 0.015 mg kg^{-1} min^{-1}) and antiemetic agents (Haloperidol, Metoclopramide, Alizapride etc.).

Concomitant clinical situations may primarily contribute to nausea after physostigmine: operations on the ear, brain or abdomen; patient's continuing medication; the presence of hypercarbia. It has been suggested that the incidence of nausea is dose-dependent (Bidway et al., 1979), 2 mg physostigmine causing nausea and 1 mg not. However, a review of several thousands of ad-

ministrations of physostigmine in various dosages and routes does not support these findings (Dworacek et al., 1979). The route of administration of physostigmine does not influence its onset of action but apparently is important in decreasing the incidence of early vomiting. Intramuscular injection of physostigmine does not diminish the incidence of nausea (15%) but does almost always eliminate vomiting. According to our own follow-up of patients, it is essential to inject physostigmine slowly and evenly, thus probably preventing excessive peak concentrations which appear to be the cause of trouble. Our recommended dose and speed of injection of physostigmine, i.e. 0.04 mg kg^{-1} and not faster than 1 mg min^{-1}, have been widely practised and cited in the standard anaesthetic literature (Atkinson et al., 1982).

Contraindications to treatment with physostigmine used to be divided into relative and absolute ones. The present clinical and experimental knowledge of physostigmine enables clinicians precisely to delineate states in which administration of this drug should be withheld. Until recently, it was not fully appreciated that the pharmacological effects of physostigmine are different from those of neostigmine. Perhaps because of that, several "relative" contraindications to physostigmine were cited. These were: bradycardia and hypotension, asthma, diabetes mellitus, mechanical obstructions of the intestinal or genitourinary tract and glaucoma treated with topical organophosphorous compounds. In own experience, no patient with these relative contraindications suffered untoward effects from physostigmine, provided that the drug was injected slowly in the absence of hypoxia or hypercapnia (Rupreht and Dworacek, 1976; Rupreht and Dworacek, 1977).

However, there are four clinical states in which physostigmine is (absolutely) contraindicated: closed craniocerebral injuries, myotonia dystrophica, intoxications with cholinesterase inhibitors, and intoxications with barbiturates.

In closed craniocerebral injuries, the levels of acetylcholine may be high and a tertiary belladonna alkaloïd is the right therapeutic agent (Lechner, 1956). Patients with myotonia atrophica or myotonic muscular dystrophy states are often encountered by anaesthesiologists. It is well-known that these patients should not be given cholinesterase-inhibitors, which may aggravate the muscle weakness (Miller and Lee, 1981). The sensorium in patients intoxicated by cholinesterase-inhibitors is often narrowed. These agents usually also act centrally and physostigmine is certainly contraindicated. Coma caused by barbiturates is a state which has recently been added to the (absolute) contraindications to physostigmine (Daunderer, 1980). In the case of barbiturates, the stores of acetylcholine in the brain are increased and physostigmine may cause worsening of the picture and sometimes convulsions. In anaesthetic practice we observed that physostigmine in the presence of barbiturates does not "waken-up" the patient. Actually, one often gets an impression that physostigmine lengthens the sluggishness and sleepiness caused by barbiturates. This was the reason why, from the very beginning of treatment of the central anticholinergic syndrome during recovery, we insisted that any previously given barbiturates must be considered no longer to be acting centrally before physostigmine was given (Rupreht and Dworacek, 1976; Rupreht and Dworacek, 1977).

A contemporary review of data about physostigmine is given in Table 7.

Table 7: Physostigmine: A contemporary (1985) profile.

Preparation	physostigmine salicylate, 1%, 1 ml ampoules, stabilized with Na-thiosulphate.
Origin	Physostigma venenosum (Balfour)-Western Africa
Source	MERCK (substance); Univ. Hospital Dijkzigt, Pharmacy; Anticholium; Köhler Chemie, FGR.
Indications	Besides Central Anticholinergic Syndrome: intoxications with anticholinergically active substances, heroin overdose, morphine depression, differential diagnosis of coma,

Table 7 (contd.)

Indications	Alzheimer disease (dementia syndromes), central hyperpyrexia, alcohol poisoning, nitrous oxide withdrawal syndrome, laryngospasm, ketamine hallucinations, psylocybine intoxications, stereotaxic procedures in general anaesthesia.
Dose (maximal, initial)	0.04 mg kg^{-1}; slowly: < 0.015 mg kg^{-1} min^{-1} (treatment of the central anticholinergic syndrome).
Route	i.v.: i.m.;
Effect	onset: within 30 sec - 10 min. duration: 90-120 min.
Activity	Cholinesterase inhibition (centrally active!) analgesia (5-HT pathway?)
Contraindications	closed cerebral injuries, barbiturate coma, ChE-inhibitor toxicity, dystrophic myotonia;
Acceptance	excellent. Recovery stay can be shortened.

1.8. Use of Physostigmine by the Dutch Anaesthetists.

Before 1974, the therapeutic use of physostigmine in anaesthesia was unknown in the Netherlands.

A questionnaire was sent in 1984 to the Dutch anaesthetists asking them whether they used physostigmine, how often, which brand and whether they used the quaternary methyl-atropine bromide (the use of this drug is one way of decreasing the incidence of the central anticholinergic syndrome in anaesthesia).

62% of the anaesthetists who replied now use physostigmine, 17% of them the preparation Anticholium (Dr. F. Köhler Chemie). The local pharmacy-shop prepares physostigmine for 83% of users. 20% of anaesthetists used physostigmine less than 10 times per year, 14% more than 50 times, others between these two extreems. 30% of the anaesthetists used the quaternary derivative of atropine.

The replies to the questionnaire are informative and show that the therapeutic value of physostigmine is now widely known and accepted. However, a further increase in the use of quaternary

atropine is mandatory in order still more to decrease anticholinergic disturbances of recovery from anaesthesia.

1.9. Addendum: Brief History of Physostigmine.

The black bean-like seeds of Physostigma venenosum (Balfour) (Fig. 3) were brought from the Calabar region of West Africa to Europe by a British medical officer Daniel (Koelle, 1968). A pure alkaloid was isolated by Jobst and Hesse in 1864 and was named physostigmine. A year later, Vee and Leven isolated the same substance, which they called eserine, probably because the beans were called "esére" (Dragstedt, 1945). Possibly the first recorded therapeutic use of the pure drug was in ophthalmology (Laquer, 1877). However, the activity of an unidentified substance from Calabar beans was well-described earlier (Christison, 1855; Fraser, 1863). Fraser used the term "ordeal beans" and reported that the drug served as a truth drug in West Africa. The accused

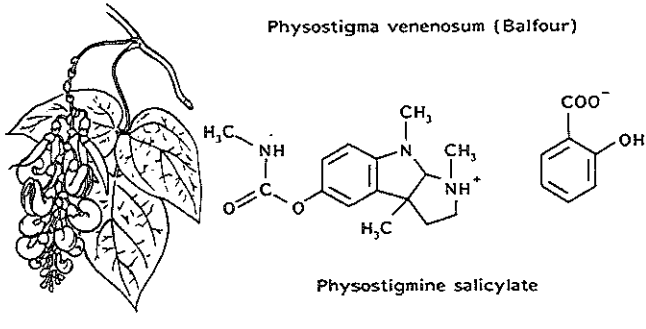


Figure 3: Physostigma venenosum (Balfour) is a woody climber native to tropical West Africa (a leaf and blossom shown left); its seeds are rich in a tertiary alkaloid physostigmine (structural formula of physostigmine salicylate on the right).

was forced to swallow a quantity of beans and was laid close to the campfire. Two issues were possible: early vomiting, survival and proclamation of innocence or slow cholinergic intoxica-

tion, proceeding from sweating and diarrhoea to compromised breathing, coma with seizures and death. Evidently, Justitia had been blinded by looking into the tropical sun for enlightment! A year after Fraser's report (1863), the extract of the Calabar beans was used in Prague as a "specific antidote" against atropine poisoning (Kleinwächter, 1864). Kleinwächter's observations were published in Berlin, within 22 days (Fig. 4). In spite of


BERLINER
KLINISCHE WOCHENSCHRIFT.
Organ für practische Aerzte.
Montag, den 12. September 1864. № 38. Erster Jahrgang.

Figure 4: The heading of the Berliner Klinische Wochenschrift of 12 September 1864, with a fraction of the text of Doctor Kleinwächter's report on the action of the extract of the Calabar bean against intoxication with atropine. Note, however, that only 22 days passed between this important clinical finding and its publication. "l.j." is short for "laufendes Jahr", meaning: "this year, current year" (according to van Gelderen's Duits-Nederlands Woordenboek, 1st Ed., Groningen, 1906).

Kleinwächter's explicit mention that the Calabar-extract could become a potent and reliable antidote for intoxication with atropine (Fig. 5), this knowledge somehow went into oblivion. Physostigmine remained in use in ophthalmology and was later replaced by a synthetic cholinesterase inhibitor, neostigmine. The use of physostigmine in anticholinergic poisoning remained unmentioned

Als beide Kranke aus unserer Anstalt forttransportirt wurden, glaubte ich kaum, dass letzterwähnter lebend nach Hause kommen werde, so bedeutend waren die Affectionen. Gegenwärtige, rein zufällige und versuchsweise eingeleitete Therapie mit Calabar bei Atropinvergiftung sollte nicht ausser Acht gelassen werden. Ich glaube nicht, dass die beobachteten Wirkungen dem Zufalle zuzuschreiben seien; die Folgen stellten sich zu rasch und zu deutlich ein, als dass man den Causalnexus hätte verkennen können. Jedenfalls wäre es sehr wichtig, um das Sachverhältniss objectiv festzustellen, zahlreiche und genaue Versuche mit Calabar als Antidot des Atropins vorzunehmen.

Die bis jetzt üblichen, mehr oder weniger planlosen und unzuverlässigen therapeutischen Proceduren bei Belladonnaintoxicationen wären, wenn sich die Wirkung des Calabar bewährte, überflüssig, und wir hätten dann bei dieser, wenigstens in unserem Spitale oft vorkommenden Vergiftungsform ein sicheres und kräftiges Antidot, welches nicht einer zufälligen Entdeckung, sondern positiven wissenschaftlichen Voraussetzungen sein Dasein verdankte.

Beide in Rede stehende Patienten befinden sich auf dem Wege der Heilung, so zwar, dass der mit Calabar behandelte bereits als genesen angesehen werden kann.

Figure 5: Doctor Kleinwächter stressed in Berl. Klin. Wochenschr. 12 September 1864, that the observed curative effect of the Calabar-extract on atropine poisoning was no coincidence. He urged, further study of this effect. Note that he was aware of the deficiencies of the then usual treatment of intoxications with anticholinergics (chaotic and unreliable). He was convinced that the calabar-extract could become a potent and reliable antidote for intoxication with atropine.

even in the standard text-books (Innes and Nickerson, 1965) and "sedatives in moderate dosages" were advocated instead. A revival of the use of physostigmine was brought about in psychiatry, where it was used to terminate the atropine-induced "somatic therapy"-coma (Forrer and Miller, 1958).

The use of physostigmine in anticholinergic poisoning was mentioned in "The Pharmacological Basis of Therapeutics" rather recently (Goodman and Gilman, 1975). Thanks to its capacity to modify central cholinergic activity, physostigmine nowadays enjoys considerable popularity in anaesthesiology, toxicology and psychiatry. No doubt erroneously, it was even called "a universal antagonist" (Friedman, 1980). The use of physostigmine to counteract central anticholinergic effects appeared in standard anaesthetic text-books in the early eighties (Atkinson et al., 1982).

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PART TWO

OWN CLINICAL DATA AND ANIMAL EXPERIMENTS CONCERNING THE USE OF PHYSOSTIGMINE IN ANAESTHESIA

CHAPTER 2.

METHYL ATROPINE BROMIDE VERSUS ATROPINE SULPHATE. A CLINICAL COMPARISON

SUMMARY

In a double blind clinical investigation we compared methyl atropine bromide to atropine sulphate in equivalent doses for their effects on changes in the heart rate and dryness of the mouth. Drugs were administered five minutes before the induction of anesthesia. Methyl atropine bromide appeared to have a stronger positive chronotropic effect on the heart rate and a more pronounced mouth drying action. Less dysrhythmias were observed after the methyl congener. Both drugs failed to alter blood pressure significantly. We concluded that methyl atropine bromide is superior to atropine sulphate because it does not produce side effects which may cause the central anticholinergic syndrome. For clinical use, however, methyl atropine bromide should be administered only in half-equivalent dose of atropine sulphate to prevent excessive tachycardia and dryness of the mouth.

INTRODUCTION

The use of anticholinergic compounds in connection to surgery goes far back into the grey mythical period. Before the general acceptance of centrally active anesthetics (ether, chloroform), atropine had been used in combination with morphine. The drug diminished nausea and provided the patient with the soothing oblivion. The use of anticholinergic premedication for patients who were to be given ether or chloroform became a sine qua non of the art of anesthesia in its early decades. These drugs provided safety against copious secretions and associated disturbances of a smooth anesthetic. The use of atropine-like substances together with the early anesthetic agents was very necessary and most anesthetists kept using these drugs even with agents and techniques which did not require it. It became a worldwide atavistic habit, and not surprisingly, the routine use of anticholinergic agents in anesthesia has been repeatedly questioned (1, 4, 5, 7).

Recently, emphasis has been placed on the central effects of anticholinergic drugs; if tertiary compounds, they will cross the blood brain barrier rapidly and may cause drowsiness, disorientation and other symptoms of what became known as the central anticholinergic syndrome (CAS) (8, 12).

This has in turn led to search for anticholinergic compounds that cannot penetrate into the brain. Glycopyrronium has gained some popularity (3, 10); it will, however, slightly penetrate into the brain and may relax the sphincter of the cardia (2) thus possibly increasing the risk of aspiration during anesthesia. The other possibility of reducing the occurrence of the CAS is to resort to quaternary belladonna compounds (6, 9, 13) which, although known and described for more than three decades, have not been used to any extent by anesthetists. Methyl atropine bromide (MAB) is a very suitable drug and we decided to compare it to atropine sulphate (AS).

METHOD

The comparison of MAB and AS was done in one hundred patients scheduled for eye, orthopedic, plastic or reconstructive surgery. The age and weight varied greatly with mean $\pm$ SD of 42 $\pm$ 15 years and 68 $\pm$ 13 kg, respectively. Excluded were those patients in whom an anticholinergic was contraindicated. Following an informed consent on a previous day the patients were brought to the induction area unpremedicated. They were checked for blood pressure, heart rate, heart dysrhythmias and dryness of the mouth immediately prior to the administration of a drug. AS or MAB 7,5 $\mu g\ kg^{-1}$ was administered intravenously five minutes prior to the induction of anesthesia in accordance with a double-blind protocol. The checks as described above were repeated after 1, 2, 3, 4 and 5 minutes. Then anesthesia was started (Thiopentone, Suxamethonium, Nitrous Oxide and Enflurane or Pancuronium-Fentanyl accordingly). Measurements during the anesthetic procedure were done again at 10, 15, 20, 25 and 30 minutes . Particular attention was paid to changes of the electrocardiogram (ECG). We graded dryness of the mouth from one to four points (table I).

TABLE I

Schedule for grading the dryness of the mouth

Points	Description
1	wet
2	normally moist
3	dry, the tongue free
4	very dry, the tongue sticks to the palate

Statistical analysis within each group of the measured effects of AS or MAB was carried out using the rank sign test of Wilcoxon for 2 paired samples. The analysis between the two groups was done using the Mann-Whitney U-test for two independent samples.

In an additional clinical follow-up we subsequently followed the incidence of the CAS during recovery from anesthesia in 2940 patients who received MAB during the anesthetic (0.0075 or 0.0037 mg kg^{-1}).

RESULTS

Disturbance of the heart rhythm was seen in 5 patients of the AS group; 4 patients with premature sinus ventricular contraction (PSVC), 1 with premature ventricular contraction (PVC). In the MAB group 1 patient had PSVC and one PVC. Dysrythmias happened in the first 4 minutes after the administration of the anticholinergic agent, no treatment was required and they disappeared spontaneously.

Dryness of the mouth was more pronounced in the MAB than in the AS group (table II).

TABLE II

Dryness of the mouth after administration of AS or MAB

Time (min)	0	1	2	3	4	5	10	15	20	25	30
AS	1,86	1,88	2,04	2,18	2,36	2,40	2,30	2,42	2,52	2,52	2,42
MAB	1,24	1,94	2,04	2,26	2,44	2,56	2,68	2,72	2,64	2,70	2,72

Blood pressure changes were minimal in both groups of the patients. Heart rate increased significantly in both groups.

However, the rise was more pronounced in the MAB group, being 50% after four minutes in contrast to 19% rise after ten minutes in AS group. In both groups, heart rates were significantly higher than the initial rate at all time intervals.
The increase of the heart rate after MAB was significantly higher than after AS (Fig.1) at all intervals.

The subsequent clinical follow-up of the 2940 patients in whom MAB was used instead of AS during anesthesia resulted in 4% incidence of CAS-like central disturbances of recovery.

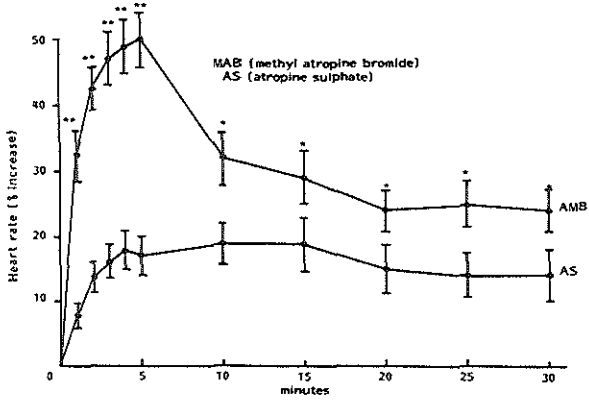

Fig. I: Effect of 7.5 µg kg^{-1} i.v. atropine sulphate or methyl atropine bromide on the increase of the heart rate. Each group counted 50 patients. Both drugs caused a significant increase of heart rate at all time intervals (Wilcoxon test). The increase in heart rate due to AS was significantly lower then due to MAB at all time periods (Mann-Whitney U-test for two independent samples; ** : $p < 0.001$; * : $p < 0.05$) Mean values are represented; verticals are standard errors of the mean.

DISCUSSION

Preanesthetic medication which is aimed at easing the induction of anesthesia or to allay patient's apprehension has repeatedly aroused controversy for several reasons (1, 4, 5, 7, 13). The unwanted postanesthetic side effects caused by the centrally active anticholinergics have been well recognized by practicing anesthetists (1, 12) and the search for clinically useful anticholinergic agents without central side effects has led to the introduction of glycopyrronium or quaternary belladonna alkaloids. Glycopyrronium was shown to decrease cardia sphincter tone (2). Mirakhur et al. (11) found that this drug caused less dysrhythmias than atropine sulphate, although his group of 20 patients is relatively small. In contrast, McCubbin et al. (10), found that glycopyrronium caused a smaller increase in the heart rate than atropine sulphate; the occurrence of dysrhythmias and the subjective well-being were the same for both agents.

When an anesthetist wishes to prevent disturbances of recovery from anesthesia, but still needs an anticholinergic, the logical choice is quaternary congeners of well-known belladonna alkaloids.

Surprisingly few data are available about clinical effects of such drugs. It is known, however, that the elevation of heart rate with, e.g., MAB is linear and not distorted by the initial central vagal stimulation as is the case with the centrally active AS (6). In our clinical comparison of equivalent doses of AS and MAB, 7.5 $\mu g\ kg^{-1}$ i.v., we found that MAB caused less dysrhythmias than AS. MAB caused a significantly higher increase in heart rate which indicates that the dosage should be reduced. None of the two drugs caused any significant change in the blood pressure. The antisialogogue action of MAB is also stronger than with AS, which can further lead to a decrease in dosage.

It was judged from the results of the present study that MAB in equivalent dose as AS caused excessive tachycardia which may be associated with unfavourable effects in some patients. The dose of MAB studied here was therefore halved for routine clinical use with excellent results.

In the clinical follow-up of the use of MAB instead of AS in about three thousand patients it was established that half the dosage of atropine sulphate (approx. 0.0037 mg kg^{-1}) is sufficient whenever an anticholinergic agent is needed. In our hospital, disturbances of postanesthetic recovery attributable to atropine sulphate occurred in 9.4 percent in a group of 3585 anesthetized patients (13). In the MAB group, the incidence of the CAS was 4 percent, which clearly shows that the use of AS may be a major factor in the onset of CAS.

We also compared AS and MAB for their effects during the reversal of the curare type neuromuscular block. Although the clinical judgment was in favour of MAB, differences among the patients were multifactorial and partly beyond control; we therefore refrained from reporting these results.

In conclusion, we feel that anticholinergic drugs should not be administered routinely in the premedication. The decision as to whether to use them and the choice of the drug should be made with the same care as the choice of the anesthetic agents or techniques to be used. On the basis of our data and overall clinical experience it is our judgment that in the anesthetist's hands MAB is superior to AS. MAB is easily obtainable and every apothecary can readily provide for it.

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CHAPTER 3.

PHYSOSTIGMINE VERSUS NALOXONE IN HEROIN-OVERDOSE.

ABSTRACT

Two groups of 10 chronically heroin addicted patients who were admitted to the Emergency Ward because of hypoventilation and coma, were treated random-aselectively with naloxone, 3 µg kg^{-1} BW iv, or with physostigmine salicylate 0,04 mg kg^{-1} BW iv. Patients in both groups completely regained consciousness and breathed spontaneously, regularly and adequately within 10 minutes. One essential difference in the treatment was that physostigmine caused no signs of acute opiate withdrawal, the patients felt fine and stayed for further control, in contrast with naloxone where the patients felt bad and occasionally escaped prematurely from the ward. Another difference is that the beneficial effect of one dose of physostigmine is shorter lived than that of naloxone. Authors emphasise the fact that treatment of heroin overdose in an addict need not jeopardize the patient's well-being by a withdrawal syndrome.

INTRODUCTION

Use and abuse of heroin may lead to numerous states of disease; some of these may be imminently hazardous to life. Respiratory depression is a well known state which calls for immediate and intensive treatment in order to prevent aggravation of the situation.

Two possible treatments are in general use at the moment: administration of an opiate antagonist and mechanical ventilation. Neither of these treatments can be regarded as a reasonably good solution to the problem. Opiate antagonists may precipitate acute withdrawal which in itself can endanger life or the patient may leave the hospital prematurely in craving for the drug. This may lead to yet another dose of heroin and to a renewed risk for life when the effect of the antagonist is worn out. The opiate withdrawal state should be regarded as the most serious illness with the most profound emotional aversion and, in our view, it should be argued as to whether it is ethical to induce it in a patient who is comatose and cannot give his consent.

Mechanical ventilation has its own hazards: it may call for muscular relaxation; aspiration and pneumothorax may be associated with it. Moreover, neurological follow-up of the ventilated patient becomes very difficult which is important in states of mul-

tiple injuries or combined intoxications. This treatment is also very expensive.

In search for a better treatment of the respiratory depression (and unconsciousness) in overdose of opiates in chronic addicts, new possibilities came to light by recent findings that physostigmine can antagonize cardiovascular and respiratory depressant effects of morphine in the conscious rabbit (1) and that physostigmine effectively reversed post-operative morphinic sedation in patients during recovery from anaesthesia leaving analgesia intact (2). There are, however, also earlier clinical observations which show usefulness of centrally active cholinesterase inhibitors in opiate respiratory depression. It was shown by Paskov et al. (3) that galanthamine, in action similar to physostigmine, i.e., a centrally active cholinesterase-inhibitor, could reverse the opiate sedation, but not analgesia. Apparently, in some patients during recovery from anaesthesia the need for analgesia was less when physostigmine was given, although consciousness was regained (4). Physostigmine also ameliorated postanaesthetic psychic and motor agitation (5) which follows reversal of opiate agents (6) or simply is due to the withdrawal of nitrous oxide at the end of an anaesthetic (7, 8).

It should be remembered, however, that somnolence, respiratory depression or analgesia are all distinctly different opiate effects which depend, in part or wholly, on different transmitter/modulator mechanisms. Jhamandas et al. (9) showed that opiates cause somnolence by decreasing release of acetylcholine (ACh) in the brain. Physostigmine is thus the drug of choice for treatment of this effect. This finding was brought into clinical practice by Weinstock (2) for acute opiate overdose during recovery from anaesthesia.

On the basis of this data we hypothesized that an addict to heroin in respiratory depression caused by an overdose might respond favourably to treatment with physostigmine. It was hoped that respiration would improve without signs of acute opiate withdrawal.

METHODS AND MATERIALS

The emergency ward called one of the three anaesthetists who worked on this trial when a patient with, presumably, heroin depression was admitted. Most heroin overdosages in Rotterdam take place soon after the working day is over, during the "happy hour". Usual patient care was administered, including infusion, blood pressure and electro-cardiographic monitoring, blood sampling, stomach tube, intubation and ventilation, if judged necessary. An arterial cannula was set for sampling of blood. All measurements and checks were made just before treatment and then at 10, 15, 20, 25 and 45 minutes. The Table I. shows which objective and subjective parameters were followed. Consciousness was rated from coma to full alert state with 0 - 1 - 2 or 3 points respectively. Subjective well-being was described in local equivalents for "rotten, bad" and "fine". Occurrence of "cold turkey" sign was registered, rated from absent (0) to severe (3 points). Arterial P_H, $PaCO_2$ (kPa), PaO_2 and Hb saturation (%) were recorded.

Patients were divided into two groups of 10. According to an a-selectively randomized list, a person, who was not involved in the treatment of the patient prepared physostigmine salicylate or naloxone hydrochloride, (per kg body weight) always in the equal volume of solvent. Both drugs are colourless so that the team did not know which drug was given. After the 0 min readings 0.04 mg kg^{-1} BW physostigmine or 3 µg kg^{-1} naloxone were slowly given (5 minutes) intravenously. It should be stressed here that after the 0 min readings, patients were artificially ventilated so as to prevent high arterial CO_2 which can cause serious dysrhythmias or heart stillstands in combination with ChE inhibitors (10). Samples of blood were taken for qualitative determination of opiates and specifically of heroin. EMIT$^{(R)}$ (Enzyme Monitoring Immunoassay Technique; Syva, Palo Alto, USA) assaying was used and presence of barbiturates, benzodiazepines and antidepressants was also determined. Anticholinergics were excluded by thin layer chromatography technique (TLC). Patients who were not "pure" heroin cases were not in-

cluded in the analysis of the trial. Unanimous subjective data is expressed verbally and the mean of numerical data is presented in the Tables.

RESULTS

All patients in both treatment groups woke from deep somnolence

TABLE 1.

Heroin-overdose Respiratory Depression: Changes after Physostigmine, 0.04 mg kg^{-1} BW i.v., of Mean Values of Physiological Functions (n=10).

Time (min)	0	10	15	20	25	45
Breaths/min	2	15	16	15	12	8
Heart rate/min	90	94	100	96	96	90
Blood pressure	130/80	120/70	130/80	130/80	120/70	130/80
Consciousness	0.16	2	2.7	3	2.1	1.4
Pupil size (mm)	1.0	1.4	1.4	1.3	1.3	1.2
Subjective	-	fine	fine	fine	fine	fine
Cold turkey	0	0	0	0	0	0
P_Ha	7.23	7.26	7.37	7.36	7.32	7.29
$PaCO_2$ (kPa)	7.3	6.3	6.2	6.6	6.6	7.2
PaO_2 (kPa)	9.1	13.4	13.9	11.1	12.5	9.7
Hb Sat. (%)	86	94	96	96	96	89

TABLE II

Heroin-overdose Respiratory Depression: Changes after naloxone, 3 µg kg^{-1} BW iv, of Mean Values of Physiological Functions (n = 10).

Time (min)	0	10	15	20	25	45
Breaths/min	2	17	17	16	17	17
Heart rate/min	71	68	71	80	72	72
Blood press.	130/80	135/80	135/80	130/85	130/85	130/85
Consciousness	0.3	1.2	1.3	2	3	3
Pupil size (mm)	2	2.3	2.8	2.8	2.8	2.8
Subjective	0	bad	bad	bad	bad	bad
Cold turkey	0	++	+++	+++	+++	+++
P_Ha	7.33	7.35	7.35	7.36	7.36	7.36
$PaCO_2$ (kPa)	7.2	4.3	4.5	4.2	4.3	5.1
PaO_2	9.2	12.9	13.8	13.6	12.9	13.2
Hb Sat. (%)	90	97	96	98	96	98

or coma within 10 minutes after the administration of physostigmine (Table I) or naloxone (Table II). There was no significant

difference in respiration or cardiovascular parameters between the two groups, for 25 minutes. Respiratory rate increased from mean 2 per minute to 17 at which level it remained in the naloxone group; it decreased again after 25 minutes in the physostigmine group and respirations appeared somehow deeper, probably in this way providing adequate blood gases (Table I). In 3 cases we decided to add naloxone after 45 minutes. Pupil diameter was smaller in the physostigmine group. "Cold turkey" component of the opiate withdrawal was seen in all the naloxone treated patients, none in the physostigmine group. All patients in the physostigmine group declared that they felt "fine" whereas the naloxone group felt "bad" (Table II).

The first group was calm and easy to manage in the observatory whereas the naloxone patients were very restless, exhibiting a dis-socialized behaviour pattern. Four escaped prematurely from the ward.

The antidepressant effect of physostigmine lasted for 30 minutes. Thereafter patients became somnolent again with accompanying changes in other parameters (Table II).

DISCUSSION

Several independent studies indicate that opiate analgesic effect, somnolence and respiratory depression, are subserved by different neurotransmitter mechanisms. During recovery from anaesthesia, as Rupreht and Dworacek reported (4), the need for analgesia after the administration of physostigmine was less although the respiration improved. This means that only somnolent opiate effect was antagonized. The fact that physostigmine can cause analgesia unassociated with respiratory depression has been reconfirmed (11, 12) in experimental studies with evidence that this effect is due to the action on the serotonin neural transmission.

On the other hand, it was shown that the opiate somnolence is possibly caused by a decreased release of brain-ACh (9) and that a similar mechanism subserves the respiratory depressant action. When physostigmine is given in opiate-induced depression, the e-

levated levels of ACh will stimulate the transmission through the reticular substance and keep the patient awake and alert (13). At the same time, presumably by raising acetylcholine levels in the brain, physostigmine will restore the sensitivity of the respiratory center for CO_2, thus ameliorating opiate-induced respiratory depression (14).

The explanation for the return of somnolence in the physostigmine group of patients can probably be found in the fact that this drug is largely hydrolized within 90 minutes (15). Additional dosage of physostigmine may produce excessive peripheral cholinergic symptoms which would necessitate administration of a peripherally active anticholinergic agent, e.g. methyl atropine bromide, so as to avoid central effects of commonly available atropine sulphate (16). Another solution for the recurrent somnolence in the physostigmine group would be a continuous drip or a combination of physostigmine with naloxone. Such a pilot study has been made with very promising results.

In conclusion, it may be said that physostigmine is, in analogy to its use post-anaesthetically, an efficient pharmacological agent for the treatment of opiate-induced respiratory depression (1). Its main advantage is that the addicted patients feel well when they wake up in contrast to the generally distressing effects caused by naloxone. Our clinical findings are also in accordance with Grumbach's findings (17) that increase in the cerebral acetylcholine decreased naloxone induced hyperirritability in rats addicted to morphine. Further pharmacological investigation may conceptualize a drug with beneficial physostigmine effects on respiratory depression and somnolence but with prolonged action.

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(Clinical Toxicology, 21: 387-397, 1984)

CHAPTER 4.
PHYSOSTIGMINE IN THE DIFFERENTIAL DIAGNOSIS OF COMA AFTER NEUROSURGERY

INTRODUCTION

Numerous studies and clinical reports have confirmed usefulness of physostigmine in the differential diagnosis of comatose states of unknown origin (1, 4, 5, 6). This case report illustrates the use of physostigmine for early differentiation between drug depression and an acute space occupying intracranial lesion after neurosurgery.

Case Report

The patient, 50 years old male, 55 kg, was operated on for a meningeoma of his right temporo-parietal region. Preoperative investigation discovered no somatic or biochemical abnormalities. The patient received 4 times 4 mg dexamethasone as preoperative antioedema therapy. The surgeon removed a large tumor (80 g) without any problems.

After premedication with atropine sulphate (0.7 mg) and lorazepam (2 mg) anesthesia was induced with thiopentone and continued with analgesic, nitrous oxide and incremental thiopentone. Relaxation was achieved with pancuronium. The anesthesia lasted 3 hours and a total of 0.85 mg fentanyl, 11 mg pancuronium and 800 mg thiopentone were administered.

At the start of the operation 60 g mannitol were given during 10 minutes. Estimated blood loss was 400 ml which we corrected with 425 ml of citrated blood; 500 ml plasma, 125 ml of 20% human albumin were also administered. After a peroperative diuresis of 1050 ml the fluid balance at the end of the procedure was 500 ml negative. Monitoring of ECG, expiratory CO_2, ventilation pressures, intra-arterial pressures, blood gases and rectal temperature showed no abnormalities during the operation.

To terminate the anesthetic, 0.4 mg naloxone, 2 mg neostigmine and 1 mg atropine sulphate were administered. Still on the operation table we extubated the patient who appeared to be fully conscious and without any neurological deficit. Control blood gases were normal. One hour later, in the recovery, we noticed that the patient became somehow sleepy and his respirations became irregular. A few minutes later he became restless

and obviously lost contact with the surroundings. At the same time we noticed initial hemiparetic signs left which progressed rapidly to complete left hemiparesis. Ninety minutes after the operation the patient reacted only to intensive pain stimulation. We suspected that the patient was bleeding. The surgeon was asked to see the patient and decided to wait [as the patient might demonstrate residual effects of the anesthetic]. Curiously enough, the blood pressure was not changed yet and the pupils were still isocoor, vigorously reacting to light.

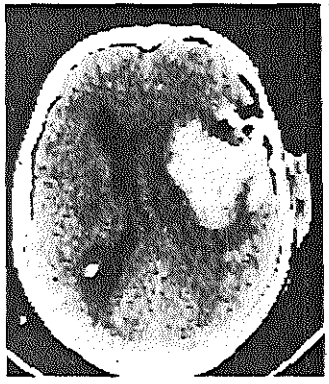

Fig. 1

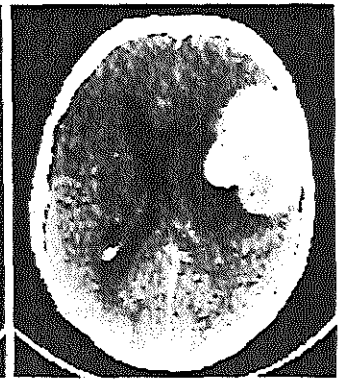

Fig. 2

Fig.1: Computer tomography scan showing cranial bone defect and intracerebral hyperdense substance, brain oedema and displacement of median structures.
Fig.2: Intracerebral hyperdense substance and dislocation of median structures before operation.

To exclude a pharmacological cause of the depression we decided to administer 2 mg physostigmine salicylate intravenously. After 3 min. the patient did show some improvement in the hemiparesis left, responded to verbal commands while the respirations became deeper and regular. However, we could not produce the alertness we had had immediately after the operation. Only half an hour later the respirations became once more irregular, the patient reacted only to pain stimulation and demonstrated no provoked or spontaneous movements left; the blood pressure remained normal. At the first signs of deteriorating blood gases we decided to reintubate and control the ventilation. We regarded the diagnosis

of an acute extracerebral hematoma as definite and took the patient to the computer tomography scan (CT scan) for the confirmation. They saw "a cranial bone defect, under it air and hyperdense substance" (see Fig. 1), "the shape of which corresponds to be shape of the tumor on the preoperative CT scan" (see Fig. 2). There were signs of edema and great dislocation of median structures, caused by "this hematoma". Four hours after the end of the operation the surgeon retrepanated and removed the hematoma.

After this operation, the patient was still comatose but reacting vigorously to pain stimulation. Later in the afternoon he reacted to verbal commands. Though the hemiparesis receded almost completely it seemed safer to postpone the tracheal extubation until the next morning. Three weeks later the patient was discharged in excellent general condition and without any neurological abnormalities.

DISCUSSION

The cholinergic transmission in the brain appears to be of primary importance for cortical arousal and the wakeful state (2, 3). Anticholinergics and other psychotropic drugs may delay and disturb the recovery from anesthesia (6). Of these our patient had received atropine sulphate, lorazepam, thiopentone and fentanyl. These drugs may completely or partially block central cholinergic transmission and interfere with arousal. Even when a certain drug does not block the central cholinergic transmission it may influence the waking up and alertness by interferring with the balance between different central transmission systems. So caused changes in wakeful state will be readily corrected by physostigmine salicylate.

Our patient was completely awake after the operation which makes a "pharmacological loss of consciousness" during his recovery-room stay highly improbable. That is why we thought of an anatomical lesion at the very first signs of patient's clinical deterioration. The surgeon seemed to have been misled into "the postanesthetic depression" by the normal size of pupils.

We administered physostigmine as a differential diagnostic agent. In the case of our patient we expected no or very slight improvement of his mental condition which should be doomed to be

transitory. Indeed, we did fail to detect a real improvement after physostigmine and concluded that the progressive comatose state was caused by an acute intracerebral hematoma. A correct diagnosis, promptly confirmed by the CT-scan, which enabled us to treat the patient adequately without any further loss of time.

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(Acta anaesth. belg., 31, 71-74, 1980)

CHAPTER 5.

PHYSOSTIGMINE REVERSAL OF DIAZEPAM

Two reports dealing with the effects of physostigmine on the state of consciousness after administration of diazepam appeared in the September 1979 issue of Anesthesiology (1) and in its supplement (2). The conclusions drawn in the two reports seem to be in contradiction. It is not surprising that the results are confusing. It seems that the authors have paid little attention to the fact that benzodiazepines primarily appear to facilitate the GABA-transmitter system, which has been found, so far, in the central nervous system (CNS) only. On the other hand, physostigmine is a pure cholinesterase inhibitor, poorly soluble in water, which can easily penetrate into the brain, as opposed to, for example, prostigmine or pyridostigmine. It will exclusively affect cholinergic transmission within the CNS through the increase in the concentration of acetylcholine.

Clinical signs of central cholinergic blockade vary greatly. Among others, coma, somnolence, short-term memory loss, excitation and aggressiveness can be seen after administration of centrally active anticholinergic drugs or after different anesthetic agents. Enflurane and cyclopropane are well known for causing postanesthetic excitation. All of these behavioral changes were studied and described as a central anticholinergic syndrome (CAS) by Longo (3).

We have used physostigmine in patients recovering from anesthesia for six years. It became obvious that physostigmine can cause arousal in comatose patients after the administration of diazepines (4). Nevertheless, we observed that improvement of the latter condition was not of the same quality as in patients where anticholinergic drugs were the cause of changes in the conscious state. These observations were confirmed by others (5, 6). The most striking results were obtained in comatose patients after administration of flunitrazepam. Physostigmine caused an apparent arousal, leaving the short-term memory loss unchanged (7).

There are many possible explanations for the positive results of physostigmine in the comatose states of benzodiazepine origin. Anticholinergic agents may have been used simultaneously; diazepines also may partly block central cholinergic synapses, or, most probably, inhibit the cholinergic system indirectly by facilitating the inhibitory GABA-transmitter system. Bearing in mind the well-known interdependence of all central transmission systems, I favor the latter explanation. With regard to the two conflicting reports, this implies that there was a central anticholinergic syndrome in all cases were physostigmine proved to be effective. No positive effect was observed only in cases without central cholinergic block.

According to our experience based on more than two thousand cases in which physostigmine was administered, we consider a dosage of 0.04 mg/kg body weight to be optimal. It has proven to be effective and safe; moreover, we have used physostigmine as a differential diagnostic agent in comatose states of unknown origin. Prophylactic atropine administration was not necessary. Whenever an anticholinergic agent was needed (for example, because of simultaneous decurarization), methyl-atropine bromide or glycopyrrolate was administered, because they do not penetrate the CNS. In most cases, slow injection of physostigmine (1 mg/min) prevented nausea, which can accompany its administration. An absolute protection from nausea can be achieved by previous administration of an antiemetic.

We would like to point out that one should beware of expressions such as "aspecific central analeptic" effects of physostigmine, which are sometimes used (6). It is necessary to realize that physostigmine possesses exclusively a cholinesterase-inhibitory action, and should thus be administered only for well-defined indications. This has been confirmed by the use of an alternative drug to physostigmine: galanthamine hydrobromide (8). Full consideration of the pharmacology of physostigmine and careful study of the indications will lead to exclusively positive results.

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(Anesthesiology, 53: 180-181, 1980)

CHAPTER 6.

DIE ANWENDUNG VON PHYSOSTIGMIN BEI DER BEHANDLUNG ZENTRAL ANTICHOLINERGISCHER INTOXIKATION *

ZUSAMMENFASSUNG

Zwei Patienten wurden aus der Stadt Rotterdam in unsere Klinik mit zentralen und peripheren Vergiftungssymptomen eingeliefert, die einem schweren anticholinergischen Syndrom glichen. Physostigminsalicylat wurde intravenös appliziert und bereits unter der ersten Injektion verbesserte sich die Symptomatologie schlagartig. Diese beiden Fälle machen den oft vernachlässigten differential-diagnostischen und heilenden Wert von Physostigmin als tertiären, auch zentral angreifenden, Cholinesterase-inhibitor deutlich.

Vor kurzem wurde in der Presse in Holland und Deutschland über eine Reihe von Vergiftungen nach Genuss von Kaffee in öffentlichen Lokalen berichtet. Es wurde angenommen, dass es sich immer wieder um die gleiche Person handelte, die das Gift verabfolgte, da die Symptome, ausführlich in der Presse beschrieben, sich ähnlich waren. Es handelte sich um einen Stoff mit starker zentraler Wirkung, höchstwahrscheinlich Atropine oder Scopolamine. Das klinische Bild äusserte sich in Halluzinationen, geistig gestörtem Zustand, Amnesie, Desorientierung, Coma, Dysarthrie, geöffnet bleibende Augen. Die Augen waren weit geöffnet und starr, Die Pupillen weit (6). Wir haben zwei von diesen vergifteten Patienten gesehen und behandelt.

ANAMNESE

Zwei junge gesunde Frauen, 19 und 20 Jahre alt, tätig als Serviererinnen im gleichen Betrieb (Kaffeestube), wurden zur Aufnahme gebracht, weil sie nach dem Trinken von Kaffee ein seltsames Verhalten zeigten. Sie waren motorisch unruhig, desorientiert in Ort und Person, sie halluzinierten hauptsächlich visuell. Bei der Untersuchung fanden wir eine Tachykardie von 110-124/min bei normalem Blutdruck von 16/11 kPa (125/80 mm Hg) und 17/11 kPa (130/80 mm Hg). Die Temperatur rektal betrug 36,9°C und 37,2°C.

Beide Frauen hatten eine extrem rote Gesichtsfarbe und weite lichtsteife Pupillen. Der Mund war trocken. Differentialdiagnos-

tisch dachten wir an eine Vergiftung mit Amphetaminen, LSD oder eine Belladonnaderivat. Da das Delirium im klinischen Bild am meisten imponierte, wurde in erster Instanz 100 mg Chlordiazepoxide intramuskulär verabfolgt ohne eine Besserung zu erreichen. Der konsultierte Anaesthesist stellte den dringenden Verdacht auf eine Intoxikation mit einem Anticholinergicum und gab den Rat Physostigmin zu verabfolgen. Schon während der intravenösen Injektion verbesserte sich das klinische Bild. Die Halluzinationen und das Delirium verschwanden sofort. Die Pulsfrequenz sank bis auf 80/min bei Sinusrhythmus im EKG. Die Pupillen wurden kleiner, beide Patienten klagten über Durst.

Es bestand bei beiden Amnesie für die Phase der Halluzination. Eine der beiden Frauen begann 90 min nach der Injektion wieder zu halluzinieren. Nach wiederholter Injektion von 1 mg Physostigmin blieb der klinische Zustand normal.

Die Patienten blieben 24 h unter klinischer Kontrolle. Kreislauf und Atmung zeigten keine Besonderheiten. Die Pupillen waren nach 24 h noch weit; die Lichtreaktion war positiv. Die Patienten klagten über Übelkeit, Durst und Sehstörungen. Gleichzeitig wurden zwei andere Patienten in Rotterdam auch erfolgreich mit Physostigmin behandelt.

DISKUSSION

Physostigmin, ein tertiärer Cholinesterase-Inhibitor, kann die Blut-Hirnschranke passieren. Es verhindert den Abbau von Acetylcholin. Der Wachzustand ist in der Hauptsache von diesem Transmitter abhängig (2, 3) und es ist anzuraten, wenn ein Patient mit einem zentral aktiven anticholinergischen Stoff vergiftet ist, die gehemmte cholinergische Transmission in der Substantia reticularis mit Erhöhung der Acetylcholin-Konzentration aufzuheben. Da die Wirkung von Physostigmin nur 90-120 min beträgt, empfiehlt es sich, die Patienten klinisch für die ersten 24 h zu überwachen. Durch eine Tropfinfusion kann die Wirkung von Physostigmin verlängert werden (4 mg/h). In unserem Institut für Anaesthesiologie benutzen wir Physostigmin schon seit 6 Jahren (4). Die initiale Dosis soll 0.04 mg/kg nicht überschrei-

ten, die Injektionsgeschwindigkeit nicht schneller als 1 mg/min sein.

Physostigmin kann in der Differentialdiagnostik eines Koma von Nutzen sein (1, 5). Volle klinische Herstellung nach Physostigmin spricht für Intoxikation mit Belladonnaderivaten, Antidepressiva, Antihistaminika oder verwandte Substanzen.
Erst später wurde aus dem Urin von beiden Frauen Scopolamin isoliert.

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(Anaesthesist, 30: 356-357, 1981; * in German)

CHAPTER 7.
PHYSOSTIGMINE IN POSTEXTUBATION LARYNGOSPASM

Dr. H. Owen's contribution dealing with the doxapram treatment of the postextubation laryngospasm (Anaesthesia 1982; 1112-4) is most welcome. The occurrence of laryngospasm appears to have become a relatively rare complication in the practice of anaesthesia, probably as the result of anaesthetis's concern to avoid it rather than a better understanding of this complication. This state is clearly reflected in the treatment of laryngospasm where few clearly defined schemes exist. We feel therefore that Dr. Owen's observations on the effect of doxapram on laryngospasm are important and would like to support them from our own experience with this drug. We differ, however, from his views as to the mechanism of action. In a study of doxapram's chemoreceptor stimulatory effect during general anaesthesia with enflurane we have followed 70 patients of different ages (2-85 years). Patients were premedicated with methyl-atropine-bromide (0.005 mg/kg), and rendered unconscious with thiopentone (3.5 mg/kg) followed by suxamethoniumm (1 mg/kg) for tracheal intubation. They breathed enflurane (2.3 vol%) in 1:2 oxygen/nitrous oxide mixture. The average duration of anaesthesia was 90 min. The normally occurring increase of end-tidal carbon dioxide concentration under this anaesthetic was not observed in patients who were given 1 mg/min (per 50 kg) doxapram.

The patients breathed room air after extubation. The recovery from anaesthesia in these patients was shortened and it was completely free from any disturbances of respiration. We noticed clearly that coughing or swallowing occurred whenever there was any secretion in the airway but this never resulted in breath-holding or laryngospasm. The effect of doxapram in this clinical picture is reminiscent of the effect of physostigmine in the central anticholinergic syndrome. One of the signs of central cholinergic blockade can be incoordination of muscles, sometimes resulting in a laryngospasm during recovery from anaesthe-

sia (1, 2). Physostigmine (0.04 mg/kg) results in better coordination of muscles, early awakening and the disappearance of laryngospasm. Our impression was that the greater respiratory drive during recovery from anaesthesia may cause deposition of secretions or foreign material in the airway and result in laryngospasm. Improved coordination of muscles, irrespective of whether physostigmine or doxapram was given, prevents laryngospasm even in patients who are not awake enough to be able to control their reflexes consciously. This explanation, one of the three offered by Dr. Owen, might bring us closer to the explanation of how doxapram or physostigmine prevent or abolish postextubation laryngospasm. We have introduced a practice of administering 0.04 mg/kg physostigmine to patients breathing enflurane or halothane 15 min before the end of surgery and extubation. This treatment results in remarkable freedom from any complication at extubation of the trachea and a shortened calm recovery.

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(Anaesthesia, 38: 394, 1983)

CHAPTER 8.

ELECTROCORTICOGRAPHIC CHANGES IN CATS AFTER INTOXICATION WITH ANTICHOLINERGIC DRUGS

SUMMARY

Atropine sulphate or atropine-methyl-bromide were administered to cats intravenously in a dose of 0.0115 mmol/kg (i.e. 4 mg/kg). Electrocorticogram changes were studied. Atropine sulphate caused the classical shift of the electrocorticogram from high-frequency-low-voltage pattern to a low-frequency-high-voltage pattern. We observed no changes of the electrocorticogram after the administration of atropine-methyl-bromide.

INTRODUCTION

Previous studies confirmed that quaternary belladonna alkaloids do not penetrate into the central nervous system (CNS). No changes of the electrocorticogram (ECoG) were detected after the administration of common therapeutic dosages of these drugs (3).

To our knowledge no studies of the ECoG-changes have been reported after the administration of high dosages of quaternary belladonna compounds. In such a case a small, unionized part of the compound still might penetrate the blood-brain barrier and block the central cholinergic (muscarinic) transmission. In order to elucidate this possibility we decided to compare ECoG-changes in cats after an intravenous administration of 400 times the therapeutic dose of atropine sulphate (AS) to those caused by an equivalent dose of atropine-methyl-bromide (AMB).

METHOD AND MATERIAL

Two groups of twelve male cats each, were studied. The weight range was 2.3-4.5 kg. Under O_2-N_2O (1:2) - halothane (2 vol%) - pancuronium (0.5 mg/h) anaesthesia the animal was intubated and ventilated with Baby Kontron (Roche). Blood gases were controlled and kept close to their normal values: PaO_2 about 120 mmHg, $PaCO_2$ at 37-42 mmHg and $HbSat_a$ at 98%. Rectal temperature was kept at 37°C. Venous, central venous, arterial and urinary catheters were placed. Ten percent glucose was given i.v. at 2 ml/kg.h rate in addition to 1 ml/kg.h Ringer solution.

ECG was continuously monitored. The head of the cat was placed into the stereotaxic apparatus (9) and four pairs of bipolar cortical electrodes were placed fronto-parietally and parieto-occipitally (Fig.1). Then, halothane was discontinued. Mingo-

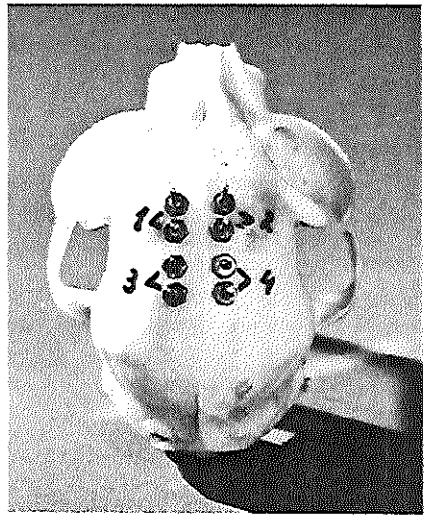

Fig. 1. The position of cortical electrodes in our experiment.

graph type E.M. 81 was used for registration of the ECoG and ABL 1 Radiometer apparatus for control of blood gases.

Three hours after the discontinuation of halothane we started the continuous registration of the ECoG. We waited until the ECoG-pattern remained unchanged for one hour and then administered one of the two belladonna alkaloids intravenously: 0.0115 mmol/kg AS to the first group and 0.0115 mmol/kg AMB to the second group of cats. Thereafter, the registration of the ECoG was continued for another hour. Five seconds of the ECoG-tracing immediately before the injection of the drugs and five seconds of the tracing at 15 minutes after the injection were studied. The discrete Fourier transformation was used to transform the time presentation of the ECoG into a frequency presentation (2). The accuracy was 0.5 c/sec.

RESULTS

The ECoG-tracing immediately before the intravenous injection of the anticholinergic drug showed mainly low voltage waves of higher and high frequency (10-20 c/sec). There were very few slow waves of not exceedingly high voltage.

This preinjection ECoG-recording (Fig.2) was identical in all experimental animals corresponding essentially to wakeful state (5). Slow waves of high voltage can be seen in all four leads after the administration of atropine sulphate. This type of synchronized ECoG-tracing resembles the sleep-pattern (4) with a

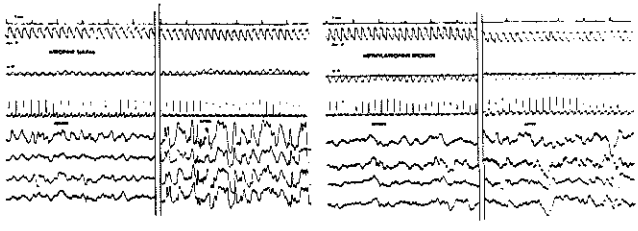

Fig. 2. Electrocorticogram in cat before and after the intravenous administration of 0.0115 mmol/kg atropine sulphate (left) or atropine-methyl-bromide (right).

decrease of high frequency waves in the ECoG. This decrease starts during the injection and is completed in 4 minutes. The increase in low frequencies occurs at the same rate and is completed within 4 minutes. Hereafter no new changes in the ECoG follow the administration of AS. AS did not cause great changes in mean heart rate (an increase from 230 to 240/min) or in mean arterial pressure (95 mm Hg to 100 mm Hg).

The power spectrum analysis (Fig. 3) revealed that highest ECoG potentials are found at low-frequency-waves (0.5-3 c/sec) revealing a pronounced synchronization of the ECoG which follows the administration of AS. The administration of 0.0115 mmol/kg of AMB caused no significant change of the ECoG-tracing (Fig. 2). Concurrently, there was a slight decrease in mean arterial

pressure (100 mm Hg to 90 mm Hg) and in mean heart rate (from 240/min to 200/min within 4 minutes).

The power spectrum of the ECoG-record (Fig. 3) showed no change in frequency distribution and potentials after the injection of AMB. The control tracing and the AMB-tracing were parallel and close to each other. There was a slight elevation of the AMB-tracing, but the difference from the control was not significant. The area covered by low frequencies in the power spectrum after injection of AMB was much smaller than the one after the administration of AS. Changes of the ECoG were completed after the fourth minute following the injection of either AS or AMB and there were no further changes in both groups for a further one hour.

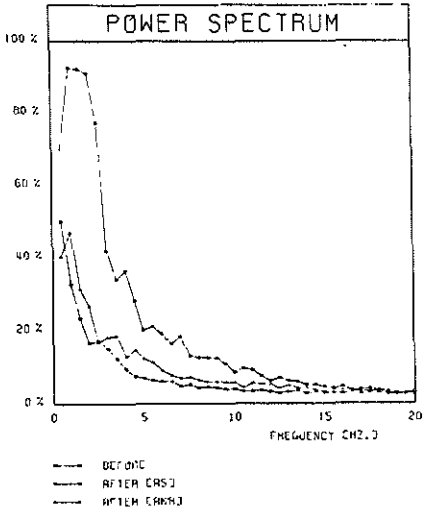

Fig. 3. The power spectrum of the ECoG in cats, before and after the intravenous administration of atropine sulphate or methyl-atropine-bromide. Note that only atropine sulphate is followed by evident changes of the power spectrum.

DISCUSSION

In our experimental model, nitrous oxide alone caused no detec-

table changes of ECoG. The person who analysed ECoG, and was not aware of the treatment, could not discern between ECoG of cats on air or nitrous oxide-oxygen mixture. The ECoG changes caused by halothane that we used during preparation of the model for some 20 min wore off very quickly, whereupon the ECoG again was not different from that of a cat ventilated by air. As nitrous oxide caused no obvious changes of the ECoG, at partial pressure that we used (480 mm Hg), the Research Ethical Committee of the Erasmus University advised us to ventilate cats during the experiment by nitrous oxide-oxygen mixture. Without treatment, no changes took place in the ECoG of the cats.

Administration of centrally active anticholinergics is followed by a dose-dependent blockade of the central muscarinic transmission (3). This manifests itself in changes of behaviour and ECoG (4). Man and animals alike may appear awake and restless whereas the ECoG is typically synchronized, resembling the sleep pattern. This picture has been described clinically and experimentally (5, 7) and aptly called ECoG-behaviour dissociation. Small concentrations of centrally active anticholinergic agents may cause disturbance of patient's recovery from anaesthesia, producing a varied behavioural picture, called the central anticholinergic syndrome (CAS; 5, 7). When this clinical picture was analysed in an experiment, it was found that the ECoG-reactions to external stimuli are abolished (4) while the neurovegetative and behavioural reactions remain unchanged. Szerb (10) stimulated the reticular formation in an atropinized animal and found that the ECoG-activation was blocked, while the cortical acetylcholine output was increased. He postulated that neuronal projections responsible for ECoG-activation and acetyl-choline output follow two separate pathways, of which one is dependent on an intact muscarinic transmission. These findings can suitably explain the ECoG-behaviour dissociation in reaction to external stimuli after the administration of a centrally active anticholinergic agent. Although it is perfectly possible to treat central effects of anticholinergic drugs by physostigmine (1, 7) it is convenient to decrease the occurrence of the CAS by using a

quaternary anticholinergic derivative which, as a rule, does not penetrate into the brain. Methyl-atropine-bromide (8) and glycopyrrolate (6) have both been used as they do not produce obvious central effects in low dosages.

The question remains, however, whether methyl-atropine-bromide in a higher dose or in a combination with other concurrently given . central anticholinergics would still not produce AS-like ECoG-changes. A small, unionized portion of this drug could penetrate into the brain when it is given in higher dosages. Our investigation was therefore designed and aimed at a detection of ECoG-changes during a heavy intoxication with AS or AMB. Changes in animals given AS were of the expected slow wave high voltage pattern, whereas AMB produced no changes in the ECoG even at the dosage which is 400 times that usually used for vagolytic purposes. From this point of view, AMB is a substitute of choice for AS when no central anticholinergic effects are wanted in order to reduce the occurrence of the CAS. Results of this investigation also suggest that CAS-like changes of behaviour in a patient who had been given AMB, are not due to this drug.

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CHAPTER 9.

THE ROLE OF A NORADRENERGIC SYSTEM IN THE ANTINOCICEPTIVE EFFECTS OF 4-AMINOPYRIDINE IN THE RAT

ABSTRACT

Antinociceptive effects of physostigmine and 4-aminopyridine after i.p. administration were studied in rats according to the Randall-Selitto nociception method. The antinociceptive action of physostigmine was not significantly influenced by atropine, naloxone or α-methyl-p-tyrosine. The antinociceptive action of 4-aminopyridine was also unaffected by simultaneous administration of atropine, naloxone or pretreatment by DL-p-chlorophenylalanine. However, 4-aminopyridine was without antinociceptive effect in rats pretreated with α-methyl-p-tyrosine. It is suggested that the antinociceptive action of 4-aminopyridine is mediated by a noradrenergic system.

INTRODUCTION

Several studies have demonstrated analgesic effects of cholinesterase inhibitors and of 4-aminopyridine (Fastier and McDowall, 1958a and b; Harris et al., 1969; Harris and Dewey, 1972; Lipman and Spencer, 1980; Saxena, 1968; Weinstock, 1980).

Mechanisms by which cholinergic agents exert antinociceptive activity have, so far, remained unresolved. However, Aiello-Malberg et al. (1979) proposed that physostigmine does not act exclusively as a cholinergic agent and may be producing its analgesic effects by increasing the brain levels of 5-hydroxytryptamine. Ireson (1970) found that atropine reversed the analgesic activity of physostigmine which indicates that the muscarinic synaptic site is of essential importance for this action of physostigmine. The possibility of antinociceptive activity of cholinesterase inhibitors through an activation of opiate receptors in the central nervous system has been examined but with contradictory results. Harris et al. (1969) reported that naloxone reversed the analgesic effect of physostigmine and oxotremorine. This finding was not confirmed by later studies (Lipman and Spencer, 1980; Pleuvry and Tobias, 1971).

4-Aminopyridine (4-AP) has potent peripheral and central muscarinic actions but is without cholinesterase inhibitory activity. Analgesic activity of 4-AP was postulated by Fastier and McDowell (1958a and b), but no experimental data were presented. Interest in 4-AP has recently increased among anaesthesiologists and pharmacologists, probably because of its interesting applicability in the treatment of botulinum toxin-induced neuromuscular block (Lundh et al., 1977) or in the reversal of opiate-induced respiratory depression (Paskov et al., 1973; Sia and Zandstra, 1981; Thesleff, 1980; Uges and Bouma, 1981; Uges and Huizinga, 1981).

We have studied the effects of 4-AP on nociception in the rat. Physostigmine was included in the study for comparison because it has been extensively investigated previously and it is more selective for cholinergic mechanisms than is 4-AP.

METHODS

Male albino Wistar rats of 5 weeks of age and weighing 125-150 g were used. This age was selected because, in our pilot study, the nociception response to pressure drastically diminished at the age of 6 weeks. This phenomenon had previously been observed by other authors (Green et al., 1951).

Rats were housed, five per cage, at 23°C, and a 12 hr day-night cycle was imposed. Food and water were given ad libitum. On the day of the experiment they were taken into the 'climate room' (noise absorbing, 25°C), and allowed to adapt to the environment for the following 2 hr. At 8.30 a.m. control analgesiometric scores (AMS) were determined according to the modified Randall-Selitto test (Randall and Selitto, 1957). We used an analgesiometer for the rat paw (Ugo Basile, Milan) which applies pressure to the paw on a surface of 1 mm^2. The pressure increases at a constant rate. The right hind paw was used, and a marking spot was placed so that stimulation was always applied at the same place. We decided to use the hind paw since in our pilot study the dorsum of the hind paw was found to be about twice

TABLE I.

Nociception to pressure stimulation after i.p. administration of various agents. Analgesiometric scores (AMS) according to the modified Randall-Selitto test, in g mm^{-2}. Mean values and standard errors of the mean are given. Figures in brackets denote number of animals. Significance of changes as compared to the control value was determined by Student t-test. *:$p < 0.05$; **:$p < 0.002$. Control values were determined at 8 a.m., all analgesiometric experiments were performed between 11 a.m. and 2 p.m. 4-AP:4-aminopyridine; αMPT: α-methyl-p-tyrosine; PCPA:p-chlorophenylalanine.

Agent	AMS (g mm^{-2})	(n)	Drug-free rats AMS (g mm^{-2}) at 8 a.m.	(n)	Saline i.p. AMS (g mm^{-2}) at 2 p.m.	(n)
Physostigmine	283 ± 21	(13)**	121 ± 27	(20)	129 ± 11	(7)
4-AP	382 ± 36	(15)**	125 ± 14	(30)	134 ± 22	(15)
Naloxone	120 ± 11	(9)	124 ± 15	(16)	128 ± 17	(7)
Physostigmine + naloxone	265 ± 45	(9)*	135 ± 17	(16)	142 ± 19	(7)
4-AP + naloxone	352 ± 34	(9)**	119 ± 15	(16)	128 ± 17	(7)
Atropine	131 ± 7	(9)	130 ± 17	(18)	135 ± 6	(9)
Atropine + physostigmine	272 ± 19	(9)*	132 ± 9	(16)	139 ± 12	(7)
Atropine + 4-AP	375 ± 27	(9)**	135 ± 10	(16)	129 ± 14	(7)
4-AP + physostigmine	392 ± 21	(9)**	138 ± 7	(16)	134 ± 4	(7)
αMPT	139 ± 25	(9)	131 ± 9	(16)	129 ± 9	(7)
4-AP + αMPT	115 ± 10	(9)	129 ± 10	(15)	130 ± 10	(6)
Physostigmine + αMPT	315 ± 45	(9)**	109 ± 17	(14)	115 ± 18	(5)
PCPA	135 ± 27	(15)	113 ± 18	(22)	121 ± 18	(7)
4-AP + PCPA	325 ± 48	(8)**	115 ± 16	(15)	120 ± 30	(7)

as sensitive as the tail at its midlength. The cut-off pressure was put at 500 g mm^{-2} in order to prevent tissue damage. The end-point of the stimulation was withdrawal of the paw (or an attempt to do so), or vocalization (a squeak) which stopped the stimulation automatically through a microphone connected to the cut-off mechanism.This vocalization cut-off mechanism had been designed at the Department of Pharmacology of the Erasmus University Rotterdam by Prof. I.L. Bonta's group and was made in the Central Research Workshop of the Erasmus University Medical School. The scoring was always done at the same time (2 p.m.), because of the diurnal rhythmicity in nociception (Frederickson, 1977). In order to prevent conditioning (Winter, 1965), the experiments on individual rats were performed only on each alternate day and not more than twice a day with a time interval between 2 tests of 5 hr or more. Rats which were given an intraperitoneal injection were used only once. Rats in which the control AMS were found to be equal to or greater than 150 g mm^{-2}, at 8.00 a.m, were not included in the study.

All drugs, diluted in saline, were injected intraperitoneally (i.p.) in a volume of 0.5 ml, 25 min before analgesiometric testing. The controls received 0.5 ml saline i.p. in order to account for possible stress analgesia (Hayes et al., 1976). Blind random administration of drugs was used and animals served as self-controls. AMS from the morning session (8.30 a.m.) were compared with those 25 min after administration of agents (2 p.m.). We kept notes on the behaviour of the rats. The person who did analgesiometry was unaware of the kind of agent given. Ethical standards for investigation of experimental pain in animals (Pain, 1980) were respected.

No significant difference in nociception was observed between the control drug-free and saline treated animals. Significance of changes in nociception for different agents, as compared to the control, was done by Student t-test. The animal number of rats per trial group was seven.

Drugs used: 4-aminopyridine (Sigma); atropine sulphate (Sigma);

naloxone hydrochloride (Endo Inc.); physostigmine salicylate (Merck), DL-α-methyl-p-tyrosine methyl ester (αMPT) (Sigma); DL-p-Chlorophenylalanine (PCPA) (Calbiochem (R)).

RESULTS

All numerical data concerning analgesiometry are collected and presented in Table I.

Drug-free control rats. The rats reacted to pressure stimulation primarily by paw withdrawal, and less frequently with a squeak. The average morning nociception score of untreated rats was 135± 4 g mm^{-2}. This value differed slightly from day to day and appeared to be insignificantly elevated in the afternoon. Injection of saline i.p. did not significantly change the response to pressure (132 ± 5 g mm^{-2}) compared with nontreated rats.

Physostigmine salicylate (0.5 mg kg^{-1}) caused a marked increase in AMS with value of 110% above morning scores at 25 min after administration ($P < 0.05$; n=13). Diarrhoea, piloerection and tremor were common side effects. Rats tended to become calm after administration of physostigmine.

4-Aminopyridine (4-AP). The antinociceptive effect of 4-AP was found to be dose-dependent (dose range: 0.25-3.0 mg kg^{-1}) and was maximal at 3.0 mg kg^{-1} with the peak value at 25 min after i.p. administration. Further increase of the dose resulted in fatalities from convulsions. At 25 min after i.p. administration of 3.0 mg kg^{-1} 4-AP there was a 185% increase in the analgesiometric score to pressure stimulation (382 ± 36 g mm^{-2}). Rats exhibited excitation and exploratory behaviour. There was less diarrhoea than with physostigmine.

Naloxone (5.0 mg kg^{-1}) itself had no effect on the response to pressure stimulation in control rats. We observed no behavioural differences between the naloxone and the saline group.

Physostigmine (0.5 mg kg^{-1}) antinociceptive activity was not significantly altered when given together with naloxone (5.0 mg kg^{-1}). Rats appeared calm after i.p. administration of the physostigmine-naloxone combination.

4-AP (3.0 mg kg^{-1}) given together with naloxone (5.0 mg

kg^{-1}) retained its antinociceptive activity (352 ± 34 g mm^{-2}). Behavioural changes were of the same type as after 4-AP given alone.

Atropine sulphate (0.5 mg kg^{-1}, i.p.) given alone caused a non-significant decrease of AMS (131 ± 7 g mm^{-2}) as compared to saline. The rats however, appeared active and restless.

Physostigmine (0.5 mg kg^{-1}) antinociceptive activity was non-significantly diminished when it was given together with atropine sulphate. Rats were lively, there was no diarrhoea.

4-AP (3.0 mg kg^{-1}, i.p.) retained its antinociceptive activity when it was given together with atropine sulphate (0.5 mg kg^{-1}). Rats appeared to be restless, able to stand against the wall and to walk around. Diarrhoea was absent.

4-AP (3.0 mg kg^{-1}) given together with physostigmine (0.5 mg kg^{-1}), was followed at 25 min after i.p. administration by the insignificantly lower AMS (392 ± 16 g mm^{-2}) than when it was given alone (432 ± 46). The rats moved around, were alert, less restless or active than after 4-AP given alone but more active than after physostigmine alone. There was more diarrhoea than after physostigmine alone.

α MPT (200.0 mg kg^{-1}) given 5 hr prior to 4-AP (3.0 mg kg^{-1}, i.p.) resulted in complete absence of 4-AP-induced antinociception in rats.

Signs of peripheral cholinomimetic activity of 4-AP were present. However, the antinociceptive effect of physostigmine (0.5 mg kg^{-1}) on pressure stimulation was not significantly altered by αMPT pretreatment.

PCPA (100.0 mg kg^{-1}, i.p.) was given to the rats daily for 3 days in order to deplete brain 5-hydroxytryptamine (Koe and Weissman, 1966). On the fourth day, these rats were given 4-AP (3.0 mg kg^{-1}, i.p.); no significant change in 4-AP antinociceptive activity to pressure stimulation was apparent.

DISCUSSION

We confirmed in this study that physostigmine is a potent antinociceptive agent. Its analgesic action was not influenced signifi-

cantly by naloxone, atropine sulphate or α MPT. This indicated that physostigmine-induced antinociception does not significantly depend on the endorphinergic, cholinergic or noradrenergic system. It has been suggested that physostigmine exerts its antinociceptive effects by causing an increase in release of 5-HT from the brain (Aiello-Malmberg et al., 1979; Lipman and Spencer, 1980).

In this study, 4-AP was the main interest because of its increased use in clinical practice, and because of the limited pharmacological data about this potent central cholinergic stimulant that is devoid of cholinesterase-inhibiting activity (Lundh et al., 1977). Analgesiometric experiments were done in the rat because it has been established that results of pain studies in this animal-model are highly reliable for extrapolation into clinical situations (Cohin, 1968).

We expected 4-AP to exert potent analgesic effects resembling more physostigmine which causes an increase in brain acetylcholine. It is evident from this study that the analgesic effect of 4-AP is pronounced. Besides the incomplete studies of Fastier and McDowall (1958a and b), there have been no other reports dealing with the antinociceptive activity of 4-AP. Most investigators were directed to its capability of reversing resistant neuromuscular blockades (Lundh et al., 1977), and morphine-induced respiratory depression (Shaw and Bentley, 1955; Sia and Zandstra, 1981).

Absence of any influence of atropine sulphate or naloxone on the antinociceptive effects of 4-AP to pressure stimulation in rats in our study indicates that analgesic activity of this drug does not depend on the functional activities of endorphinergic or cholinergic mechanism. However, it seems that 4-AP exerts its antinociceptive effects through noradrenaline in the central nervous system. This was supported by the finding in this study that αMPT in a dose of 200 mg kg^{-1}, i.p., which completely depletes noradrenaline stores (Spector et al., 1965) abolished the antinociceptive action of 4-AP. Besides, there is ample evidence that

noradrenaline can mediate antinociceptive effects of morphine in the periaqueductal gray (Yaksh, 1979). An intrathecal injection of noradrenaline into the spinal cord of the rat also produces a dose-dependent analgesia (Akaike et al., 1979); Liebeskind, 1981; Yaksh and Reddy, 1981). Further, it is known that noradrenaline is the neurotransmitter in the descending inhibitory system originating from the nucleus reticularis paragigantocellularis (Tebecis, 1974) which was recently located as the site of the analgesic action of morphine and enkephalins (Takagi, 1980). In addition, Andén and Leander (1979) found that 4-AP could accelerate the turnover of noradrenaline in the spinal cord. Altogether, it is probable that the descending noradrenalinedependent inhibitory pathway is the site where 4-AP exerts its analgesic action by increasing noradrenaline release. The finding that PCPA does not change the 4-AP antinociceptive activity, excludes the involvement of 5-hydroxytryptamine and gives a further support for the noradrenergic mechanism of the 4-AP antinociceptive action.

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PART THREE
ROLE OF NITROUS OXIDE IN DISTURBED RECOVERY FROM ANAESTHESIA

CHAPTER 10.
NITROUS OXIDE IN ANAESTHESIA

10.1. General aspects.

Nitrous oxide appears to be the most ubiquitously used agent in contemporary anaesthesia. It makes the greatest contribution to the effect of a general anaesthetic and retains its position as the most venerable agent for relief of pain caused by surgery. This gas has outlasted many anaesthetic agents but was, until recently, the least studied. Many desirable properties made it stand the test of time: nonflammability, negligible cardiovascular effects, low solubility, and lack of apparent toxicity.

The comprehensive description of nitrous oxide by Davy (1800), and his specific mention that this gas can "destroy physical pain", preceded its use for anaesthetic purposes by several decades. The mechanism of its action remained obscure. Paul Bert (1833-1866) demonstrated in 1878 that nitrous oxide is not an asphyxiant per sê, provided that the supply of oxygen to the body is maintained (Bert, 1878). A century after the introduction of nitrous oxide into anaesthesia it was definitely established that the gas can produce an anaesthetic state without concomitant hypoxia (Faulconer et al., 1949). The notion that nitrous oxide produces analgesia by causing cerebral hypoxia was definitely discredited by Clement (1951) who concluded that nitrous oxide possessed analgesic properties independent of its capacity to produce hypoxia. Consequently, the gas used to be described as entirely nontoxic (Parkhouse et al., 1960). However, it was evident that prolonged exposure to nitrous oxide induces leucocytopenia (Lassen et al., 1956). Moreover, it was known that ni-

trous oxide was capable of inducing drug-addiction (Editorial. Another martyr to anaesthesia. Anesth. Analg. 7: 1-4, 1928).

The advent of more knowledge about the synaptic transmission in the brain revived interest in the mechanism of the actions of nitrous oxide. Nowadays, we can discern and study separately the following central effects of nitrous oxide:

1. antinociception (analgesia)
2. anaesthesia (unconsciousness)
3. amnesia
4. suggestibility, illusions
5. mood modification
6. addiction
7. subjective hyperaccusis and objective decrease of auditory perception
8. nausea
9. diminishing effect on the sense of smell.

The antinociceptive and the addictive capacities of nitrous oxide probably are closely interrelated, judging by the fact that the gas is capable of inducing the release of brain opioid peptides (Quock et al., 1985). Nausea and vomiting may be a consequence of the sympathetic stimulation produced by nitrous oxide. Subjective hyperaccusis during induction of anaesthesia with nitrous oxide is often reported by patients. However, controlled measurements showed that auditory perception is in fact decreased during exposure to nitrous oxide. A pressure build-up in the middle ear cannot be the only factor and it appears that the decrement is most likely caused by a disturbance of sound transmission in the middle ear that is not associated with the narcotic properties of the gas (Fowler et al., 1980).

Among systemic effects of nitrous oxide, interference with vitamin B_{12} was studied (Chanarin, 1982; Deacon et al., 1978; Deacon et al., 1980; Amos et al., 1982; Nunn et al., 1982). It

was established that there is no harm in this respect in anaesthetic exposures of up to six hours (O'Sullivan et al., 1981; Nunn and Chanarin, 1985). According to a recent review of the cardiovascular effects of nitrous oxide, the absence of a marked depression of the cardiovascular system distinguishes this gas from the potent inhaled agents (Eisele, 1985).

For the practising anaesthetist, apparently, the study of the antinociceptive and anaesthetic effects of nitrous oxide are of primary interest.

10.2. Nitrous Oxide Withdrawal in our Clinical Practice:
Rhythmic Convulsant Motor Unrest. Clinical Observations.

During prolonged anaesthesia, after the relaxation has worn off, the patient may open his eyes on request, provided that he is anaesthetized according to the nitrous oxide - analgesic - relaxant technique.

Furthermore, an analysis of anaesthesias conducted with nitrous oxide, analgesic and relaxant, the so called "balanced anaesthesia", may show that after an initially smooth course, a patient's physiological state often becomes deranged. In other words, a balanced anaesthesia appears to become unbalanced. Additional administration of the analgesic and relaxant may not help and supplementation with a potent inhaled agent may be necessary in order to ensure a smooth course of anaesthesia (Fig. 1). Such observations may indicate that the effects of nitrous oxide are wearing off, this gas being the only component of anaesthesia that cannot be intermittently reinforced, as it is given during the whole anaesthesia at the maximal concentration, nowadays usually 67 vol%.

After prolonged anaesthesia including nitrous oxide we also observed a form of rhythmic convulsant motor unrest that can be distinguished from the more aimless and coarse shivering. This

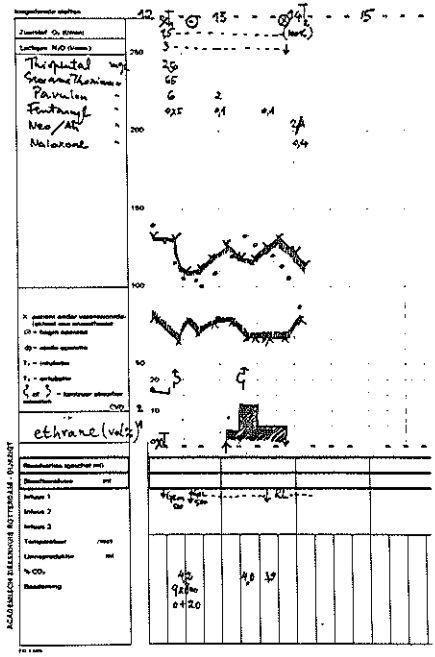

Figure 1: A fragment of an anaesthetic record which shows that the cardiovascular parameters are "deranged" after 45 min of anaesthesia regardless of the repeated administration of relaxant and analgesic. The satisfactory state of clinical anaesthesia was achieved by the addition of a halogenated anaesthetic. An analysis of this anaesthesia justifies the impression that nitrous oxide had lost its potency. 15 min after this anaesthesia we observed convulsant behaviour in the patient, who otherwise appeared conscious. No aberrant body temperature was measured in this patient.

disturbance of recovery also does not fit well into the picture of motor activity characteristic of delirant forms of the central anticholinergic syndrome. The following features of this postanaesthetic unrest were observed:

1. It appears after a latent period of 6-15 min after the end of anaesthesia, mostly in conscious patients.

2. the motor unrest is convulsion-like, intermittent, and may be found in patients who otherwise are completely lucid and in appropriate psychic contact with the surroundings. Conscious patients may describe it as extremely unpleasant or threatening. No voluntary control is possible and the patient may feel distressed.
3. facial or mimic musculature is first involved, followed, in severe cases, by convulsive seizures of the extremities.
4. unrest is not dependent on the central or peripheral body temperature and can thus be differentiated from the common shivering which may accompany overcooling of the patient.
5. the convulsant postoperative restlessness subsides, if untreated, within 30-50 min, regardless of the body temperature.
6. this type of convulsant behaviour is unlikely in patients depressed from drugs.
7. it is more common after prolonged anaesthesia and in cases where opiate antagonists have been given.
8. in all cases of convulsant motor unrest, nitrous oxide was used during anaesthesia.
9. the convulsant postanaesthetic behaviour can be differentiated from the "active" form of the central anticholinergic syndrome. Physostigmine completely abolishes motor unrest due to central anticholinergic activity. Physostigmine, however, only mitigates or reduces the rhythmic postanaesthetic motor unrest, rather than totally abolising it.
10. piloerection and "goose-pimples" appearance of the skin are present.
11. meperidine (pethidine), 12-25 mg i.v. abolishes this rhythmic convulsant behaviour promptly and completely regardless of the body temperature. (The origin of this therapy for the postanaesthetic motor unrest can be traced back at least 20 years - Hekman and Schlutter, personal communication).
12. re-administration of subanaesthetic concentrations of nitrous oxide (30-40%) abolishes the rhythmic convulsant unrest within 4-6 min.

In evaluation of this clinical picture it was suggested that the rhythmic convulsant postanaesthetic motor unrest and its accompanying discomfort might be due to the withdrawal of nitrous oxide. This suggestion was supported by the observation that re-administration of nitrous oxide stopped the unrest.

Our Study of Rhythmic Convulsant Motor Unrest during Recovery - A Sign of Nitrous Oxide Withdrawal

Motor disturbances during recovery from anaesthesia may be due to the central action of anticholinergic drugs, which can be treated with physostigmine. However, a distinct type of convulsant rhythmically occurring motor unrest does not subside completely after this treatment. It has been observed that rhythmic convulsant unrest promptly disappears after the administration of meperidine (pethidine) or re-administration of subanaesthetic concentrations of nitrous oxide. This successful treatment indicates that the withdrawal of nitrous oxide might be the cause of the convulsant motor unrest. The disappearance of this muscle unrest after pethidine confirms this view as the interaction of nitrous oxide with the endorphinergic system is well-established (Berkowitz et al., 1977). The aim of this study was to elucidate the causative factor of the convulsant unrest during recovery from anaesthesia and to determine the best treatment of it.

Patients and diagnostic parameters

All patients recovering from anaesthesia which included nitrous oxide were followed during a 3 month period.

Two senior anaesthetists, experienced in diagnosis and treatment of the central anticholinergic syndrome observed the patients from 5-10 minutes after the end of anaesthesia until 35 min of recovery. Attention was paid to the presence of the central anticholinergic syndrome, which was treated with physostigmine (0.04 mg kg^{-1}). In the presence of convulsant muscle unrest rectal temperatur was recorded and conscious patients were asked whether they felt cold or apprehensive. Convulsant motor unrest was

then treated aselectively either with 25 mg pethidine slowly i.v., readministration of 30% nitrous oxide by a non-return anaesthesia system, 50% oxygen in air by a face mask, or air. The time lapse before the disappearance of convulsant activity was recorded. Duration of anaesthesia in these cases was also recorded.

Observations and Findings

720 patients were seen during the recovery. The central anticholinergic syndrome was diagnosed and treated with physostigmine in 40 patients (5.4%). Motor convulsant unrest was seen in 34 patients (4.5%). Most patients with convulsant motor unrest were lucid and could hold the face mask in place. Rectal temperature was normal in 28, elevated in 3 and decreased in 3 patients. 15 patients reported feeling cold before treatment of the unrest, 10 were apprehensive or otherwise feeling uncomfortable. Pain was reported 11 times, always bearable. The convulsant unrest subsided after pethidine within 3 ± 1 min (8 patients), after the inhalation of 30% nitrous oxide within 4 ± 2 min (9 patients), after 50% oxygen in air within 20 ± 8 min (8 patients) and in patients without treatment after 23 ± 9 min (6 patients; 2 patients of this group required analgesics and were dropped from the follow up). Some patients regarded the presence of convulsant unrest as being more troublesome than pain. In five patients, the unrest followed naloxone, administered at approximately 10 minutes postoperatively. Feelings of cold subsided simultaneously with the relief from unrest; one of these patients was hypothermic. Motor unrest disappeared permanently in all pethidine-cases. It reappeared in 3 patients who removed the nitrous oxide mask after 10 min inhalation. Readministration of the gas again stopped the unrest. In cases of postanaesthetic rhythmic motor unrest, the length of anaesthesia varied greatly but was never shorter than 80 minutes.

DISCUSSION

The observation that readministration of a subanaesthetic concen-

tration of nitrous oxide stops the convulsant motor behaviour during recovery indicates that nitrous oxide withdrawal may be a causative factor. Motor unrest and apprehensive discomfort could be signs of withdrawal in patients who have developed acute physical dependence upon nitrous oxide. The curative effect of pethidine in "uncomfortable and frightening postoperative shivering" has been documented previously (Claybon and Hirsh, 1980; Roy et al., 1983). It was also observed that "spasticity" occured in 20-50% of patients after general anaesthesia without pethidine as contrasted with 10% in the pethidine group (Soliman and Gillies, 1972). These observations are in accordance with the finding that postanaesthetic restlessness is negatively correlated with the total dose of analgesics during operation (Tammisto and Tigerstedt, 1979).

It appears that the term "shivering" cannot cover all types of postanaesthetic motor unrest and it would be better reserved for cases of obvious hypothermia. In fact, several authors concluded that postanaesthetic motor unrest was not correlated with the level of body temperature (Artusio, 1951; Cohen, 1967; Tammisto and Tigerstedt, 1979). The feeling of cold in our patients was not related to a decrease in rectal temperature. It is possible that they frankly misinterpreted unfamiliar nitrous oxide withdrawal motor activity for the more familiar feeling of cold.

There is ample evidence that depression of central functions by nitrous oxide is followed by withdrawal excitation. It was found that mice develop convulsions during withdrawal from nitrous oxide (Harper et al., 1980) and that nitrous oxide depresses epileptogenic response to enflurane in cats, although partial tolerance to this effect soon develops (Stevens et al., 1983). Stevens (1984) also suggested that nitrous oxide withdrawal may be the principal cause of convulsions after enflurane. These data confirm our observations that the withdrawal of nitrous oxide causes convulsant behaviour during recovery. Other findings on the interaction of nitrous oxide with the endorphinergic system may

help to elucidate the excellent curative effect of pethidine in nitrous oxide withdrawal motor unrest (Berkowitz et al., 1977; Rupreht et al., 1984).

It may be asserted that some patients develop a convulsant motor unrest during recovery from anaesthesia due to the nitrous oxide withdrawal. The nitrous oxide withdrawal is accompanied by unpleasant feelings of cold or distress, all these signs forming a syndrome. Readministration of a subanaesthetic concentration of nitrous oxide or pethidine are both effective and logical treatments of this clinical picture.

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PART FOUR

OWN EXPERIMENTAL AND CLINICAL DATA CONCERNING THE USE OF NITROUS OXIDE IN ANAESTHESIA

CHAPTER 11.

ELIMINATION OF IRRITATING COMPOUNDS DURING CHRONIC EXPOSURE TO GASES

SUMMARY

Ammonia (NH_3, a degradation product of urea) and intestinal gases which accumulate in the experimental circuit during the long-term experimental exposure of rats to gases might cause disturbing irritation in the behavior of the animals. A relatively simple and cheap experimental arrangement has been suggested for the elimination of these irritating compounds. This system also guarantees the maintenance of a constant concentration of the investigated gases. In order to facilitate the comparison of the results of various studies, the standardization of the basic experimental procedure for the long-term exposure to gases has been suggested.

INTRODUCTION

New insights into the action of anaesthetic agents (Wood et al., 1977) have brought to light the essential differences between an acute and a chronic exposure to biologically active gases. Chronic or long-term exposure to gases can be defined in terms of phenomena which cannot be seen at the moment of complete saturation by a gas (acute exposure) but will appear after a prolonged exposure, or by the effects which initially can be seen but will disappear during the prolonged exposure. Effects of chronic exposure to anaesthetic gases have been studied with increasing frequency (Green and Eastwood, 1963; Goldstein and Pal, 1971; Kripke et al., 1976 and 1977; Berkowitz et al., 1977, Pope et al., 1978; Vieira, 1979). Incidentally, the accumulation of various unwanted gases in the exposure chamber appears to be one of the basic methodological problems in the studies of chronic effects of inhalation of anaesthetic agents. These gases are produced in the metabolism of the exposed animals, or are the degradation product of their excrements. In experimental prolonged exposure to gases, it is therefiore of particular importance to

efficiently eliminate the carbon dioxide (CO_2), ammonia vapour (NH_3, developed from urine), intestinal gases which include nitrogen (N_2), hydrogen (H), methane (CH_4), and odoriferous gases such as skatole, indole, volatile amines and short chain fatty acids.

Experimental conditions for studies of the prolonged exposure to gases vary greatly with different authors (Pope et al., 1978; Koblin et al., 1979; Hynes and Berkowitz, 1979; Coate et al., 1979; Harper et al., 1980).

The elimination of CO_2 has not been standardized. Some investigators keep it close to 0% (Pope et al., 1978; Koblin et al., 1980), at an unspecified concentration (Vieira et al., 1980), or close to 1% (Koblin et al., 1979). Different concentrations of this potent biological gas certainly indicate differences in experimental conditions. The CO_2 absorbing granules which are simply spread on the bottom of the exposure box cannot satisfactorily eliminate CO_2 because of the channelling (Adriani, 1956). In the quoted studies of the chronic exposure to gases, no attempt was made towards the elimination of the above mentioned unwanted gases in the exposure circuit. The temperature, relative humidity, and the pressure in the exposure cage are different in most studies. This makes any comparison of results of various studies difficult.

The need to standardize the experimental conditions during the chronic exposure to gases and the problems related to the elimination of unwanted compounds from the exposure circuit have prompted this study. We have described alternatives for the improvement of experimental conditions in long-term exposure studies of rats to anaesthetic gases.

MATERIALS AND METHODS.

In our investigations of long-term exposure of rats to nitrous oxide we used the following experimental set-up (numbers correspond to Figure 1):

a) exposure chamber with two compartments (plexi-glass). Each compartment had a volume of 75 litres and could house 25

rats. Such an arrangement facilitates the simultaneous performance of the control experiment (Number 1).

b) a soda-lime CO_2 absorber was included in the circuit placed after the exposure box and before the inlet of fresh gases (Number 12).

c) CO_2-monitoring device was a Gould NK-3 capnograph with a correction for N_2O interference (Number 5).

d) flowmeters (Rotameters MFG Co.Ltd) and a gas-mixing device (Siemens-Elema O_2-N_2O-air mixer) regulated partial pressure of gases (Number 16).

e) oxygen analyser (IBC-celesco, O_2-combustion cell) was used monitoring of the O_2-partial pressure (Number 7).

f) a sample of the exposure gases was taken to the mass-spectrometer twice daily for double check of gas concentrations.

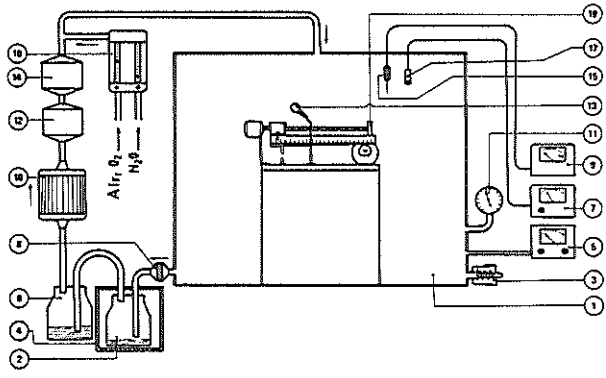

Figure 1.
Schematic presentation of the experimental set-up for the long-term exposure to gases. A plexi-glass exposure box (1), one compartment is represented. Attachment for a mass spectrometer (8). Humidity and a temperature regulating unit (2 and 4). Elimination of ammonia (6). Electric pump (10). Activated charcoal (12). Soda-lime container (14). Flowmeters and a gas-mixing unit (16). Temperature sensor (15). Pressure monitor (11). Temperature display (9). Carbon-dioxide monitor (5). Bleed valve and a gas scavenging device (3). Oxygen sensor (17) and oxygen display (7). Inside the box, an analgesia-meter (19) and a microphone (13) are shown.

g) an electric membrane pump (ERMAF, Rotterdam), capacity 45 litres min^{-1}, was used to induce the circulation of gases. The box was aerated with conditioned gases every two minutes (Number 10).

h) a bleed valve (AMBU PEEP-valve), set at 1.0 cm H_2O regulated the pressure in the box (Number 3); the pressure being monitored by an MM-80 manometer (Dwyer Mark II; Number 11).

i) long plastic tubing between the pump and the exposure box prevented noise in the box.

j) a scavenging system for exhaust gases was attached to the bleed valve to prevent the pollution of the environment by the exhaust gases.

k) the humidity and temperature in the exposure box were regulated by a heat exchanger. The relative humidity in the box was kept at 70 and the temperature at 25°C, which is close to ideal conditions. The rectal temperature of the rats was maintained between 37 and 38°C.

l) a 12 hr day-12 hr night cycle was maintained by artificial illumination.

Male Wistar rats (125-150 g) were used and housed in the exposure chamber with food and water ad libitum.

The Elimination of Ammonia and other Trace Gases

The rats, put into the described experimental set up, showed no behavioural changes when 25 animals were kept in the box and the fresh air flow was 1.0 l min^{-1}. However, the rats became irritated after 20 hr exposure to the air in the circuit. We suspected that this behavior was due to the presence of ammonia vapour and to the accumulation of the intestinal gases in the experimental environment. In particular, the offensive smell of the exhaust gases indicated high concentration of ammonia. An attempt was made to quantify concentrations of the offensive gases by a "multi-gas detector" (Dräger). The Dräger NH_3-test tube estimated the NH_3 concentrations in the exposure chamber at 50 parts per million (ppm). The gas chromatograph can be used for

the same purpose, with similar efficiency.

One way of eliminating unwanted gases from the circuit is by increasing the flow of fresh gases. In our circuit an increase of 300% in the fresh gas flow was necessary to eliminate NH_3. This method of gas elimination is associated with an increase in costs and environment pollution. Another method for the elimination of NH_3 from the exposure circuit is to bind it chemically. We included a bubble bottle into the exposure circuit containing diluted phosphoric acid (H_3PO_4, pH 0.3). Bromphenol-blue was added to the acid and when the solution turned blue, the acid was renewed. After this procedure for binding NH_3, the smell of exposure gases improved and the NH_3-detector indicated that the concentration of this gas was below 5 ppm.

Non-odoriferous intestinal gases, such as N_2 and CH_4 also accumulate to considerable concentrations in a circuit with a low flow of fresh gases. CH_4 could be detected qualitatively by the Dräger gas-detection tubes. There is no convenient method for binding CH_4 chemically. After an increase of fresh gas flow from 1.0 to 2.0 l min^{-1}, we failed to detect this gas again. However, after the elimination of NH_3 and H_2S (this gas binds to the soda-lime) some odour in the exposure box persisted. The doubling of the fresh gas flow for the elimination of CH_4 could not prevent it. Odoriferous gases, such as indole, skatole, volatile amines, and short-chain fatty acids are readily sensed by nose even in concentrations of 0.01 ppm (Moncreff, 1964). Although it was impossible to quantify concentrations of these gases by the Dräger gas-detection tubes, we included a 4 litre container of activated charcoal into the circuit. Following this, the residual odor disappeared.

With the described improvements we could use our gas-exposure circuit continuously for 5 days and more, keeping 25 rats per box at a fresh gas-flow of 2 litre min^{-1}. All manipulations inside the box were done through rubber gloves from outside and an interruption of the exposure to the gas supply was not necessary.

RESULTS

Rats living under the described conditions in our gas-exposure box for 5 days showed no difference in behavior, growth, and sleep-waking pattern when they were compared to rats living in the stable. The consumption of fluid and food as well as the weight increase were equal for both groups. In order to test further biological reactivity of animals in our exposure circuit, we determined their reactivity to pain after 5 days in both groups. Pressure stimulation (pain) on the uninflamed hind paw of the rat was used (modified Randall-Selitto, 1957). No significant difference in sensitivity to pressure pain was observed in rats of the two groups, counting 25 animals each. The mean and the standard error of the pressure which they tolerated was 122 ± 24 and 128 ± 24 g mm^{-2}, respectively.

DISCUSSION

In the present study, we described methods for the elimination of NH_3 and intestinal gases from a semi-closed circuit for the long-term exposure of rats to gases. An elaborate experimental arrangement is necessary for the study of prolonged exposure to gases. Some living conditions for animals undergoing chronic exposure to gases are not yet standardized. Various organic and inorganic gases accumulate in the exposure chamber when low flow rates of fresh gases are used. The accumulation of all unwanted gases must be prevented in order to create constant experimental conditions.

The odor threshold for ammonia in humans is around 50 ppm. The gas becomes intolerable at 100 ppm (Leithe, 1971). NH_3 causes irritation and damage to airway surfaces and rats appear to be particularly sensitive to this gas. In the exposure box they calmed down only when the "gas-detector" or the nose failed to detect any offensive smell indicating the presence of NH_3. Chemical binding of NH_3 as suggested in this study proved to be convenient and efficient.

There are no data available about the effects of other non-

odoriferous gases which accumulate in the exposure circuit during the prolonged exposure. It was convenient to absorb such trace gases onto the activated charcoal. After this procedure, quantitative or qualitative tracing of these gases in our exposure circuit was negative at any time of the exposure.

N_2 and CH_4 should be eliminated because they may significantly dilute exposure gases. An increase in fresh gas flow rate from 1.0 to 2.0 litre min^{-1} was the most practical measure to eliminate them. Relative humidity should not exceed seventy or be less than fifty. Very low environmental humidity causes dryness of the nasal mucosa; too moist gas may induce excessive grooming and excitation in the rats. The permitted concentration for CO_2 during the long-term exposure to gases has not been established. It appears plausible to keep it close to 0%, thus simulating its concentration in normal air.

In conclusion, it is evident that apart from the need for a standardized technique for the long-term exposure to gases, a further improvement of experimental conditions for animals is of importance, particularly the elimination of the accumulated NH_3 and intestinal gases. These requirements fulfilled, it will certainly improve the reliability of results and will also facilitate comparison of similar data of other authors. In addition, we used our gas-exposure box extensively for the study of tolerance to nitrous oxide in rats (see Chapter 14). Demanding minimal control corrections, the system reliably provided us with any concentration of the investigated gas for any length of time. The system also appeared to be cost-saving.

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(J. Pharmacol. Meth., 8: 109-114, 1982)

CHAPTER 12.

THE INVOLVEMENT OF THE CENTRAL CHOLINERGIC AND ENDORPHINERGIC SYSTEMS IN THE NITROUS OXIDE WITHDRAWAL SYNDROME IN MICE

SUMMARY
The nitrous oxide withdrawal syndrome in mice was used as an experimental model to examine some of the factors which may play a role in postanesthetic excitation. Predisposition to nitrous oxide withdrawal convulsions as judged by duration of susceptibility was decreased significantly after pretreatment with the cholinesterase inhibitors, physostigmine and galanthamine, or with the opiate receptor blocking agent naloxone. Results are discussed in relation to the central anticholinergic syndrome, endorphin release, and disturbances which follow nitrous oxide anesthesia in humans and animals.

INTRODUCTION

Patients demonstrating emergency delirium after general anesthesia have been treated successfully with physostigmine salicylate (1). This type of delirium is a part of the very complex clinical picture described by Longo (2) as the central anticholinergic syndrome (CAS).

Considering the possible factors promoting this syndrome in our patients, we suspected that nitrous oxide might have a significant facilitatory role in the etiology of CAS (3,4). An animal model for study of the factors involved in CAS is not yet established. However, an excitatory syndrome in mice after exposure to nitrous oxide (and other anesthetics) has been described (5, 6). This syndrome is characterized by signs of excitation such as grimacing, violent jerking, twirling, convulsions, etc., and is elicited by gently lifting the mouse by the tip of the tail. Smith et al. (7), suggested that the same pathophysiologic mechanisms involved in this withdrawal syndrome might contribute to the occurrence of emergence delirium following anesthesia in humans.

In this study, we used the nitrous oxide withdrawal syndrome in mice as an experimental model to examine certain factors which

may play a role in postanesthetic excitation. Specifically, we examined the role of the cholinergic and endorphinergic systems. These transmitter/modulator systems were considered mainly because of the therapeutic value of physostigmine in the treatment of CAS, and because of recent evidence suggesting a role for enkephalins in certain postanesthetic phenomena (8).

METHODS

Male mice, F_1 R_y breed, 25 $\pm$ 4 g, were used. Mice of this breed were chosen because we could reliably provoke nitrous oxide withdrawal convulsions in them. The experiment involved exposure of mice to a mixture of 1.4 atm nitrous oxide, and 0.6 atm oxygen for a period of 60 min. Each mouse was used only once. None displayed convulsions prior to the anesthetic exposure. The pressure chamber used, was a 500 ml-glass bell with an attachment for fresh gases, a manometer, and an overflow valve. Soda lime was placed in the bell to ensure the elimination of CO_2 (monitored by an infrared analyzer). The gas temperature in the bell was held at 22°C with the aid of a waterbath in which the bell was immersed. The mice were placed one at a time into the chamber for exposure to the gas mixture. After 60 min, the pressure was reduced to ambient pressure over a period of one minute. Then, each mouse was lifted gently from the bell and tested for withdrawal convulsions every five minutes until no convulsions were observed for two consecutive tests. The convulsive movements consisted of twirling and jerking with extension and flexion of the legs. During testing, the mice were lifted and held by the tail for up to ten seconds. The test was considered negative if convulsions did not occur within this time. The rectal temperature of mice at the end of the exposure was always above 34°C (34.5 $\pm$ 0.4) and was not influenced by the drugs administered. Mice in the control group showed the same decrease in rectal temperature without detectable changes in behavior. All experiments were performed between 0930 and 1200 h by a technician who was unaware of the drug treatment. Each experimental group consisted of 12 mice.

DRUGS

The following commercially available drugs were used: physostigmine salicylate, galanthamine hydrobromide, and naloxone hydrochloride. Drugs were dissolved in 0.9% NaCl and were injected intramuscularly either 1 min before, or 1 min after exposure of mice to the gas mixture. The drug dosages were expressed in the terms of their salts, and were administered in a volume of 0.05 ml.

Statistical Evaluation.

In order to test whether the mean duration of predisposition to convulsions in the four pretreated groups and that in the non-pretreated group were equal, a one-way analysis of variance (ANOVA) was performed. Comparisons between each of the four pretreated groups separately with the non-pretreated group are based on Tukey's 95% confidence intervals for contrasts. The same analysis was performed for the four groups in which the agent was administered after exposure to N_2O and for the group which was not treated after the exposure.

RESULTS

Overall Comparisons

Among the groups which received saline, physostigmine, galanthamine, naloxone, or no agent, before exposure to N_2O, a highly significant difference in duration of predisposition to convulsions was seen ($F_{4,55} = 38.9$, $P < 0.0001$). The analogous overall comparison among the groups which received an agent after exposure to N_2O and the one which received none, also reveals a highly significant difference in duration of predisposition to convulsions ($F_{4,55} = 42.8$, $P < 0.0001$).

Control

None of the mice displayed a convulsion prior to the anesthetic exposure if lifted and held by the tail for up to ten seconds. However, all mice subjected to this procedure demonstrated a con-

vulsive pattern during the withdrawal period which followed an exposure to nitrous oxide for 60 min. The average time period during withdrawal in which the convulsions could be elicited in the nontreated mice was 64.6 min (Table I). For saline-treated mice given either before exposure to nitrous oxide or after it was discontinued, the periods of susceptibility were 52.1 and 61.2 min, respectively. These times did not differ significantly from that observed in untreated mice.

Physostigmine

In the group of mice pretreated with physostigmine (0.4 µg/g) the period of susceptibility during withdrawal was decreased significantly (17.5 min). A similar significant decrease was observed when the same dose of physostigmine was given in the first minute after nitrous oxide was discontinued (23.7 min).

Table I:
The influence of Drugs on the Duration of Predisposition to N_2O-Withdrawal Convulsions (min; Mean ± SD).

Agent	Agent Administered before Exposure to N_2O	Agent Administered after Exposure to N_2O
None	64.6 ± 16.8	64.6 ± 16.8
Saline (50 µl/g)	52.1 ± 8.9	61.2 ± 6.8
Physostigmine (0.04 µg/g)	17.5 ± 6.2*	23.7 ± 3.1*
Galanthamine (50 µg/g)	33.3 ± 4.4*	67.5 ± 12.5
Naloxone (0.8 µg/g)	23.4 ± 13.4*	72,9 ± 6,6

*Denotes significant difference compared with the nontreated group, as follows from Tukey's 95% confidence intervals (n=12, all groups). All drugs were administered intramuscularly.

Galanthamine

This alkaloid (5 µg/g), which has anticholinesterase properties and which easily penetrates the blood brain barrier, significantly decreased the period of time in which the seizure phenomena could be elicited (33.3 min) when administered before the ani-

mals were exposed to the gas mixture. The same dose of galanthamine administered in the first minute of the withdrawal period failed to affect significantly the time period in which the animals were predisposed to convulsions (67.5 min).

Naloxone

Naloxone (0.8 µg/g) administered to mice before exposure to nitrous oxide, decreased significantly the time of predisposition to convulsions. One mouse did not convulse at all during a period of 100 min, while others started to convulse 5 min after the exposure to the gas was discontinued. The average time during the withdrawal period in which the animals retained the tendency to convulse was significantly less than in the control group (23.4 min). However, the same dose of naloxone, administered in the first minute after N_2O was discontinued, failed to influence the duration of time in which the convulsant phenomena could be elicited.

DISCUSSION

In these experiments the time of susceptibility to withdrawal convulsions in mice following nitrous oxide was decreased significantly after pretreatment with the cholinesterase inhibitors, physostigmine and galanthamine, or the opiate receptor blocking agent naloxone. The cause of such postanesthetic excitation (the withdrawal syndrome) is not known. Presumably, these phenomena are a reflection of the complex interaction of anesthetics on excitatory and inhibitory synaptic transmission (9-11). Specific information concerned with the functional activity of the transmitter systems during the withdrawal period following nitrous oxide is limited. Recent data indicate that some anesthetics such as halothane, enflurane, and ketamine reduce the turnover rate of acetylcholine in all regions of the rat brain examined (11). However, nitrous oxide (75%) had no effect on acetylcholine turnover in the rat brain (12).

That the cholinesterase inhibitors used in the present study de-

creased the time of predisposition to convulsions following exposure to nitrous oxide suggests a possible important role for central cholinergic transmission in the modulation of the neuronal activity responsible for the postanesthetic excitatory withdrawal phenomena. The anticonvulsant effect of the cholinesterase inhibitors during a withdrawal period might be a direct one, via normalization of the inhibited cholinergic system, or an indirect one, by acting on other transmitter/modulator systems via a hyperactive cholinergic system.

The explanation for the differences in action between physostigmine and galanthamine observed in this study is not known, but the possibility that each drug possesses specific and different pharmacodynamic characteristics is not excluded.

Based upon our clinical experience in the treatment of CAS we concluded that the beneficial effect of physostigmine is related exclusively to cholinesterase inhibition (13, 14). Furthermore, we observed in our patients that nitrous oxide might be a precipitating factor for the postanesthetic excitation as a part of CAS (3, 4). The results of this study indicate that physostigmine and galanthamine decreased susceptibility to nitrous oxide withdrawal convulsions in mice. All of this suggests the possibility of using the nitrous oxide withdrawal syndrome in mice as an animal model for CAS in humans. At present we would like to encourage this idea and a further search for additional relationships between CAS in humans and the proposed animal model.

The anticonvulsant effect of naloxone given to mice before exposure to N_2O also could be explained by a cholinergic dysfunction caused by nitrous oxide. Namely, it has been postulated that nitrous oxide releases endorphins (8), which may in turn decrease the release of acetylcholine (15). Therefore, the anticonvulsant effect of naloxone, similarly to physostigmine, might be ascribed to normalization of the cholinergic system. However, other explanations related to the monoaminergic system(s) are also possible. Endorphins and exogenous opiates are reported to inhibit activity of some central noradrenergic nuclei (16) and reduce transmitter release from cerebrocortical noradrenergic

nerve endings (17, 18). Functional insufficiency of the noradrenergic system facilitates seizure activity (19). Thus, an anticonvulsant effect of naloxone might be due to inhibition of the endorphin-induced changes in noradrenergic functional activity. However, since endorphins are modulators of various transmitter systems, the anticonvulsant effect of naloxone might be much more complex than that suggested above. Despite these uncertains, the anticonvulsant effect of naloxone during withdrawal from nitrous oxide might be of significant value in suggesting further studies of the role of endogenous opioid substances in postanesthetic excitatory phenomena.

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CHAPTER 13.

EFFECT OF PHOSPHORAMIDON - A SELECTIVE ENKEPHALINASE INHIBITOR - ON NOCICEPTION AND BEHAVIOUR

SUMMARY

Phosphoramidon (100-350 µg i.c.v.), a selective enkephalinase inhibitor, induced in the rat a decrease of nociception to pressure stimulation without evident respiratory depression. In addition, intensive behavioural changes such as grooming (licking the fur, face washing and scratching), mounting behaviour and wet dog shakes were observed. Naltrexone pretreatment (1 mg/kg i.p.) caused a significant decrease in the phosphoramidon-induced nociception and behavioural changes. Puromycin (30 µg i.c.v. or 7.5 mg/kg i.p.) caused no changes in nociception or behaviour.

Using the recently discovered, selective, enkephalinase inhibitors, it has become possible to modulate the concentrations of endogenous opioid peptides. Several studies in vitro have shown that administration of a relatively specific enkephalinase inhibitor is associated with an increase in concentrations of endogenous opioid pentapeptides (13, 15). Other studies in vivo demonstrated that specific enkephalinase inhibitors such as thiorphan and phosphoryl-L-leucyl-L-phenyl induced antinociceptive action and/or potentiated an analgesic effect of other drugs. This effect was blocked by naloxone, an antagonist of opiate receptors (1, 15).

However, other highly selective enkephalinase inhibitors such as hydroxamic acids or glucopeptide phosphoramidon (11) were not tested in vivo for analgesia and other central effects.

The present study was designed to compare the effects of the selective enkephalinase inhibitor phosphoramidon, and the non-selective protein-synthesis inhibitor puromycin, on analgesia and behaviour.

The sensitivity to noxious pressure stimulation was determined on the uninflamed hind paw of male Wistar rats (125-150 g) according to the Randall-Selitto analgesiometric method (14). The Ugo Basile (Milan) analgesiometer for paw withdrawal was used. Nociception was expressed in analgesiometric scores (AMS) 1 g

mm^{-2}. The cut-off value of the pressure stimulation was 500 g mm^{-2}, so as to prevent physical damage to the paw. The sign of the pain response in this test was a squeak or a paw withdrawal. The rats were divided into 5 groups of 11 animals each. Nociception was determined at 0, 15, 30, 60, 90, 120 and 150 min time intervals after drug treatment. The first group of animals was treated with phosphoramidon (350 µg/2 µl intracerebroventricularly, i.c.v.). The rats in the second group were pretreated with naltrexone (1 mg/kg/0.5 ml, i.p.) 30 min before phosphoramidon treatment (i.c.v.). The third and fourth group received puromycin i.p. (7.5 mg/kg) or i.c.v. (30 µg/15 µl over a 90 sec period) respectively. Animals in the fifth group were injected with artificial cerebrospinal fluid (CSF [12]) and used as a control.

All animals were chronically implanted with stainless steel cannulae in the left lateral cerebral ventricle. The cannulae were used for i.c.v. administration of phosphoramidon (groups I and II), cerebrospinal fluid (control group V) and puromycin (group IV).

The following drugs were used: phosphoramidon (Peninsula Lab.) diluted in CSF; puromycin (ICN Nutritional Biochemical) dissolved in saline or in CSF for i.p. and i.c.v. administration respectively; naltrexone (Endo Lab.) was dissolved in saline.

Statistical evaluation of the results was done using the Student's t-test. Intraventricular administration of phosphoramidon (100-350 µg/2 µl) was followed by a significant increase in nociception scores compared with control rats. The most pronounced analgesic effect was observed 30 min after drug administration and declined to normal values after 60 min. Naltrexone pretreatment (1 mg/kg i.p. 30 min prior to phosphoramidon) completely prevented the antinociceptive effect of phosphoramidon (Fig. 1). No significant differences in intensity and duration of nociception were observed within the dose range 100-350 µg of phosphoramidon. Lower doses of phosphoramidon (25 and 50 µg) did not affect nociception.

Behavioural changes following phosphoramidon were multiple but

mainly belonged to the category of maintenance behaviour (11). Grooming (licking the fur, face washing and scratching) became excessive in all animals during the first 5-10 min after i.c.v. administration of phosphoramidon. The most pronounced element of this behaviour was scratching. It started within 5 min, and reached peak intensity of 10-12 scratches/min after 30 min and lasted several hours. Wet-dog-shakes started within a few minutes after i.c.v. administration of phosphoramidon, reached a peak of incidence of 15 shakes/min within 15 min and lasted about 100 min.

An additional and differential behavioural element observed in all animals was mounting behaviour in the absence of a female. The onset of this remarkable change in behaviour occurred within 10 min after i.c.v. administration of the drug and lasted 2-3 h.

All behavioural phenomena were abolished or significantly reduced by naltrexone (1 mg/kg i.p. 30 min prior to phosphoramidon).

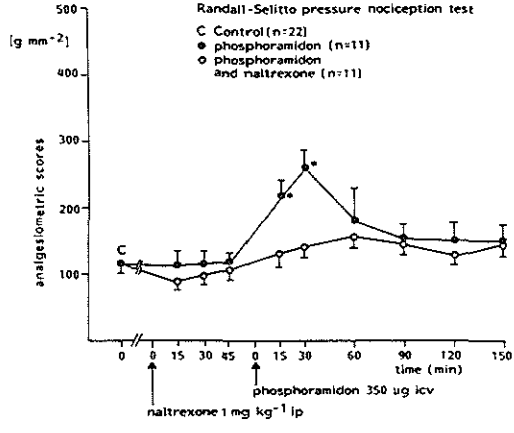

Fig.1. Effect of naltrexone (1 mg/kg) on phosphoramidon (350 µg i.c.v.) antinociception in rats. The significant increase of the nociceptive threshold after phosphoramidon (*$P < 0.001$, Student's t-test) does not occur in rats pretreated with naltrexone. Nociception was determined by withdrawal of the uninflamed hind paw from the pressure stimulation (modified Randall-Selitto test).

Puromycin administration (7.5 mg/kg i.p. or 30 µg/15 µl over 90 sec i.c.v.) was not followed by any changes of behaviour or nociception for a period of 5 h. No signs of respiratory insufficiency were observed in this study.

The analgesic effect of phosphoramidon observed in this study is probably due to a certain level of accumulated enkephalins which is the result of enkephalinase inhibition. It seems that decrease in enkephalinase activity by increasing the dose of phosphoramidon is minimal or does not occur and, therefore, is irrelevant for nociception. This might explain the absence of a dose-response relationship in the range of 100-350 µg phosphoramidon.

Phosphoramidon-induced increase of pain threshold could be related to the activation of opiate receptors, since the opiate antagonist naltrexone abolished this effect. Analgesia induced by phosphoramidon was not accompanied by signs of respiratory insufficiency, which might be of importance when comparing with morphine-like substances.

The mounting behaviour which the male rats displayed after phosphoramidon is very intensive and supports the idea that brain endorphins are possible mediators of pleasurable states (17), while it is not in accordance with some other published data (7, 10). Evidently this contradictory subject needs further detailed investigation in order to specify the role of endogenous opioid peptides in sexual behaviour and pleasurable states.

Another point of interest after administration of phosphoramidon is the intensive maintenance behaviour consisting of licking the fur, face washing, scratching (grooming) and wet dog shakes. The grooming was observed after morphine (8) and was more intensive after opioid peptides (9). The biological significance of excessive grooming is not clear. However, some authors have related this behaviour to sexual excitement (2) which might be of interest, since mounting, an element of the copulatory behaviour, was observed in this study.

Why animals shake is not known but the suggestion that this is a form of adaptive behaviour aimed at maintaining a normal body temperature (18) is not generally supported (3). However, it is

well established that one of the major signs of opiate withdrawal is a wet shaking (18). This behaviour can also be induced by acute i.c.v. administration of β-endorphin (11) and by many other physical procedures and non-opiate drugs (19). We observed that (D-Ala^2)-Met-enkephalinamide (DALA)- or δ receptor peptide (agonist of δ-opiate receptors)-induced wet dog shakes were always associated with epileptiform electrocortical EEG (*). Similarly other authors have reported that body shaking evoked by DALA was associated with electrographic seizures in the hippocampus (4). This might suggest that wet dog shakes are the behavioural expression of the central epileptiform processes. Consequently, the phosphoramidon-induced shaking might be result of the increased neuronal excitability due to the accumulated enkephalins, which are known as substances capable of inducing the seizure phenomena (5, 6).

Puromycin, a compound which does not significantly affect enkephalinase (16), did not alter either pain threshold or behaviour in our experiments. This might indicate a specificity of changes in nociception and behaviour after enkephalinase inhibition.

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(Neurosc. Lett., 41: 331-335, 1983)

CHAPTER 14.

ENKEPHALINASE INHIBITION PREVENTED TOLERANCE TO NITROUS OXIDE ANALGESIA IN RATS

SUMMARY
Tolerance to nitrous oxide (N_2O) antinociception was studied in rats in accordance with the Randall-Selitto pressure nociception test. Both N_2O (70% in 30% O_2) and the relatively selective enkephalinase inhibitor phosphoramidon (350 µg i.c.v.), which blocks the biotransformation of enkephalins, were administered. They both induced a significant analgesic effect which vanished within 45 min. The rapidly developed tolerance to N_2O analgesia does not affect the anaesthetic state since the animals remained motionless for the duration of exposure lasting 3 h. In the animals treated with the enkephalinase inhibitor phosphoramidon, no development of tolerance to N_2O-antinociception occurred during the exposure lasting 3 h. The results indicate that tolerance to N_2O analgesia can be abolished by activation of the enkephalinergic system, which might suggest a possible insufficiency of this system during tolerance to N_2O.

Tolerance to antinociception, the anaesthetic effect and other effects of nitrous oxide (N_2O) has been found both in animals (1-5) and in humans (6). Development of tolerance to N_2O appears to be a rapid process. In our experiments, the antinociceptive effect of N_2O to pressure stimulation was not detectable in the animals after 1 h of exposure to this narcotic gas (7). From the clinical point of view, tolerance to N_2O is an undesirable phenomenon and its relevant importance in the field of human medicine is not yet completely understood. Furthermore, a mechanism controlling tolerance to the N_2O analgesic effect is not yet fully understood, but the involvement of an endogenous opiate system has been suggested (2, 8). However, in contradiction of this theory, it was found that animals tolerant to N_2O were not tolerant to morphine (9), and the opiate antagonists did not facilitate N_2O withdrawal seizures (10).

In an attempt to clarify further the involvement of the endorphinergic system in tolerance to N_2O, we studied the relationship between the development of tolerance to N_2O analgesia and increased activity of the enkephalinergic system. This was achieved by using a relatively specific enkephalinase inhibitor, phos-

phoramidon. This drug blocks the biodegradation of enkephalins and consequently potentiates the functional activity of enkephalins (11).

MATERIALS AND METHODS

Four groups of 11 male Wistar rats (125-150 g) were used. Sensitivity to pain, i.e. analgesiometric scores in g mm^{-2}, were determined according to a modified Randall-Selitto pressure nociception test (12). According to this test, pressure stimulation is applied to the back of the uninflamed hind paw until the rat withdraws the paw. The cut-off stimulus was set at 500 g mm^{-2}. Rats which tolerated more than 150 g mm^{-2} during control measurements were not used. An intracerebroventricular (i.c.v.) administration of 2 µl artificial cerebrospinal fluid (CSF) did not change nociception to pressure stimulation, which had been established in a pilot study. All tests were performed between 11.00 hours and 13.00 hours in order to avoid changes in circadian rhythms (13). Care was taken to keep experimental conditions constant in accordance with the method previously described (14). The anaesthetic state was defined as a N_2O-induced loss of spontaneous motor activity.

Control group

No medication was given. Analgesiometric scores were measured at exactly the same time intervals as used for all other groups, i.e. at 0, 15, 30, 45, 60, 90, 120 and 150 min. Tests were performed in a plexiglass exposure box using an Ugo Basile analgesiometer.

N_2O group

Rats were cannulated intracerebroventricularly 10 days prior to testing (see phosphoramidon group). 2 µl of CSF were injected prior to exposure of animals to 70% N_2O and 30% O_2. Analgesiometric scores were recorded according to the scheme described for the control group.

Phosphoramidon group

Ten days before exposure to N_2O, these rats were cannulated into the left lateral cerebral ventricle in accordance with the Rezek and Havlicek method (15) under a urethane anaesthetic. After recording basal analgesiometric scores, phosphoramidon 350 µg in 2 µl CSF was injected into the ventricle and analgesiometric scores were again determined (see control group) whilst the rats were breathing air in the exposure box.

Phosphoramidon and N_2O group

Rats in this group were cannulated 10 days before the test. After the basal nociception test, phosphoramidon 350 µg in 2 µl CSF was injected i.c.v. and the animals were put into the exposure box to breathe 70% N_2O and 30% O_2. Analgesiometric scores were determined at the same time intervals as in the control group.

A dose of 350 µg phosphoramidon was selected since this substance affected nociception in a dose-related manner in a range of 100-500 µg i.c.v.. In all groups changes of behaviour were recorded. The results of the analgesiometric measurements of the test group were compared against those of the control group for the significance of difference, using Student's t-test.

RESULTS

Control group

The average analgesiometric score was 130 ± 18 g mm^{-2} (Fig.1). When reaching this point, the rats vigorously withdrew their paw from pressure stimulation. The scores at the fourth and fifth time intervals had a tendency to decrease slightly, which might be due to the conditioning of animals to the test procedure.

Sensitivity to pressure nociception in this group was not altered significantly during the test period from 11.00 to 13.00 hours.

N_2O group

The antinociceptive effect of 70% N_2O to pressure stimulation

reached a maximum after 15-25 min. It then rapidly decreased and approximated the control values after 45 min (Fig.1). The rats displayed very active behaviour during the first 15 min and then gradually became anaesthetized, i.e. motionless. After 45 min exposure to N_2O, there was little activity in the box and this situation continued until the end of the 3-h test. These findings are equivalent to those determined previously, where only N_2O 70% was administered (7).

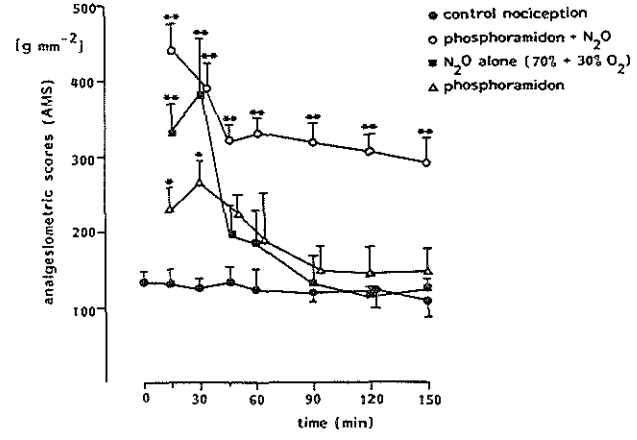

Fig.1.
The effect of phosphoramidon on the analgesic activity of nitrous oxide in rats. AMS: analgesiometric scores for pressure nociception (g mm^{-2}; Randall-Selitto pressure nociception test). Phosphoramidon was given intracerebroventricularly (350 µg in 2 µl artificial liquor) immediately after 0 min measurements. Nitrous oxide was mixed with oxygen (70:30, vol%). Each point represents the mean ± s.e. mean for 11 rats. Student's t-test was used to calculate the significance of the difference between the test groups and the control group (**p < 0,001; *p < 0.05). Note that phosphoramidon prevented the development of tolerance to N_2O analgesia.

Phosphoramidon group

Fifteen min after administration of phosphoramidon, 350 µg i.c.v., there was a significant increase in nociception scores (225 ± 12 g mm^{-2}) as compared with the control group. This an

tinociceptive effect persisted for 30 min after i.c.v. injection (217± 15 g mm^{-2}) but was absent after 60 min and thereafter. Behavioural changes caused by phosphoramidon intracerebroventricularly included hyperactivity, excessive grooming and copulatory activity.

Phosphoramidon and N_2O group

When phosphoramidon (350 µg intracerebroventricularly) treated animals were exposed to N_2O, an intense antinociceptive effect was observed after 15 min (448 ± 35 g mm^{-2}). This effect was significantly more intense ($P < 0.05$) compared with the effects of phosphoramidon or N_2O given separately. This antinociceptive effect then decreased slightly to values which are similar to peak N_2O antinociceptive effects. They remained significantly higher than N_2O analgesic scores at identical time intervals (see Fig. 1). No tolerance to this analgesic effect was detected during the 3 h of exposure. Rats in this group were active and not anaesthetized, indicating that motor activity was unaffected, as was the case when only N_2O was administered.

DISCUSSION

The results of this study indicate that administration of the enkephalinase inhibitor phosphoramidon potentiates the N_2O antinociceptive effect and prevents the development of tolerance to N_2O analgesia. This effect is probably due to the activation of the opiate system, since the analgesic effect of phosphoramidon is completely reversible by naltrexone (16). It is of interest to note that acutely developed tolerance to N_2O (occurring within 45 min) was not associated with tolerance to the N_2O anaesthetic effect, since the animals remained motionless for the duration of the 3-h-long exposure. Similar dissociation of N_2O antinociceptive and anaesthetic effects has also been observed in humans (see Chapter 15).

Two basically different mechanisms, both involving the endogenous opiate system in the development of tolerance to N_2O analgesia, have been considered. Firstly, changes at the presynaptic

level resulting in a decreased release of endorphins (2). Secondly, the postsynaptic alteration of opiate receptors, such as decrease of opiate receptor density during prolonged exposure to N_2O (8).

Our results support the view that the endogenous opiate system is involved in the development of tolerance to N_2O analgesia. It may be suggested that insufficiency of the endorphinergic system is probably the main factor causing tolerance to N_2O analgesia, since the activation of this system abolishes development of tolerance. However, this study does not completely resolve the fundamental dilemma of establishing which part of the synapse, (presynaptic or postsynaptic) is involved during tolerance to N_2O analgesia. It is evident that increased functional activity of the enkephalinergic system which follows the intracerebroventricular administration of enkephalinase inhibitor may compensate for the suggested insufficiency of both, either release of enkephalins or density of post-synaptic opiate receptors.

The observation that neither of the two antagonists, naloxone and naltrexone, modified the severity or duration of the nitrous oxide withdrawal seizure (10) might not necessarily contradict our statement that endogenous opioids are involved in tolerance to the N_2O analgesic action. There is evidence that tolerance and physical dependence in certain circumstances can be dissociated and may not necessarily be a unitary phenomenon. For example, a highly opiate-tolerant vas deferens of the mouse failed to display any sign of dependence as judged by the inability of naloxone to precipitate a withdrawal sign (17). The possible link between physical dependence on N_2O and the opiate mechanism could be demonstrated by the fact that withdrawal convulsions in mice, which had been acutely exposed to N_2O, were significantly attenuated by an enkephalinase inhibitor (18).

Another possible argument against the involvement of endogenous opioids in tolerance to N_2O analgesia, might be the observation that animals tolerant to N_2O are not tolerant to morphine (9). However, the absence of cross-tolerance is not bilateral since the rats with a developed tolerance to morphine showed a decrea-

sed analgesic response to N_2O (9). Evidently, an observation of this unique unilateral cross-tolerance is not a strong argument against the hypothesized link between the tolerance to N_2O analgesia and endogenous opiates.

We have thus established the fact that by using an enkephalinase inhibitor (phosphoramidon) it is possible to abolish tolerance to the N_2O analgesic effect. This, in turn, raises the question as to whether tolerance to other substances, in particular opiates, could also be modulated by enkephalinase inhibitors. Moreover, the potentiation and prolongation of the N_2O analgesic effect in clinical anaesthesia might well be achieved. Additional studies are required to find an answer to these questions which are of both fundamental and clinical importance.

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CHAPTER 15.

TOLERANCE TO NITROUS OXIDE IN VOLUNTEERS

ABSTRACT

Nociception and loss of awareness during exposure to anaesthetic concentration of nitrous oxide (N_2O) were studied in eight male medical students. Cold water nociception test, where a hand is immersed in 0° C stirred water, was used for measurement of nociception. At irregular intervals an auditory command was given to oppose two fingers and this served to monitor consciousness. The selected inspiratory concentration of N_2O used per individual was sufficient to induce a loss of consciousness for more than 2.5 min, within 10 min of exposure to N_2O. This concentration of N_2O varied from 60% to 80%. The experimental exposure to N_2O lasted 3 h. In all volunteers significant antinociception was observed within 2 min of exposure to N_2O. The maximal analgesic effect was observed between 20 and 30 min of exposure to N_2O. The analgesic effect of N_2O gradually decreased and was absent in all eight volunteers within 150 min. Two volunteers regained consciousness at 77 and 91 min of exposure, whilst still breathing 60 and 80% N_2O. These results show that tolerance to antinociceptive effects of N_2O in man rapidly develops and that awareness may occur in some volunteers during prolonged exposure to N_2O.

Tolerance to various effects of N_2O has been established in animals using different experimental models (1-5). The time necessary for development of tolerance to various N_2O-effects was found to be in range of 10 min to 2 h. We found that various actions of N_2O in rats are dissociated and follow their own time course: for example tolerance to the analgesic effect of N_2O was evident within 1 h, while tolerance to the behavioural effects of N_2O occurred after several hours to 1 day (6). It has been reported that, with respect to analgesia, some "adaptation of the nervous system" to a constant (low) concentration of N_2O may occur in some subjects (7). However, no clinical data have been provided so far to classify the relationship between the length of exposure to anaesthetic concentrations of N_2O and development of complete tolerance to antinociceptive and anaesthetic actions of this gas. Thus, the aim of this study was to determine the time interval necessary for development of tolerance to the effects of N_2O in man. Therefore, an interdisciplinary triple clinical study in human volunteers was designed to

register the changes in the antinociceptive, anaesthetic and electrocorticographic effects during a prolonged exposure to N_2O. These data on tolerance to N_2O are essential for understanding of the anaesthetic state during N_2O-anaesthesia in clinical medicine.

VOLUNTEERS AND METHODS

Volunteers

8 male medical students, who were selected from 40 students involved in preliminary instruction, were 24.2 ± 0.7 years, weighing 69.1 ± 2.9 kg and free of anamnestic or acute health ailments. They volunteered to participate in this clinical study after detailed theoretical and practical instruction related to all aspects of N_2O-anaesthesia. Only well-informed subjects who volunteered on the basis of scientific curiosity were allowed to participate in the investigation.

Minimal effective concentration of N_2O (N_2O-MEC).

Measurements were performed between 10.00 and 14.00 hours. We used the lowest N_2O-inspiratory concentration which resulted in objective loss of consciousness of more than 2.5 minutes, within 10 minutes. This concentration was called N_2O-MEC and it was determined individually one week before the 3-h tolerance test.To determine the N_2O-MEC, the subjects breathed 40% N_2O in O_2 for 10 min while the medical psychologist tested their awareness and ability to respond to a command to approach the middle finger to the thumb of the right hand. The commands were taped, at irregular time intervals and against white noise. When the subject continued responding after 10 minutes, the concentration of N_2O was increased every 10 min by 10% until complete loss of consciousness was achieved. The maximal N_2O-MEC in this study was 80%. The ear-phone commands for motor reaction of the right hand were delivered at irregular intervals in order to avoid conditioning to the stimulus based on regularity.

The N_2O-tolerance test followed 1 week after the determination

of the N_2O-MEC and lasted 3 h. This duration was chosen because it is about twice the average duration of anaesthesia in a typical large hospital in the Netherlands. The practical reasoning behind the period was that it is important to know whether a subject can become tolerant to the anaesthetic and analgesic effects of N_2O, but it is even more important to know whether this is likely to happen within the limits of the average duration of clinical N_2O-anaesthesia.

Before the performance of N_2O-tolerance test, the electrocorticogram-(ECoG)-electrodes were attached to the scalp, the earphone was tested, an intravenous cannula was placed and kept patent. The volunteer was comfortably placed on an operating table and all safety measures which are usual for anaesthesia, were respected. The volunteers had not eaten or drunk for at least 8 h before the test. After these precautions, the previously individually established N_2O-MEC was applied.

The exposure to the N_2O-MEC was planned to last 3 h, or until the moment when the subject would become fully and adequately responsive to stimuli while still breathing N_2O-MEC. After the end of the experiment the volunteers were asked to rest for 2 h and were then taken home. In addition, they were asked to make a written record of the whole experience together with observations during the first few days following the study. In particular, we inquired about sleeplessness, psychological phenomena, malaise and nausea or vomiting.

The non-return anaesthetic system which we used was equipped with two reserve balloons with a capacity of 15 l. This enabled us to administer the gas smoothly, also during occasional excitation-hyperventilation, while keeping the flow of fresh gases at approximately 12 l min^{-1}.

Cold water nociception test (CWNT), also called the cold water immersion pain test or cold pressor pain test, was performed in

accordance with a previously established method (8). Shortly after the 2.5 min of unconsciousness had been established, we tested the subjects for their reaction to immersion of the left hand and underarm into 0°C-cold-stirred water. The normal sensitivity of subjects to the CWNT had been determined ten days earlier, at 11.00 h. The cut-off time for the CWNT in our experiments was 300 s. This experimental procedure did not result in any damage to the immersed tissue.

The CWNT was performed first at 2 min of the inhalation of the N_2O-MEC and then at 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150 and 180 minutes during exposure to N_2O.

Electrocorticogram. The ECoG was recorded for an EEG spectral analysis before, during and 1 h after exposure to N_2O. Behavioural signs were recorded at the same time.

With respect to its objective and the set-up, the study was approved by the Ethics Committee for Experimentation on Human Beings of the Medical Faculty of the Erasmus University, Rotterdam.

RESULTS

CWNT. The perception of intense pain during the immersion of the hand into stirred 0°C-cold water in our volunteers breathing air, occurred within 24.6 $\pm$ 4.5 s (mean $\pm$ s.e.mean; n=8).

N_2O-MEC. The average minimal inspiration concentration of N_2O in O_2 which caused objective unconsciousness within 10 min was 70%. Two subjects required 60%, two 80% and four 70% N_2O in O_2.

All subjects were amnesic for commands while breathing the N_2O-MEC. They all had the individual experience that no time passed while they were breathing N_2O-MEC which may be considered as a retrograde confirmation of subjective unconsciousness.

Nociception during the 3-h exposure to the N_2O-MEC. While the subjects were breathing the individual N_2O-MEC their hand was immersed in the 0°C-cold and stirred water. The volunteers responded by withdrawing the arm. The withdrawal was occasionally

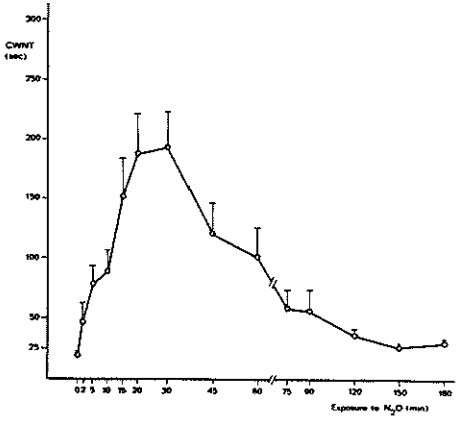

Fig. 1. Nociceptive effect of N_2O in eight volunteers as measured by the cold water nociception test (CWNT). The subjects were breathing the individual minimal effective concentration of N_2O which, within 10 minutes, caused a loss of consciousness for 2.5 min or longer. Each point represents the mean ± s.e. mean for eight volunteers. Note the rapid increase of N_2O-antinociception, with the maximum at 20-30 min after exposure to N_2O and the development of complete tolerance to this effect within 2.5 h. Values for the CWNT from 2 min to 120 min of exposure to N_2O are significantly different from the control values at 0, 150 and 180 min of exposure to N_2O (Student's *t*-test; $P < 0.001$).

accompanied by motor or autonomic changes (see Side effects). In five immersions no response was seen to the immersion and the nocistimulation was stopped at 300 sec.

A significant prolongation of the CWNT was observed after 2 min exposure to N_2O-MEC (Fig. 1). The interval between immersion and withdrawal rapidly increased and was maximal between 20 and

30 min of exposure to N_2O. At 45 min the mean of the CWNT was significantly less than at 30 min, although it was still significantly higher than the control value of the CWNT (Fig. 1). At this stage of exposure, the CWNT approximated the control value in two volunteers.
The antinociceptive effect of N_2O then gradually decreased and reached the control value at 150 min after the exposure to N_2O-MEC, in all volunteers.

Awareness during exposure to the N_2O-MEC. In the assessment of unconsciousness, fluctuations in non-responsiveness to verbal commands was noticeable. Two of the eight volunteers regained consciousness while breathing the N_2O-MEC, at 77 and 91 min, respectively. They resumed answering the ear-phone commands and correctly calculated and answered questions. No signs of excitation or vivacity preceded the arousal and they remained calm, as if the N_2O-sedative effect persisted at that stage. The exposure to N_2O-MEC for these two volunteers was discontinued at 90 and 110 min, respectively. The six other volunteers did not regain consciousness within the 3 h of exposure to the individual N_2O-MEC. Six subjects were completely amnesic for the whole exposure to N_2O and two for the period preceding their regaining awareness under the N_2O-MEC.

Side-effects. Unco-ordinated movements of the non-immersed arm or head and signs of general motor excitation occurred a few times. Disturbances of the heart rate and breathing pattern were common. Breath-holding or hyperventilation was most pronounced. The occurrence of tachycardia or bradycardia accompanied the CWNT but this was unpredictable. Vomiting was not observed until the 45-min exposure to N_2O whereupon it occurred occasionally, often together with the nocistimulation. When necessary, the vomit was suctioned from beneath the mask which was kept in place in order to ensure a constant concentration of inspired gases.

The swallowing and coughing reflex remained well co-ordinated

and efficiently active at all times, and no laryngospasm was observed during the whole study. Sweating occurred occasionally but ceased without requiring any specific measures.

After effects of the N_2O were also observed. Nausea was observed in six of eight volunteers but it lasted the whole afternoon in only 2 cases. During the withdrawal of N_2O, all volunteers reported feeling cold and had "goose-pimples" on the skin, although the rectal temperature was not decreased. These signs, similar to those of the opiate withdrawal syndrome, gradually disappeared within 2-3 h. Sleepiness, which was accompanied by tiredness, was common, although two volunteers proceeded with their daily activities 2 h after the end of the study. Headache was reported by three subjects; in one it reacted well to aspirin. Two subjects reported "fine feelings" during the 3-h recovery period. Two subjects reported feelings of "déjà vu", a sort of flashback for 3 days, especially when they were tired. However, these feelings were not bothersome. Amnesia for the first N_2O-withdrawal hour was established in 6 volunteers who breathed N_2O for 3 h. N_2O-withdrawal amnesia was not convincing in the two subjects who regained consciousness while they were breathing N_2O.

Acceptability of the test was good. Only two volunteers explicitly stated that they would not like to repeat the test.

DISCUSSION

In this study, tolerance to N_2O-induced antinociception in man developed within 150 min. Tolerance to the anaesthetic effect developed in two volunteers within 2 h of exposure to N_2O.

In measurements of the antinociceptive effect of rather low concentrations of N_2O on hypoxic and pressure pain, it was noticed that "some adaptation of the nervous system" occurred (7). The authors did not consider this phenomenon to be tolerance and they made no effort to measure all aspects of this phenomenon in function of time. Other authors have suggested that the post-

anaesthetic unrest could be attributed to the N_2O withdrawal in a patient who became tolerant to the effects of this gas (9, 10).

For a clinician, the most relevant information from the present study is that a prolonged exposure to N_2O results first in an increasing analgesic state, reaching a maximum between 20 and 30 min. The situation changes during prolonged exposure to N_2O since complete tolerance to N_2O analgesia may develop between 45 and 150 min. It might be expected that tolerance to N_2O-induced analgesia would influence the course of a prolonged surgical N_2O anaesthesia in man. However, in clinical circumstances the situation is very complex since various other agents are being used in addition to N_2O. Furthermore, it is known that stress-analgesia may be an important mechanism during surgical procedures which could mask the decreased N_2O analgesic potency.

The mechanism of tolerance to N_2O-induced analgesia is not known. However, it was suggested that exposure to N_2O results in a decrease of opiate receptor density (11) which might explain the development of tolerance to N_2O-induced antinociceptive effect. It is not clear whether this is the only phenomenon responsible for tolerance to N_2O-analgesia, since tolerance to N_2O-antinociception in rats has been prevented by inhibition of enkephalinase (12). This, in turn, might indicate an impaired release of endorphins during N_2O-induced tolerance.

The present data indicate that awareness during surgery and N_2O anaesthesia is possible. Indeed, recently the view was put forward that one should expect awareness during surgery, assuming in all cases that the patient may be aware (13). In particular, this is implied by our finding that two of eight volunteers started to respond adequately to external stimuli after 77 and 91 min of exposure to the N_2O-MEC.
Anaesthetized patients may perceive stimuli during prolonged N_2O anaesthesia and may be able to remember them. In accordance

with such a state of affairs during anaesthesia, it has been emphasised "that everyone in the operating room must be mindful of conversations during the course of anaesthesia regardless of the drugs employed" (14). However, the duration of exposure to N_2O which would allow all subjects to regain consciousness while still breathing N_2O remains uncertain.

The observation that all the volunteers started to show retching or vomiting signs during exposure to N_2O needs further attention. In a clinical situation, where patients undergo some degree of pain, nausea ascribable to N_2O seems to be rather rare.

In conclusion, it may be said that although the mechanism of tolerance to N_2O in man remains uncertain, it is of clinical importance to emphasize that tolerance to N_2O-induced analgesia develops within 45 min, and complete tolerance to the anaesthetic effects of N_2O may occur in some cases within 2 h after the start of exposure to N_2O-MEC.

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CONCLUDING REMARKS AND SUMMARY

The present thesis is chiefly concerned with disturbances during recovery from anaesthesia. This area has been poorly studied. Medicine has tended to leave the patient's well-being during the period of "recovery" to the powers of nature.

At one time, anaesthetists considered anaesthesia as a good surrogate for sleep. It has proved to be notoriously difficult to eradicate this simplicism because it offers a readily understandable, if misleading, explanation of the action of anaesthetic agents. Such thinking is even perpetuated in the standard pharmacological vocabulary. For example, it is known that no drug or technique has been found to induce a state of natural sleep, yet we still talk about "hypnotics". Ought an anaesthetist, then to promise his patient that anaesthesia will be "just like a pleasant sleep"? It is doubtful to what extent contemporary anaesthesia, erroneously likened to invigorating sleep, is really safe. That most illustrious anaesthesiological professional society, the Association of Anaesthetists of Great Britain and Ireland, displays a noble coat of arms with the motto "In somno securitas". There are occasions when one is inclined to put a question mark after this statement. Fortunately, it is understood nowadays that a good anaesthetic should be less of a pharmacological manipulation which depresses vital functions and more of a maintenance of normal physiological functions in terms of optimal body homeostasis. In other words, an anaesthetic based on preserving, restoring and supporting the functioning of the body will probably more closely resemble a pleasant sleep than the classical "borrow'd likeness of shrunk death" (Shakespeare, Romeo & Juliet, Act IV, Scene 2, line 104).

With this aim in view, one must know how anaesthetic agents act, on the one hand, and how the central nervous system reacts to them, on the other. Close observation of our patients before, during and after anaesthesia will identify inadequacies in our treatment or understanding of phenomena. These may, in turn, be

remedied by diligent clinical or experimental research, to the benefit of both the patient and the profession.
Treatment of the central anticholinergic syndrome with physostigmine, as described in this thesis, resulted in safer conduct of the patient through the immediate postanaesthetic period. Further clinical observations indicated that physostigmine probably possessed analgesic properties. This has been confirmed in several investigations. It also became evident that physostigmine can antagonize opiate-induced respiratory depression without interfering with the analgesic action of the opiate. This action is based on restitution of the sensitivity of the respiratory centre to carbon dioxide, a property of physostigmine now often used in the treatment of postanaesthetic respiratory depression. The same action of physostigmine also proved beneficial in the treatment of the respiratory depression caused by heroin overdose. A remarkable feature of this treatment was the absence of the acute opiate withdrawal syndrome which is such a horror to opiate addicts when opiate antagonists are used for treatment of an overdose.

The use of physostigmine during recovery from anaesthesia resulted in a shortening of the period during which intense observation was needed. This is also desirable on economic grounds.

Knowledge of the central anticholinergic action and its treatment has been useful in other therapeutic areas than anaesthesia. Intoxications can be differentially diagnosed more quickly and, in cases of predominantly central anticholinergic action, aetiologic treatment can be instituted. Another area for the therapeutic use of physostigmine is the group of presenile dementias, Alzheimer's disease being the best known example.

It has been observed that anaesthesia and surgical stress, separately or together, may impair the elderly patient's cognitive function and mental performance in general. It may take weeks or months before such a patient recovers. However, we have seen in

practice that elderly patients receiving physostigmine throughout anaesthesia are less likely to suffer from postanaesthetic decrease in mental ability (unpublished). It appears also that continuous administration of physostigmine during anaesthesia does not interfere with the action of individual drugs and certainly does not modify the anaesthetized state. In this area, further research is urgently needed to establish whether general anaesthesia may be a cause of diminished mental performance or even result in an Alzheimer-like state, and to find out how to avoid this, or how best to treat it should it occur.

Further research in the area of the analgesic properties of physostigmine is also of importance. It may result in the development of drugs with potent antinociceptive action but devoid of the inevitable respiratory depressive effects of opiates.

At first sight, the link between the actions of physostigmine and the effects of nitrous oxide as described in this thesis may not be obvious. However, in the course of differentiating and treating the signs of central cholinergic blockade, it was seen that the rhythmic convulsant type of disturbances, usually accompanied by cold-turkey skin appearance, only partially responded to physostigmine. It was concluded that this disturbance may not be wholly due to the cholinergic blockade. Further analysis of this clinical picture showed that the culprit was probably nitrous oxide: to be more precise, withdrawal from nitrous oxide. Readministration of subanaesthetic concentrations of nitrous oxide to such patients during recovery from anaesthesia promptly abolished the rhythmic convulsant state. Meperidine was also very efficient for this treatment. This opiate withdrawal-like clinical state was discussed in the light of information that the analgesic action of nitrous oxide is primarily a result of its interference with the endorphinergic system. It has been suggested that the consciousness-decreasing effect of nitrous oxide is also in part due to interference with the endorphinergic system, but no conclusive evidence has been brought forward.

Several experimental models have been developed for analysis of the above clinical observations. In a study of nitrous oxide withdrawal in mice, we showed that the cholinergic and endorphinergic central nervous systems are both involved in the reaction to withdrawal of nitrous oxide. Opiate agents and physostigmine both decreased the symptomatology, while in certain circumstances opiate antagonists promoted the predisposition to convulsions.

The principal experimental model used in our study of nitrous oxide actions was rats during short and prolonged exposure to nitrous oxide. Analgesia and the behavioural anaesthetic state were primarily studied. It was found that tolerance to nitrous oxide analgesia in rats develops rather rapidly and may persist after withdrawal of the animals from the gas. Behavioural changes in rats exposed to nitrous oxide proceed from the initial excitation into the "anaesthetized state" but the rats eventually resume their normal behaviour in spite of continuing to breathe nitrous oxide. This may take as long as five hours, whereas the antinociceptive effect may last no more than an hour, which confirms the notion that various effects of nitrous oxide run an independent course and may partly or wholly depend on interaction with various central nervous system mechanisms.

At present, a major difficulty in the study of the effects of nitrous oxide, and of other gases as well, is the lack of standardization of the experimental environment of exposure to gases. Consequently, comparison of measurements from different studies of the effects of gases is unreliable or impossible. The establishment of standards for experimental exposure to gases (humidity, noise, temperature, elimination of irritating gaseous compounds, etc.) is badly needed, and it may prove to be essential for progress in this scientific field.

With the establishment of measurable tolerance of rats to nitrous oxide analgesia, the question arose how to prevent this ef-

fect, which obviously is unwelcome when extrapolated to human anaesthesia. On the basis of data that nitrous oxide analgesia depends on interference with the endorphinergic system, we speculated that inhibition of enkephalinase may prevent development of tolerance to nitrous oxide analgesia.
Phosphoramidon, a selective enkephalinase inhibitor, was chosen and we described its analgesic and behavioural effects. When given to rats before exposure to nitrous oxide, no development of tolerance to analgesia was seen. This finding is of importance as it eliminates the undesirable phenomenon of the development of tolerance to nitrous oxide analgesia during anaesthesia. As such, it may have far reaching clinical implications.

The fundamental dilemma of establishing which part of the synapse (presynaptic or postsynaptic) is involved during tolerance to nitrous oxide analgesia, is not yet completely resolved. It is evident, however, that increased functional activity of the enkephalinergic system which follows the intracerebroventricular administration of the enkephalinase inhibitor may compensate both for insufficient release of enkephalins and for changes in density of postsynaptic opiate receptors.
It is conceivable that a drug will be developed for i.v. use in man which will penetrate into the brain and potentiate the effects of nitrous oxide, at the same time preventing the development of tolerance to them. In this area of great social and economic importance, nitrous oxide may significantly contribute to the understanding and treatment of addiction. Further research must be encouraged in view of inadequacies in the present treatment of addiction-disease.

A further investigation into the properties of nitrous oxide was performed on volunteers with the aim of obtaining very essential information for the clinician on the development of tolerance to this gas in man. Data were ascertained for the interval needed before humans develop tolerance to the antinociceptive effect of

nitrous oxide in the cold water immersion test. It was also established that complete tolerance develops to the anaesthetic effects of nitrous oxide. The latter, however, takes much longer than the former. The information provided by this study will doubtless contribute to a more rational conduct of clinical anaesthesia.

The fact that nitrous oxide may abolish the opiate withdrawal-like state after anaesthesia may be of importance in yet another area in dire need of therapeutic progress - treatment of addictive states. Indeed, nitrous oxide has already been used in the treatment of withdrawal from opiates and alcohol. Moreover, future investigations may show whether it is possible to induce antinociception to surgical pain only by reinforcement of the endorphinergic system. Results of such research may change the present role of (exogenous) opiates in medicine. Undoubtedly, we shall also learn more about the mechanism(s) of anaesthesia as it has already been shown that (exogenous) endorphins may induce not only antinociception but also an anaesthetic state.

To conclude this review essay, it may be said that we live in an age of many discoveries but without epochal discoverers. Science is based on interdisciplinary search for facts and information. In anaesthesiology, too, immense progress has been made by a multitude of tiny steps and thrusts. "Definite truths" fade away as new information becomes available. Nevertheless, who can imagine a conscientious anaesthetist treating his patients only with an impressive array of electronic paraphernalia, or with a premixed witches' brew of drugs, without any personal involvement in what he is doing? There can be no progress in the field of anaesthesia without genuine concern for the welfare of the patient. The present work, then, is the modest effort of an anaesthetist aiming to improve the general well-being of those who entrust their lives to him.

AFRONDENDE OPMERKINGEN EN SAMENVATTING

De onderhavige dissertatie heeft voornamelijk betrekking op stoornissen tijdens de herstelfase na algemene anesthesie. Op dit gebied zijn nog weinig navorsingen gedaan. De medische wetenschap was geneigd het welzijn van de patiënt gedurende deze fase over te laten aan de natuurkrachten.

Vroeger beschouwden anesthesisten anesthesie als een goed vervangingsmiddel voor slaap. Het is gebleken, dat het heel erg moeilijk is deze simplistische denkwijze uit te wissen, omdat het een gemakkelijk te begrijpen, maar misleidende, verklaring biedt voor de werking van verdovende middelen. Deze manier van denken is zelfs vastgelegd in het gangbare farmacologische woordgebruik. Het is bijvoorbeeld bekend, dat geen medicijn of procédé om een staat van natuurlijke slaap teweeg te brengen, is ontdekt maar toch spreken we nog van "slaapmiddelen". Zou een anesthesist dan aan zijn patiënt mogen beloven dat anesthesie net zoiets is als een aangenaam slaapje? Het is te betwijfelen of en tot op welke hoogte de hedendaagse anesthesie, foutief vergeleken met slaap, werkelijk veilig is. Het zeer vermaarde anesthesiologische genootschap, the Association of Anaesthetists of Great Britain and Ireland, voert een edel blazoen met het motto "In somno securitas". Er zijn momenten, waarop men geneigd is een vraagteken achter deze uitspraak te zetten. Gelukkig wordt tegenwoordig begrepen dat een goede anesthesie minder een farmacologische handeling moet zijn die de vitale funkties verlaagt, maar meer een handhaven van de normale fysiologische funkties ten opzichte van optimale lichaamshomeostasis. Met andere woorden, een anesthesie gebaseerd op het behouden, het herstellen en het ondersteunen van de lichaamswerking, zal waarschijnlijk meer lijken op een aangename slaap dan het klassieke "borrow'd likeness of shrunk death" (Shakespeare, Romeo & Juliet, acte IV, scène 2, regel 104).

Met dit doel voor ogen moet men enerzijds weten hoe verdovende middelen op de patiënt werken en anderzijds hoe het centrale

zenuwstelsel daarop reageert.
Een nauwkeurige observatie van onze patiënten vóór, gedurende en na anesthesie, zal de tekortkomingen in onze behandeling vaststellen en zal ons het waarneembare doen begrijpen. Deze zouden, op hun beurt, verholpen kunnen worden door toegewijd klinisch en experimenteel onderzoek in het voordeel van zowel de patiënt als de professie.

Behandeling van het centrale anticholinergische syndroom met fysostigmine, zoals beschreven in dit proefschrift, heeft een veiliger begeleiding van de patiënt gedurende de onmiddellijke verkoevertijd tot gevolg gehad. Verdere klinische waarnemingen toonden aan dat fysostigmine waarschijnlijk ook analgetisch werkte. Dit is bij verschillende onderzoekingen bevestigd. Het werd ook duidelijk dat fysostigmine een door opiaten veroorzaakte ademhalingsdepressie kan antagoniseren zonder afbreuk te doen aan de analgetische werking van opiaten. Deze werking is gebaseerd op het herstel van de gevoeligheid van het ademhalingscentrum voor kooldioxide, een eigenschap van fysostigmine, nu vaak gebruikt bij de behandeling van post-anesthetische ademhalingsdepressie. Dezelfde werking van fysostigmine bleek ook nuttig bij de behandeling van ademhalingsdepressie, veroorzaakt door een overdosis van heroïne. Een merkwaardig aspekt van deze behandeling is de afwezigheid van het akute opiaat-onthoudingssyndroom, dat zo'n verschrikking is voor opiaatverslaafden als opiaat-antagonisten worden gebruikt bij de behandeling van een overdosis.

Het gebruik van fysostigmine gedurende de verkoevertijd had een verkorting tot gevolg van de tijdsduur, waarin intensieve observatie nodig was. Dit is ook belangrijk om economische redenen.

Kennis van de centrale anticholinergische werking en haar behandeling is behalve in anesthesie ook nuttig geweest op andere therapeutische gebieden. Vergiftigingen kunnen differentieel diagnostisch sneller worden vastgesteld en, in gevallen van hoofdza-

kelijk een centrale anticholinergische werking, kan worden begonnen met een aetiologische behandeling.

Een ander gebied voor het therapeutische gebruik van fysostigmine is de ouderdomsdementies, waarvan de ziekte van Alzheimer het best bekende voorbeeld is. Het is vastgesteld dat anesthesie en chirurgische stress, samen of apart, de cognitieve funktie van de oudere patiënt en zijn mentaal gedrag in het algemeen zouden kunnen benadelen. Het kan weken of maanden duren voordat zo'n patiënt herstelt. We hebben evenwel in de praktijk gezien dat oudere patiënten, die gedurende anesthesie fysostigmine krijgen, minder kans hebben op een post-anesthetische teruggang in hun mentale vermogen (ons lopend onderzoek). Het blijkt ook dat een voortdurende toediening van fysostigmine gedurende anesthesie, de werking van afzonderlijke geneesmiddelen en zeker de verdovingstoestand niet beinvloedt. Op dit gebied is diepgaand onderzoek noodzakelijk teneinde na te gaan of algehele anesthesie een oorzaak zou kunnen zijn van een verminderde mentale prestatie of zelfs van een op de ziekte van Alzheimer gelijkende situatie tot gevolg zou kunnen hebben en om vast te stellen hoe we dit kunnen vermijden of om dit te kunnen behandelen, mocht het gebeuren.

Een verder onderzoek op het gebied van de pijnstillende eigenschappen van fysostigmine is ook belangrijk. Het zou kunnen resulteren in de ontwikkeling van medicijnen met een krachtige antinociceptieve werking maar gespeend van de onvermijdelijke ademhalingsdepressieve uitwerkingen van opiaten.

Op het eerste gezicht is de schakel tussen de effekten van fysostigmine enerzijds en de uitwerkingen van lachgas anderzijds, zoals in dit proefschrift beschreven, misschien niet geheel duidelijk. Evenwel, gedurende het vaststellen en het behandelen van de symptomen van een centrale cholinergische blokkade, werd gezien dat het type van stoornissen, die ritmisch en convulserend zijn en gewoonlijk vergezeld gaan van kippevel, alleen gedeeltelijk reageren op fysostigmine. Men kwam tot de slotsom dat deze

storing waarschijnlijk niet helemaal te wijten is aan de cholinergische blokkade. Een verdere analyse van dit ziektebeeld gaf aan, dat het waarschijnlijk een gevolg was van lachgas. Om preciezer te zijn: van het onttrekken van lachgas. Het opnieuw toedienen van sub-anesthetische concentraties van lachgas aan zulke patiënten gedurende de verkoevertijd, maakte onmiddellijk een einde aan de ritmische convulsies. Meperidine was ook zeer geschikt voor deze behandeling. Dit klinische beeld, dat op het onttrekken van opiaten lijkt, werd besproken op grond van gegevens dat de analgetische werking van lachgas in de eerste plaats een gevolg is van de interaktie met het endorfinergische systeem. Er is ook verondersteld dat de bewustzijnsdalende werking van lachgas gedeeltelijk toe te schrijven is aan de interaktie met het endorfinergische systeem. Geen overtuigend bewijs voor dit laatste is echter naar voren gebracht.

Verschillende experimentele opstellingen zijn ontwikkeld voor onderzoek naar de bovengenoemde klinische waarnemingen. Bij een studie inzake het onttrekken van lachgas aan muizen toonden we aan, dat zowel het cholinergische als het endorfinergische systeem bij de lachgas-onttrekkingsreaktie betrokken zijn. Opiaten en fysostigmine verminderden beide de symptomatologie, terwijl onder zekere omstandigheden opiaat-antagonisten de neiging tot convulsies bevorderden.

De voornaamste proefopstelling, gebruikt in onze studie wat betreft lachgaswerkingen, bestond uit ratten die voor een korte of een lange tijd aan lachgas werden blootgesteld. Lachgas-analgesie en het gedrag tijdens anesthesie werden in de eerste plaats bestudeerd.
Men zag dat in ratten de tolerantie voor lachgas-analgesie zich tamelijk snel ontwikkelt en kan voortduren nadat de dieren geen gas meer toegediend krijgen. Gedragsveranderingen bij ratten, die blootgesteld werden aan lachgas, bestaan in eerste instantie uit opwinding, gevolgd door een verdovingstoestand. Maar de dieren hervatten uiteindelijk hun normale gedrag niettegenstaande

het feit dat ze doorgaan lachgas in te ademen. Dit kan zelfs vijf uur duren terwijl het antinociceptieve effekt niet langer dan een uur duurt. Dit bevestigt de veronderstelling dat verschillende uitwerkingen van lachgas een onafhankelijk patroon volgen, d.w.z. geheel of gedeeltelijk kunnen afhangen van de wisselwerking met verschillende centrale zenuwstelselmechanismen.

Een grote moeilijkheid bij de studie van de werkingen van lachgas, en ook andere gassen, is op het ogenblik het gebrek aan standaardisatie van de experimentele omgeving inzake blootstelling aan gassen. Dit heeft tot gevolg dat het vergelijken van metingen van verschillende studies inzake de uitwerking van gassen onbetrouwbaar of onmogelijk is. Het instellen van normen voor experimentele blootstelling aan gassen (vochtigheid, geluid, temperatuur, eliminatie van hinderlijke gassen, enz.) is dringend nodig en zou zeer belangrijk kunnen zijn voor de vooruitgang op dit wetenschappelijke gebied.

Met het vaststellen van een meetbare tolerantie van ratten voor lachgas-analgesie, kwam de vraag naar boven hoe dit verschijnsel, dat in menselijke anesthesie zeer ongewenst is, verhinderd kan worden. Op grond van gegevens dat lachgas-analgesie afhankelijk is van interakties met het endorfinergische systeem, namen we aan dat inhibitie van enkefalinase de ontwikkeling van tolerantie voor lachgas-analgesie zou kunnen voorkomen.
Phosphoramidon, een selectieve enkefalinase inhibitor, werd gekozen en we beschreven de analgetische en gedragsuitwerkingen ervan. Er werd geen ontwikkeling van tolerantie voor analgesie gezien toen het werd gegeven aan ratten, voordat ze aan lachgas werden blootgesteld. Deze bevinding is van belang omdat het het ongewenste verschijnsel van de ontwikkeling van de tolerantie voor lachgas- analgesie gedurende anesthesie uit de weg ruimt. Verstrekkende gevolgen van deze vinding zijn voor klinische anesthesie denkbaar.
De fundamentele en netelige kwestie wat betreft het vaststellen

van welk deel van de synaps (presynaptisch of postsynaptisch) betrokken is bij de tolerantie voor lachgas-analgesie, is nog niet helemaal opgelost. Het is duidelijk dat een verhoogde funktionele aktiviteit van het enkefalinergische systeem die volgt op een intracerebroventriculaire toediening van een enkefalinase inhibitor, zou kunnen opwegen tegen zowel onvoldoende vrijmaking van enkefalinen als voor veranderingen in de dichtheid van postsynaptische opiaat-receptoren. Het is denkbaar dat voor intraveneus gebruik bij mensen een medicijn zal worden ontwikkeld, dat tot de hersens zal doordringen en de uitwerking van lachgas krachtiger zal maken. Hiermee zal tegelijkertijd de ontwikkeling van tolerantie voor lachgas verhinderd worden.

Ook op het gebied van verslaving, dat van groot sociaal en economisch belang is, zou lachgas in belangrijke mate kunnen bijdragen aan het begrijpen en behandelen van het fenomeen. Verdere navorsingen moeten worden aangemoedigd gezien de onvolkomendheden in de huidige behandeling van verslaving. Inderdaad wordt lachgas reeds gebruikt bij de behandeling van opiaat- en alcoholontwenning.

Ook zouden toekomstige onderzoekingen kunnen aantonen of het mogelijk is antinociceptie voor chirurgische pijn tot stand te brengen alleen door het endorfinergische systeem te versterken. De resultaten van een dergelijk onderzoek zouden de huidige rol van (exogene) opiaten in de medische wetenschap kunnen veranderen. Ongetwijfeld zullen we ook meer te weten komen over het mechanisme (de mechanismen) van anesthesie daar er al is aangetoond dat (exogene) endorfinen niet alleen een antinociceptieve maar ook een anesthetische toestand teweeg kunnen brengen.

Een verder onderzoek naar de eigenschappen van lachgas werd verricht bij vrijwilligers met het doel belangrijke informatie te verkrijgen voor de clinicus inzake de ontwikkeling van tolerantie voor dit gas bij mensen. Men verzekerde zich van gegevens wat betreft de tijdsduur, die nodig is, voordat mensen een tole-

rantie ontwikkelen voor de antinociceptieve werking van lachgas in de koud water immersietest. Ook werd vastgesteld dat een volledige tolerantie voor de anesthetische werking van lachgas zich inderdaad ontwikkelt. De tijd die nodig is voor dit laatste is evenwel veel langer dan voor de eerste. De gegevens, verkregen door deze studie zullen ongetwijfeld bijdragen tot een verstandiger beleid van klinische anesthesie.

Om deze overzichtsverhandeling te besluiten zou misschien gezegd mogen worden, dat we in een tijd van vele ontdekkingen leven maar dat we geen baanbrekende ontdekkers hebben. De wetenschap is gebaseerd op een interdisciplinaire speurtocht naar feiten en gegevens. Ook in de anesthesie is stap voor stap een enorme vooruitgang geboekt. "Onomstootbare waarheden" vervagen als nieuwe gegevens beschikbaar komen. Niettemin, wie kan zich een plichtsgetrouwe anesthesist voorstellen die zijn patiënten alleen maar behandelt met een indrukwekkende verzameling van electronische paraphernalia of met een te voren klaargemaakt toverbrouwsel, zonder enige persoonlijke betrokkenheid bij hetgeen hij doet? Er kan geen vooruitgang op het gebied van de anesthesie zijn zonder een oprechte belangstelling voor het welzijn van de patiënt. Dit proefschrift is dan ook een bescheiden poging van een anesthesist, die tot doel heeft het algemene welzijn te verbeteren van de mensen, die aan hem zijn toevertrouwd.

CURRICULUM VITAE

Rupreht Jože

Geboren, 13 december 1946 te Pirešica.

Opleiding:

Eindexamen klassieke gymnasium in mei 1965, Gymnasium te Celje, Slovenië, Joegoslavië.

Artsdiploma in april 1971, Medische Faculteit, Universiteit van Ljubljana.

Militaire Medische Academie, Belgrado, 1971-1972.

Opleiding tot anesthesist, Academisch Ziekenhuis Dijkzigt, Rotterdam, 1973-1977.

Inschrijving bij de Specialisten Registratie Commissie der Koninklijke Nederlandsche Maatschappij tot Bevordering der Geneeskunst als anesthesist, september 1977.

Staflid anesthesioloog bij de Afdeling Anesthesiologie, Academisch Ziekenhuis Rotterdam, Dijkzigt en een honoraire aanstelling bij de Medische Faculteit der Erasmus Universiteit Rotterdam, 1977 tot heden.

Lidmaatschap:

European Academy of Anaesthesiology;
Association of Anaesthetists of Great Britain and Ireland;
Anesthesia History Association (USA, Canada, Mexico);
Nederlandse Vereniging voor Anesthesiologie;
Slovensko zdravniško društvo.

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The author of this thesis has been involved in the following publications.

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