SEPPO MUSTOLA

Measuring Hypnosis, Analgesia, and EEG Burst Suppression Pattern During Intravenous Anaesthesia

Effective Doses, Catecholamine and Cardiovascular Responses

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ACADEMIC DISSERTATION

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MEASURING HYPNOSIS, ANALGESIA, and EEG BURST SUPPRESSION PATTERN DURING INTRAVENOUS ANAESTHESIA:

Effective Doses, Catecholamine and Cardiovascular Responses.

CONTENTS:

LIST OF ORIGINAL PUBLICATIONS 5

ABBREVIATIONS 6

A. INTRODUCTION 7

B. REVIEW OF LITERATURE 10

B.1. Intravenous anaesthesia 10

B.1.1. Intravenous anaesthetics 12

B.1.1.1. Propofol 14

B.1.1.2. Thiopental 16

B 1.1.3. Ketamine 18

B.1.2. Intravenous opioids 20

B.1.2.1. Alfentanil 21

B.1.2.2. Remifentanil 22

B.2. Responses to laryngoscopy and intubation 23

B.2.1. Regulation of cardiovascular system 23

B.2.2. Cardiovascular and catecholamine response 24

B.2.3. Attenuation of the cardiovascular and catecholamine responses 25

B.3. Clinical measures of adequate anaesthesia 29

B.3.1. Physiology and neuroanatomy of the clinical measuring points 29

B.3.2. Clinical measuring points in anaesthesia monitoring 34

B.3.2.1. Hypnosis 34

B.3.2.2. Analgesia 35

B.3.2.3. Electroencephalography (EEG) 37

B.3.2.3.1. Burst suppression pattern (BSP) 38

C. PURPOSE OF THE STUDY 40

D. MATERIAL AND METHODS 41

D.1. Patients and experimental animals 41

D.1.1. Experimental animals 41

D.1.1.1. Rabbit anaesthesia 41

D.1.2. Surgical patients 43
D.1.2.1. Anaesthesia methods 43
D.2. Trial designs 45
D.2.1. Objectives of the studies 46
D.2.2. Clinical measuring points 47
D.2.2.1. Rabbits 47
D.2.2.2. Surgical patients 48
D.2.3. Anaesthesia monitoring 48
D.2.4. EEG monitoring 49
D.2.5. Cardiovascular measurements 49
D.2.6. Catecholamine measurements and analysis 50
D.2.7. Analysis of plasma concentrations of intravenous anaesthetics 50
D.3. Statistical methods 51
E. RESULTS 53
E.1. Responses at different measuring points 53
E.1.1. Cardiovascular responses 53
E.1.2. Plasma catecholamines 55
E.2. Effective doses 56
E.3. Effective concentrations 58
E.4. EEG and BIS 60
E.5. Other results 61
F. DISCUSSION 63
F.1. General aspects 63
F.2. Cardiovascular and catecholamine responses 66
F.3. Anaesthetic efficacy of IV anaesthetics 68
F.4. EEG and BIS 70
F.5. Clinical implications 72
G. SUMMARY AND CONCLUSIONS 74
REFERENCES 76
ACKNOWLEDGEMENTS 97
ORIGINAL COMMUNICATIONS 99

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original communications and referred to in the text by their roman numerals.

I. **Mustola S, Rorarius M, Baer G, Rosenberg P, Seppälä T, Harmoinen A (2000).** Potency of propofol, thiopentone and ketamine at various endpoints in New Zealand white rabbits. Lab Anim 34: 36-45.

II. **Mustola S, Baer G, Metsä-Ketelä T, Laippala P (1995).** Haemodynamic and plasma catecholamine responses during total intravenous anaesthesia for laryngomicroscopy. Anaesthesia 50: 108-113.

III. **Mustola S, Baer G, Toivonen J, Salomäki A, Scheinin M, Huhtala H, Laippala P, Jäntti V (2003).** Electroencephalographic burst suppression versus loss of reflexes anesthesia with propofol or thiopental: Differences of variance in the catecholamine and cardiovascular response to tracheal intubation. Anesth Analg 97: 1040-1045.

IV. **Mustola S, Baer G, Neuvonen P, Toivonen J**. Requirements of propofol at different endpoints without adjuvant and during two different steady infusion of remifentanil (submitted).

V. **Särkelä M, Mustola S, Seppänen T, Koskinen M, Lepola P, Suominen K, Juvonen T, Tolvanen-Laakso H, Jäntti V (2002).** Automatic analysis and monitoring of burst suppression in anesthesia. J Clin Monit Comput 17: 125-134.

ABBREVIATIONS

ADR	adrenaline
ANS	autonomic nervous system
ASA	anaesthetic risk groups according to the American Society of Anaesthesiologists
BIS	bispectral index
BSP	burst suppression pattern of the EEG
CA	catecholamines
CNS	central nervous system
CL_{95}	95% confidence limits
DAP	diastolic arterial pressure
EC_{50}	effective concentration when 50% of patients have lost their reaction to a stimulus
EC_{95}	effective concentration 95% (see above)
ED_{50}	effective dose when 50% of patients have lost their reaction to a stimulus
ED_{95}	effective dose 95% (see above)
EEG	electroencephalography
HPLC	high-pressure liquid chromatography
HR	heart rate
IV	intravenous
LOC	loss of consciousness
MAC	minimal alveolar concentration
NOR	noradrenaline
OAA/S	observer's assessment of alertness/sedation scale
PNS	parasympathetic nervous system
SAP	systolic arterial pressure
SNS	sympathetic nervous system
TIVA	total intravenous anaesthesia

A. INTRODUCTION

Awareness during anaesthesia has an incidence of 0.2-2% (Ranta et al 1998, Sandin et al 2000, Ranta 2002). Despite its rarity, it is a serious problem causing persistent psychological disturbances resulting in individual suffering and inability to work (Ranta et al 1998). For the clinician, unconsciousness is only one aspect of anaesthesia. For the patient, unconsciousness is an all-or-none response: he either knows what has happened, or he does not. For the surgeon, anaesthesia is a state that enables him to perform the procedure; thus, a conscious immobile patient might be sufficient. However, anaesthesiologist and surgeon are interested in intra and postoperative prevention of pain, intraoperative depression of reflexes, and a level of anaesthesia that would not cause postoperative morbidity. Replacement of "level of anaesthesia" by "level of intraoperative medication" would help to clarify the problem.

Different terms are used for similar facts; "awareness" and "consciousness" obviously have the same meaning. "Adequate hypnosis", "anaesthesia", and "unconsciousness" are also used as synonyms. There are two levels of consciousness during anaesthesia (Ghoneim 2000). First, a patient actually remember some events during anaesthesia; i.e. explicit memory. Second, a patient can have subconscious perception of events during anaesthesia which may be elicited by specific tests; i.e. implicit memory. The possibility of implicit memories has been questioned, because mood changes are seen after anaesthesia even without adverse intraoperative events (Bailey and Jones 1997). Patients also may recall disturbing dreams (Ghoneim 2000). An additional confusing phenomenon is that patients may obey orders during anaesthesia without any recall afterwards (Cormack 1993). It has been proposed that drugs causing amnesia, like benzodiazepines, might be used routinely (Cormack 1993) or when consciousness is suspected during anaesthesia (Ghoneim 2000). Others, however, argue this practise to be ethically unsound (Sandin et al 2000). Adequate anaesthesia has been proposed as a continuum (Griffiths and Jones 1990, Ghoneim 2000); adequate anaesthesia results in complete unconsciousness, lighter anaesthesia results in dream recall or implicit memory, and still lighter anaesthesia results in explicit memory.

The EEG has been used to measure depth of anaesthesia for over 50 years. However, good correlations were found only under laboratory conditions with one drug a time. Technical progress has now enabled the calculation of scores from the raw data almost in real time; such were, for instance, aperiodic analysis and power spectrum analysis (Levy 1984, Levy 1986). Again, these tools worked well with one drug and no surgical disturbance. Recently, several new scores have been developed: bispectral index (BIS) (Sigl and Chamoun 1994), ENTROPY (Sleigh and Donovan

1999), and auditory evoked potential index (AEP_{index}) (Gajraj et al 1998). These scores measure the level of the effect of medication on the cerebral cortex. Below certain scores, the patient's mental function is disturbed (sedation) and at deeper levels mental function is inhibited (unconsciousness). However, patients medicated down to the level of EEG burst suppression may display exact protective movements suggesting preserved orientation and observation without memory (Baer G, pers. comm.). Patients whose EEG score indicates "unconscious" may have some implicit memories. Finally, at the same level of EEG depression, some patients may have explicit memories (Ghoneim 2000).

The concept of MAC (minimum alveolar concentration) for volatile anaesthetics provided a useful measure to evaluate the depth of anaesthesia (Eger et al 1965). One MAC prevents 50% of patients from reacting to skin incision and is about twice the concentration needed to produce unconsciousness (Newton et al 1990). Later, other noxious stimuli have been employed in place of skin incision, e.g. trapezius muscle squeeze, tetanic electrical stimulation, laryngoscopy, intubation, and laser stimulation (heat stimulus). With IV anaesthetics effective dose 50% (ED_{50}) and effective concentration 50% (EC_{50}) have been used as an equivalent to 1 MAC of volatile anaesthetics (Davidson et al 1993). Monitoring of end tidal volatile concentrations and infusion automats providing certain drug concentrations in the bloodstream gave a sense of security. However, MAC measures the blockage of noxious stimuli in the spinal cord {Rampil et al 1993}; fortunately, with most drugs unconsciousness is a definite side effect of this level of intraoperative medication. Employing one drug only, the level of anaesthesia (medication) has been deepened by increasing drug delivery to the patient until surgery was possible to perform. With ether, due to severe side effects, the level of "surgical anaesthesia" was near to the level of dangerous anaesthesia. The level of anaesthesia was and is still evaluated using clinical signs such as protective movements and the eyelash and pupillary light reflexes (Guedel 1936).

The most distressing feature of consciousness during anaesthesia is pain perception during surgery. The patient can be conscious but cannot move (Ghoneim 2000). Therefore, less use of neuromuscular blockers and deeper levels of medication have been advised (Cormack 1993). Movement as a reaction to painful stimuli is mainly due to spinal reflexes, which appear also in unconscious patients (Cormack 1993). On the other hand, apparent lack of reflex activity does not prove unconsciousness and complete areflexia requires a very deep level of medication. The correlation between different autonomic and somatic reflexes is variable and there is no consensus on which of them correlate best with consciousness (Cormack 1993). Measurement of unconsciousness during anaesthesia is very difficult, and there is no reliable method of detecting

consciousness during anaesthesia (Drummond 2000), whch is why surrogate measures of adequate anaesthesia are still widely used.

In the present study we compared propofol, thiopental, and ketamine (rabbits) during different surrogate measures of the depth of anaesthesia (later end-points). In human studies we used loss of eyelash reflex, loss of pupillary light reflex, loss of counting, and loss of obeying verbal command as hypnotic end-points. As analgesic end-points we used electrical tetanic stimulation, laryngoscopy, intubation, and laryngomicroscopy (a longer lasting noxious stimulus). In experimental animals we used loss of righting reflex and tail clamping as hypnotic and analgesic end-points, respectively. Furthermore, in rabbits we used a more centrally mediated end-point, loss of purposeful movement to intranostril instillation of ammonia vapour. In humans we used the onset of electroencephalographic (EEG) burst suppression pattern (BSP) as a measure of deep level of medication, i.e. EEG end-point.

B. REVIEW OF LITERATURE

B.1. Intravenous anaesthesia

IV anaesthesia is a smooth, reliable and fast anaesthetic technique. Pharmacokinetically there are short-acting IV anaesthetics, which do not cause gas pollution, are inexpensive, easy to titrate, and easy to administer. Some IV anaesthetics have analgesic properties (ketamine) while others do not (propofol, thiopental). Furthermore, IV anaesthetics do not cause airway irritation during induction as is seen with most volatile anaesthetics; recovery can be faster with volatile anaesthetic than with IV anaesthetic (Van Hemelrijck et al 1991). After IV anaesthesia recovery is smooth. Postoperatively, propofol possesses significant antiemetic properties, and ketamine analgesic activity (McCollum et al 1988, Gan et al 1996, Reves et al 2000).

The partial pressure of inhaled anaesthetic in the exhaled air can be measured non-invasively and equals the arterial value. IV anaesthetics are generally delivered on a dose per kilogram of body weight rule, real-time measurement of blood drug concentration is not possible, and the excretion of overdoses cannot be hastened. For this reason, manually (Roberts et al 1988, Maitre and Shafer 1990) and computer controlled (Shafer et al 1988a, Tackley et al 1989, White and Kenny 1990) infusion pumps have been developed. They enable the administration of IV anaesthetics in accordance with their pharmacokinetic profile. Accuracy of the prediction of blood concentration of propofol by a computer-controlled infusion device has been tested (Vuyk et al 1995a). The performance of the computer-controlled infusion device was similar with the pharmacokinetic parameters sets described by Cockshott et al (1987), Gepts et al (1987), Shafer et al (1988b), and Tacley et al (1989). The measured concentrations of propofol exceeded the predicted concentrations by approximately 25% (Vuyk et al 1995a). The parameter set of Kirckpatrik et al. (1989) produced the most unreliable results. There are considerable interindividual variations, the therapeutic concentration is highly dependent on the surgical stimulus, and predicted concentrations are not accurate for all patients (Vuyk et al 1995a). Therefore, despite the use of manually or computer controlled infusion pumps, the dosage and rate of IV anaesthetics administration must be adjusted to meet individual patient needs. The Observer's Assessment of Alertness/Sedation (OAA/S) scale was developed to measure the level of alertness in subjects who are sedated. The OAA/S scale has proved to be reliable and valid to measure the depth of sedation (from light to heavy) as compared to a Visual Analogue Scale and two performances tests (Digit Symbol Substitution Test and Serial Sevens Subtraction) (Chernik et al 1990).

Pharmacokinetic characterization of IV anaesthetic drugs are mostly described using a multicompartment mammillary model that yields two distribution half-lives and a terminal "elimination" half-life; i.e. a three-compartment model. The model consists of unit disposition functions of the form $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$ where C(t) is the central compartment drug concentration profile resulting from a bolus input as a function of time (t), and α, β, and γ are exponential rate constants of the relationship, $\alpha>\beta>\gamma$. Elimination half-life is calculated as $\ln 2/\gamma$, and distribution half-life $\ln 2/\alpha$ (central) and $\ln 2/\beta$ (rapid peripheral). A, B, and C are constants (y-axis intercepts). Principal pharmacokinetic parameters are clearance (CL), volume of distribution (V), and half-lives ($T_{½}$). Also, intercompartmental rate constants are usually calculated.

The equation is in form $C_{(T+t)} = A(1 - e^{-\alpha T})e^{-\alpha t} + B(1 - e^{-\beta T})e^{-\beta t} + C(1 - e^{-\gamma T})e^{-\gamma t}$ during IV infusions where T is duration of infusion and t is post infusion time. When a drug's pharmacokinetic behaviour can be presented by a one-compartment model, the elimination half-life can be used to describe the time required for the concentration to decrease by a certain percentage when the infusion is stopped. In multicompartment pharmacokinetic models, distribution of the drug between central and peripheral compartments is a significant contributor to central compartment drug disposition. Elimination half-life may be of little value in describing multicompartment models (Shafer and Varvel 1991). The reason for the inadequacy is that the terminal elimination half-life does not take into account the distribution of the drug to tissues after discontinuation of the drug infusion. To find better ways to measure the offset of drug action, the "context-sensitive half-time" was introduced to clinical practise (Hughes et al 1992). The "half-time" is the time required for the drug concentration in the central compartment to decrease by 50% after discontinuation of drug administration. The term "context" relates to the duration of drug infusion before its discontinuation. By incorporating the effect compartment, the context-sensitive half-time of the pharmacodynamic effect can be modelled. This concept of "context-sensitive half-time" has clinically relevant implications for the administration of IV anaesthetics and would allow a more accurate prediction of recovery from IV infusion anaesthesia after the termination of surgery (Hughes et al 1992).

When predicting the effect-site concentration (and effect) of an IV anaesthetic agent after bolus or during infusion, the equilibrium half-life between blood and effect-site has important clinical implications (Jacobs and Reves 1993). The effect-site is the hypothetical compartment that relates the time course of plasma drug concentration to the time course of drug effect where k_{e0} is the rate constant of drug elimination from the effect-site and $t_{½}$ k_{e0} is $\ln 2/k_{e0}$. After a bolus dose or start of anaesthetic infusion, the effect-site concentration starts from zero and increases over time until it

equals the plasma concentration. When the k_{e0} is available for an IV anaesthetic, theoretical effect compartment concentrations can be simulated. When dealing with anaesthetic drug infusions, it should be taken into account that the 90% equilibrium between blood and brain (effect-site) will occur within about three to four equilibrium half-lives (Glass et al 2000).

B.1.1. Intravenous anaesthetics

An ideal IV anaesthetic should produce a rapid, smooth, and safe induction of and emergence from anaesthesia. It should have a large distribution volume, rapid degradation to inactive and non-toxic metabolites, no accumulation, and dosing of the drug should not be influenced by hepatic or renal insufficiency. It should have minimal effects on cardiovascular and respiratory functions or functions of other organs, and preferably have analgesic properties at sub-anaesthetic doses. It should be non-irritating to tissues or veins and have low potential to hypersensitivity reactions. It should not raise intracranial pressure. It should be water-soluble, inexpensive, stable in solution, and have a long shelf life. None of the presently available IV anaesthetics matches all these specifications (Reves et al 2000). Pharmacokinetic parameters of IV anaesthetics are presented in Table 1.

Table 1. Pharmacokinetic parameters of intravenous anaesthetics and opioids.

Drug	CL_{ss} (ml/kg/min)	Vd_{ss} (l/kg)	t½ (h) (elimination)	Time to peak effect (min)	T½ k_{e0} (min^{-1})	Context-sensitive t½ (min)	References
Propofol	22-30	1.5-4	3-10	1-2.5	1-3.5	20-50	Gepts et al 1987, Kirkpatrick et al 1988, Shafer et al 1988b, Hughes et al 1992, Shafer 1993, Smith et al 1994, Schnider et al 1999
Thiopental	1.5-4	1.5-4	5-15	1-2	1-2.5	100-200	Ghoneim and Korttila 1977, Morgan et al 1981, Homer and Stanski 1985, Stanski and Maitre 1990, Hughes et al 1992, Shanks et al 1993, Cordato et al 1999
Ketamine	12-18	2.5-3.5	2-3	1-2	-	25-50	Idvall et al 1979, Clements and Nimmo 1981, Domino et al 1982, Reves et al 2000
Fentanyl	10-20	3-5	3-4	3-5	4-6	100-300	Camu et al 1982, Scott et al 1985 & 1991, Maitre et al 1987, Hughes et al 1992, Egan et al 1996
Alfentanil	4-8	0.5-1.0	1-2	1-2	1-1.5	40-50	Camu et al 1982, Scott et al 1985, Maitre et al 1987, Hughes et al 1992, Egan et al 1996
Sufentanil	10-15	2.5-3.0	2-3	4-6	5-6	20-50	Scott et al 1991, Shafer and Varvel 1991, Hughes et al 1992, Bailey et al 2000
Remifentanil	40-60	0.3-0.5	0.1-0.2	1-2	1-2	3-5	Egan et al 1993, Westmoreland et al 1993, Egan 1995, Kapila et al 1995, Minto et al 1997

CL_{ss} = clearance at steady-state, Vd_{ss} = volume of distribution at steady-state, t½ = half-life, t½ k_{e0} = equilibrium half-life between plasma and effect-site

B.1.1.1. Propofol

Propofol is a substituted phenol (2,6-diisopropylphenol) that was first introduced in the early 1980s (Rogers et al 1980, Major et al 1981). Recovery from either a single injection or IV infusion was and is very rapid (Major et al 1981, Prys-Roberts et al 1983, Grant and Mackenzie 1985). The potency of propofol compared to thiopental varies from 1:1.3 to 1:2.9 (Grounds et al 1986, Naguib et al 1992). It is more suitable for use in infusion anaesthesia than thiopental (Kashtan et al 1990).

Propofol is insoluble in aqueous solutions but is highly lipophilic. The initial distribution clearance of propofol (3-4 l/kg/min) is similar to that of thiopental (Shafer 1993), but subsequently it is much more rapid because of its high metabolic clearance rate. Total body clearance of propofol at steady state is 22-30 ml/kg/min, the distribution volume at steady state is 1.5-3 l/kg, and the elimination half-life 3.5–10 h after infusion (Gepts et al 1987, Kirkpatrick et al 1988, Shafer et al 1988b), but recovery from its clinical effects is rapid. Propofol has a context-sensitive half-time of less than 25 min after infusions as long as 3 hours, which increases to only 50 min after more prolonged infusions. This is due to the fact that the long elimination half-life is related to slow elimination from highly lipophilic tissue compartments and is largely irrelevant in clinical situations (Shafer and Stanski 1992). Propofol has a large steady-state volume of distribution, indicating extensive redistribution of the drug into muscle, fat, and other poorly perfused tissues (Kirkpatrick et al 1988, Shafer et al 1988b). The concentration in the central compartment decreases both because of metabolism and continuing redistribution after termination of infusion of propofol. Because the capacity of the peripheral compartments is large, redistribution from the central compartment can still occur even after prolonged drug administration. The complete elimination of propofol from the body may take many hours or even days but have little effect on clinical recovery.

For successful induction of anaesthesia, i.e. an effective dose when 95% of patients (ED_{95}) have lost consciousness, 2.0 to 2.5 mg/kg of propofol is needed and ED_{50} of propofol is 1-1.5 mg/kg (Major et al 1981, Rolly and Versichelen 1985, McCollum and Dundee 1986). The duration of hypnosis is 5-10 min after single anaesthetic dose (Major et al 1981) and is slightly longer than that of thiopental (Flaishon et al 1997). ED_{95} of infants needs an induction dose of 3.0-3.5 mg/kg (Westrin 1991) and ED_{95} of elderly patients is 0.5-1.5 mg/kg (Dundee et al 1986). Infusion rates of 4 to 18 mg/kg/h are required during TIVA with propofol depending on the surgical procedure and concomitant anaesthesia drugs (Fragen et al 1983, Turtle et al 1987, Sear et al 1988, Reyneke et al 1989, Milligan et al 1990). The need for reduced dose requirements of propofol in the elderly (Scheepstra et al 1989) is related to pharmacokinetic rather than pharmacodynamic factors

(Kirkpatrick et al 1988). Children require a larger induction dose (Valtonen et al 1989) and an increased maintenance rate of infusion than adults because the volume of central compartment, and thus the volume of distribution is larger than that of adults (Jones et al 1990, Kataria et al 1994). Gender does not seem to significantly influence propofol pharmacokinetics (Kay et al 1986), but there are studies that report faster emergence from propofol anaesthesia in women than in men (Gan et al 1999, Høymork et al 2001). Considerable variation in the blood concentration of propofol and other drugs has been observed during infusion schemes designed to achieve a predetermined blood concentration. Variations occur between groups of patients given an identical infusion scheme, despite attempts to normalize for variables such as weight, age, and gender (Coetzee et al 1995, Vuyk et al 1995a).

ED_{50} values of propofol for the onset of BSP have been about 5.5-6.5 mg/kg with an initial bolus and infusion thereafter (Illievich et al 1993) or with infusion only (Cheng et al 1996). Effective concentrations of propofol when 50% of patients (EC_{50}) have lost their consciousness are for loss of eyelash reflex 2-2.5 μg/ml and for loss of response to verbal command 3-4.5 μg/ml, respectively (Smith et al 1994, Vuyk et al 1996, Kazama et al 1997). EC_{50} for loss of purposeful movement to noxious stimulus is for tetanic stimulation or laryngoscopy 8-11 μg/ml, for skin incision 10-15 μg/ml, and for laryngoscopy followed by intubation 15-20 μg/ml (Smith et al 1994, Kazama et al 1997). EC_{50} to induce BSP has been 7-9 μg/ml (Illievich et al 1993). The reduction of EC_{50} for loss of response to verbal command was minimal with fentanyl whereas the reduction of EC_{50} for noxious stimuli varied from 30% to 50% when increasing fentanyl concentration from 0.6 ng/ml to 3 ng/ml was used (Smith et al 1994, Kazama et al 1997). Age reduces the requirements of many anaesthetic drugs by approximately 20% for each decade of years above 20 years of age (Smith et al 1994). EC_{50} of propofol for skin incision with temazepam premedication was 8.1 μg/ml (Davidson et al 1993). Midazolam reduced the dose of propofol necessary to prevent a response to a tetanic stimulus by 50% (Short et al 1992). In conjunction with 70% nitrous oxide, the concentrations of propofol during superficial surgery are in the range of 2.0-5.5 μg/ml (Turtle et al 1987, Shafer et al 1988b, Davidson et al 1993). It has been suggested that the lowest concentration of propofol that produces LOC is 1.2 μg/ml regardless of opioid doses (Vuyk et al 1996). EC_{50} to awakening is 0.7-1.2 μg/ml (Shafer et al 1988b). It has been recommended that during TIVA with propofol, the plasma concentration of propofol should be maintained above 3.3 μg/ml, which is equal to a propofol infusion of approximately 5 mg/kg/h (Smith et al 1994).

Propofol affects the respiratory system similarly to the action of thiopental, i.e. it causes central respiratory depression, but laryngeal reflexes are more depressed compared to thiopental at equivalent doses (Barker et al 1992). Cardiovascular changes after IV induction have demonstrated that in comparison to thiopental propofol has more of a depressive effect on systolic and diastolic arterial pressures, and reduces peripheral vascular resistance more severely than thiopental (Price et al 1992). Propofol also significantly decreases myocardial contractility, cardiac output and stroke volume, and has venodilating properties without significantly affecting heart rate (HR) (Coetzee et al 1989, Mulier et al 1991, Illievich et al 1993).

Propofol does not release histamine, but can induce an anaphylactic reaction. Propofol possesses significant antiemetic activity (McCollum et al 1988). Pain at the injection site is a usual complaint (Hynynen et al 1985b). During longer infusions of propofol urine colour can change to green (Blakey et al 2000).

B.1.1.2. Thiopental

Thiopental is a thiobarbiturate. It was first used in surgical patients at the Mayo clinic in 1934 and thus has been in clinical practise already for 70 years. It has remained the standard IV anaesthetic for evaluation of new IV anaesthetics. Despite its long elimination half-life (12h), it is still widely used as an induction agent all over the world because of its rapid onset of action and being a standard when compared to the faster degrading competition, propofol.

Sodium thiopental is a water-soluble and highly lipophilic molecule. Total body clearance of thiopental ranges from 1.5 to 4 ml/kg/min, distribution volume at steady state from 1.5 to 3 L/kg, and elimination half-life from approximately 5 to12 hours (Ghoneim and Korttila 1977, Morgan et al 1981). During longer infusion, thiopental shows nonlinear kinetics, which is probably due to saturation of the thiopental-oxidizing hepatic enzyme system resulting in accumulation of thiopental because its elimination half-life can exceed 30-80 hours (Stanski et al 1980, Turcant et al 1985). Thiopental has a context-sensitive half-time of 100 min after infusions as long as 3 hours, which increases to 200 min after more prolonged infusions. Gender does not significantly influence thiopental pharmacokinetics but advancing age does increase the terminal half-life and decrease distribution volume (Christensen et al 1981, Homer and Stanski 1985, Stanski and Maitre 1990). Also, children have higher clearance rate (Sorbo et al 1984).

In healthy adults the ED_{95} of thiopental for induction of anaesthesia is 4-6 mg/kg and ED_{50} is 2-4 mg/kg. ED_{95} of children and infants is 5-7 mg/kg for induction of anaesthesia (Jonmarker et al 1987)

and for elderly people 2-3 mg/kg (Homer and Stanski 1985, Steib et al 1988). The duration of hypnosis is 4-8 min after a single anaesthetic dose. The elderly and women need less than the young and men as an induction dose (Avram et al 1993). Decreased requirements of thiopental in the elderly might be due to decreased initial volume of distribution and decreased cardiac output (Stanski and Maitre 1990, Avram et al 1993, Shanks et al 1993). Higher requirements of thiopental in children and infants might be due to greater cardiac output in relation to body weight or faster central distribution kinetics (Jonmarker et al 1987). Thiopental administered by a continuous infusion for maintenance of anaesthesia is rarely used because of its prolonged recovery time. A successful thiopental infusion achieves a blood concentration of 15-20 μg/ml on induction, 10-20 μg/ml during maintenance of anaesthesia, with a mean plasma concentration on awakening of 5-7 μg/ml (Fragen and Avram 2000). Premedication with an opioid, benzodiazepine, or alpha-2-agonist decreases the induction dose of thiopental by approximately 30% (Fragen and Avram 2000).

In young and healthy 20-30 years old patients, ED_{50} of thiopental to produce BSP is approximately 10-12 mg/kg, and decreases to 6-7 mg/kg in patients 60-70 years of age (Homer and Stanski 1985). EC_{50} of thiopental to induce BSP is 30-40 μg/ml (Bührer et al 1992, Hung et al 1992, Shanks et al 1993). EC_{50} of thiopental for syringe dropping, loss of verbal command or loss of eyelid reflex is 11-20 μg/ml. EC_{50} of thiopental for loss of corneal reflex, for loss of purposeful movement such as reaction to tetanic stimulation, trapezius squeeze, or laryngoscopy are 30-50 μg/ml, and to laryngoscopy followed by intubation approximately 80 μg/ml (Becker 1978, Becker and Tonnesen 1978, Hung et al 1992).

Thiopental when compared to propofol is less depressant to the cardiovascular system when arterial blood pressure, total peripheral resistance, or cardiac output are measured (Grounds et al 1985, Stowe et al 1992), but more depressant as seen in the isolated guinea pig myocardial preparation and in human atrial strips (Azari and Cork 1993, Gelissen et al 1996). Thiopental depresses myocardial function more than propofol in the acute ischemic heart than in the normal heart (De Hert et al 1990) and may evoke reductions in coronary flow that are profoundly exaggerated under conditions of coronary endothelial dysfunction (Moore et al 1994). Thiopental also increases HR, which results in increased myocardial oxygen consumption.

Thiopental decreases plasma cortisol levels but does not prevent adrenocortical stimulation from the stress of surgery. Thiopental injection causes release of histamine and occasionally urticarial rash, but anaphylactic reactions are rare. Pain on injection site is rare but extravasated thiopental produces local pain, oedema, erythema, and sometimes tissue necrosis (Fragen and Avram 2000).

B 1.1.3. Ketamine

Ketamine is an arylcyclohexylamine and is structurally related to phencyclidine. Racemic ketamine was introduced in 1965 and approved for clinical use in 1970. Ketamine has been used widely in veterinary medicine (Green et al 1981, Borkowski et al 1990). Ketamine produces a clinical anaesthetic state in which the eyes remain open showing a slow nystagmus; corneal and pupillary light reflexes remain intact, as do laryngeal protective reflexes (Carson et al 1973). Varying degrees of hypertonus and myoclonic movements are seen, and spontaneous respiration is preserved. The preserved reflexes and spontaneous movements make it difficult to judge adequacy of anaesthesia.

Ketamine is water-soluble, painless and non-irritating following parenteral injection, and has high lipid solubility (White et al 1982). The clearance of ketamine at steady state is 12-18 ml/kg/min, the volume of distribution at steady state 2.5-3.5 L/kg, and the elimination half-life 2-3 hours after a single bolus (Clements and Nimmo 1981, Domino et al 1982). Ketamine has been used as an infusion anaesthetic (1-3.5 mg/kg/h, mean 2.5) with rapid recovery, cardiovascular stability, and an elimination half-life of 80 min (Idvall et al 1979). Neither gender nor age seems to significantly influence ketamine pharmacokinetics. The context sensitivity half-time of ketamine is about the same as with propofol, 20-50 min (Reves et al 2000).

ED_{95} of ketamine to induce anaesthesia after an intravenous bolus dose is 1.5-3.0 mg/kg with consciousness returning after 10-15 minutes. Children need 2.5-3.0 mg/kg (Westrin 1991), and elderly patients 0.5-2.0 mg/kg as an induction dose (ED_{95}) (Reves et al 2000). ED_{50} for loss of verbal command is 0.4-0.9 mg/kg and ED_{50} for loss of reaction to tetanic stimulation 0.6-1.3 mg/kg (Hong et al 1993). ED_{95} for loss of response to tetanic stimulation is 1-2.5 mg/kg (Hong et al 1993). EC_{50} of ketamine that caused one-half of the maximal median frequency decrease in the EEG was 2.0 μg/ml for racemic ketamine and 0.8 μg/ml for S-(+)-ketamine (Schüttler et al 1987). During successful IV anaesthesia, plasma concentrations of ketamine have been 0.6-2.0 μg/ml in adults, and children require plasma concentrations of 0.8-4.0 μg/ml (Reves et al 2000). Infusion rates of 1 to 5 mg/kg/h are required during TIVA with ketamine depending on concomitant anaesthetic drugs and types of surgery (White et al 1982).

Ketamine is an effective analgesic even at sub-anaesthetic doses in humans, but not in all animals (Green et al 1981). Ketamine has been used as an analgesic during TIVA with propofol

(Guit et al 1991). Analgesia occurs at lower blood concentrations than loss of consciousness; the plasma concentration of ketamine at elevated pain threshold is 0.1 μg/ml or higher. The analgesic action is postulated to be due to N-Methyl-D-aspartate receptor interaction and inhibition of dorsal horn wide dynamic range neuronal activity. Ketamine has excitatory effects on the CNS and can induce generalized high voltage synchronized theta and delta wave activity and petit mal like activity in the hippocampus (Kochs et al 1988, Reves et al 2000). Even at higher doses, ketamine does not induce BSP (Rosen and Hagerdal 1976).

Ketamine has minimal effect on the central respiratory drive. It is an effective bronchodilatator but sometimes considerably increases salivation (Reves et al 2000). Ketamine increases the rate-pressure product and the cardiac index, but does not significantly change the stroke index (Idvall et al 1979). The cardiovascular effects are thought to be produced by direct stimulation of the CNS. Ketamine is a direct vasodilator but in postganglionic adrenergic neurons, ketamine inhibits the re-uptake of catecholamines resulting in no alteration of peripheral vascular resistance. On the other hand, it increases pulmonary vascular resistance. The centrally mediated sympathetic stimulation usually overrides the direct myocardial depressant effect of ketamine. With doses used to induce anaesthesia, ketamine depresses cardiac function less than thiopental or propofol (Stowe et al 1992).

During ketamine anaesthesia, patients experience psychic reactions like vivid dreams or hallucinations, which may be fantastic, interesting, disturbing or nightmarish quality for the patient. The postoperative alterations in mood state and body image, floating sensations, illusions and delirium (Perel and Davidson 1976, White et al 1980) may be a nightmare for the patient and personnel. The quality of the hallucinations depends on the patient's psychic state of mind before anaesthesia induction, which might be positively influenced during the pre-anaesthetic round; on the other hand, the disturbed short-time memory makes it difficult to co-operate rationally afterwards with the strange events (Baer and Parkas 1981). Thus, ketamine can be the ideal anaesthetic during the harsh circumstances of war or catastrophes (anaesthesia and analgesia with one drug), but totally unsuitable, for example, in gynaecologic surgery of ambulant patients (the patient fearing cancer, infertility, pregnancy) (Dundee1971, Coppel et al 1973). Benzodiazepines efficiently attenuate these psychic disturbances, but also depress respiration and protective laryngeal reflexes (Coppel et al 1973, Korttila and Levänen 1978).

Clinical trials have shown that the anaesthetic potency of the ketamine isomer S-(+)-ketamine is twice that of the racemic mixture. A bolus dose of 2 mg/kg of racemic ketamine equals a dose of 1 mg/kg of S-(+)-ketamine, producing comparative effects in endocrine and cardiovascular parameters

(Adams et al 1992). Recovery is significantly faster and cognitive performance better after S-(+)-ketamine than after racemic ketamine (Doenicke et al 1992).

B.1.2. Intravenous opioids

Opioids act via the central and peripheral μ-opioid receptors. Opioid receptor distribution within the neuraxis coupled with the widespread association between opioid receptors and cardiovascular and autonomic regulatory areas within the CNS define much of the pharmacophysiological basis for opioid-induced hemodynamic effects (Bailey et al 2000). The ventrolateral periaqueductal gray region, a key central site mediating analgesia, also affects hemodynamic control, and different opiate receptor subtypes occupy this site (Keay et al 1997). Activation of μ-opioid receptors suppresses somatosympathetic reflexes at the level of the spinal cord and modulates them at the brain stem. These actions contribute to the anaesthetic capabilities of opioids. Opioids can also modulate the stress response through receptor-mediated actions on the hypothalamic-pituitary-adrenal axis. Most opioids reduce sympathetic and enhance vagal tone (Sato et al 1995). The predominant and usual effect of opioids on the HR is to produce bradycardia resulting from stimulation of the central vagal nucleus but blockade of sympathetic chronotropic actions may also play a role in opioid-induced bradycardia (Bailey et al 2000).

Opioids do not reliably produce unconsciousness (Lang et al 1996, Jhaveri et al 1997, Veselis et al 1997), but they do reduce MAC of inhaled anaesthetics (Brunner et al 1994, Tammisto et al 1995, Lang et al 1996) and requirements of IV anaesthetics (Short et al 1992, Wessen et al 1993, Wang et al 1996, Kazama et al 1998, O'Hare et al 2001) during anaesthesia. Opioids are widely used as analgesics to supplement general anaesthesia for various surgical procedures.

Equipotent dose ratios (mg/kg) of alfentanil, remifentanil, fentanyl, and sufentanil measured by EEG quantitation are approximately 100:10:10:1 (Scott et al 1985, Scott et al 1991, Bailey et al 2000, Thomson et al 2000). This ratio of equipotency was also confirmed in a later clinical study (Ahonen et al 2000a). Equipotent plasma concentration ratios (ng/ml) that produce maximal EEG effect in 50% of patients (EC_{50}) of alfentanil, remifentanil, fentanyl, and sufentanil are approximately 800:20:15:1 (Scott et al 1985, Scott et al 1991, Shafer and Varvel 1991, Egan et al 1996). Pharmacokinetic parameters of intravenous opioids are presented in Table 1.

B.1.2.1. Alfentanil

Alfentanil is a tetrazole derivative of fentanyl and is a potent μ-agonist. It came to use in clinical practise in the early 1980s. It has adverse effects similar to the other opioids: ventilatory depression, nausea, vomiting, muscular rigidity, and bradycardia. Alfentanil does not release histamine upon injection. When compared with fentanyl, alfentanil has a faster onset (1-2 min) and one-third the duration of action, one fourth to one tenth of the potency, and less lipid solubility (Camu et al 1982, Hynynen et al 1985a). In the base of equipotent plasma concentrations the potency of fentanyl is 30 times greater than that of alfentanil (Langevin et al 1999).

When compared to fentanyl alfentanil has a lower total body clearance (4-8 vs. 10-20 ml/kg/min), smaller volume of distribution at steady state (0.5-1.0 vs. 3-5 L/kg), and shorter elimination half-life (1-2 vs. 3-4 h) (Camu et al 1982, Maitre et al 1987, Egan et al 1996). The elderly need less alfentanil when compared to young people (Helmers et al 1984, Scott and Stanski 1987). After infusion of 3 h, the context-sensitive half-time and terminal elimination half-life of alfentanil is about 50 and 80 min (vs. fentanyl about 200 and 240 min), respectively (Shafer and Varvel 1991, Westmoreland et al 1993, Kapila et al 1995). Because of its pharmacokinetic profile, alfentanil is more suitable for infusion anaesthesia than fentanyl. The clearance of alfentanil is reduced in patients with hepatic impairment (Ferrier et al 1985) whereas fentanyl kinetics is unchanged (Haberer et al 1982). The free fraction of alfentanil and the volume of distribution at steady-state are increased in chronic renal failure (Chauvin et al 1987). TIVA with propofol and alfentanil for renal transplantation resulted in slower recovery than in previous studies of ASA 1-2 patients (Kirvelä et al 1994). Propofol inhibits enzymatic degradation, decreases greatly the fast distribution clearance, and decreases minimally the elimination clearance of alfentanil (Janicki et al 1992, Mertens et al 2001).

When compared to fentanyl, clinical studies during surgical procedures show that alfentanil produces an earlier peak analgesic effect, faster recovery of consciousness, and a more pronounced narcotic effect without increased adverse effects (Fragen et al 1983, De Grood et al 1985, Jenstrup et al 1990, Raftery and Sherry 1992). Alfentanil is useful for supplementation of analgesia for outpatient surgical procedures and as an infusion for maintenance of analgesia during surgery (Raftery and Sherry 1992, Langevin 1999). EC_{50} of alfentanil to induce maximal EEG effect is 500-600 ng/ml (Scott et al 1985). Alfentanil has been successfully combined with propofol for induction of anaesthesia followed by tracheal or nasotracheal intubation without muscle relaxant; given before

propofol it reduces injection pain of propofol (Saarnivaara and Klemola 1991, Coghlan et al 1993, Fletcher et al 1994).

B.1.2.2. Remifentanil

Remifentanil is a synthetic 4-anilidopiperidine opioid and was brought into clinical practice in the early 1990s. Pharmacodynamically, remifentanil equals the other fentanyl congeners, for example alfentanil. Remifentanil produces physiological changes consistent of potent μ-agonist activity; including analgesia, sedation, ventilatory depression, nausea, vomiting, muscular rigidity, bradycardia and pruritus. It does not release histamine upon injection. The onset of action of remifentanil is similar to that of alfentanil (1-2 min), but its offset is considerably more rapid. The reason for this is that remifentanil has an ester side chain, which is rapidly hydrolysed by non-specific plasma and tissue esterases. The rapid hydrolysis of remifentanil results in brevity of action, precise and rapidly adjustable effects, non-cumulative opioid effects, and rapid recovery after cessation of administration (Rosow 1993).

Remifentanil is lipophilic and widely distributed in body tissues with an extremely rapid clearance of 40-60 ml/kg/min, the volume of distribution at steady state is 0.3-0.5 L/kg, and the terminal half-life is only 10-20 min (Egan et al 1993, Westmoreland et al 1993). Because of its unique metabolic pathway and rapid clearance, remifentanil represents a new pharmacokinetic class of opioids. Unlike the other fentanyl congeners, termination of the therapeutic effect of remifentanil mostly depends on metabolic clearance rather than on redistribution (Egan 1995). The context-sensitive half-time of remifentanil is only 3-5 minutes, and is independent of infusion duration (Westmoreland et al 1993, Kapila et al 1995). Age has an effect on the pharmacokinetics and pharmacodynamics of remifentanil, but gender has not (Minto et al 1997). Pharmacokinetics and pharmacodynamics of remifentanil are not altered in patients with renal or liver diseases (Dershwitz et al 1996, Hoke et al 1997), or are altered clinically slightly (Dahaba et al 2002), i.e. the central clearance is reduced and the elimination half-life is prolonged. Co-administration of propofol decreases the central volume of distribution, the distributional clearance, and elimination clearance of remifentanil, but remifentanil does not influence propofol kinetics (Boullion et al 2002).

Remifentanil's brevity of action ensures not only a rapid resolution of adverse effects but also a rapid offset of its analgesic effect. Therefore, appropriate postoperative analgesia should be established before discontinuation of remifentanil infusion. The unique pharmacokinetic profile of remifentanil facilitates real-time management of intraoperative stress, as well as provision of

optimal intraoperative analgesia without compromising recovery for a variety of surgical procedures (Hogue et al 1996).

TIVA with remifentanil include fewer cardiovascular side effects, a low incidence of postoperative nausea and vomiting and an attenuated neurohumoral stress response to surgery. The therapeutic potency of remifentanil is approximately 20 times greater than that of alfentanil with an EC_{50} to induce maximal EEG effect of 10-20 ng/ml (Egan et al 1996). Remifentanil is about 40-times more potent than alfentanil when whole blood concentrations of remifentanil and alfentanil are compared at equipotent doses to depress the minute ventilatory response (Glass et al 2000). On the other hand, alfentanil concentrations are usually measured in plasma and remifentanil in whole blood; when these are compared, remifentanil is 70 times more potent than alfentanil (Glass et al 2000).

B.2. Responses to laryngoscopy and intubation

B.2.1. Regulation of cardiovascular system

The hypothalamus is the highest level of integration of the autonomic nervous system (ANS). It is under the influence of the cortex and the limbic system. The hypothalamus controls ANS via the pituitary (and its dependent endocrine glands) and via direct descending nervous pathways such as those used in cardiovascular regulation. The afferent fibres of the ANS go with peripheral nerves towards the central nervous system (CNS). The peripheral efferent pathways of the ANS consist of neurons outside the CNS. Primary parasympathetic neurons affecting cardiovascular control are located in the brainstem, hence are subject directly to the cortical, hypothalamic, and afferent impulses delivered to the brainstem (Moss and Renz 2000). The sympathetic neurons operate via nervous relays that descend from neurons located in the lateral portions of the formatio reticularis in the brainstem (vasomotor centre) through the bulbospinal tract in the intermediolateral column of the spinal cord to the primary neurons of the sympathetic nervous system (SNS). The sympathetic preganglionic neuron bodies are located in the anterolateral grey matter of the thoracic and lumbar spinal cord from where their axons travel inside the anterior nerve roots to the sympathetic ganglia (Moss and Renz 2000). Most of the sympathetic ganglia lie in the paravertebral chains, which are interconnected and contain rami to the spinal nerves. The postganglionic fibres for the head, neck, trunk, and extremities travel mostly with the somatic nerves. All smooth muscles of blood vessels receive their motor innervation from the fibres of SNS, which control the tonus of blood vessels.

The sympathetic celiac ganglion gives branches to the adrenal medulla. The parasympathetic nervous system (PNS) is cholinergic, whereas the SNS is adrenergic (NOR) except for the adrenal medulla and the sweat glands, which are cholinergic (Moss and Renz 2000).

The baroreceptors of the aorta and carotid arteries sense pressure; when the blood pressure increases, baroreceptors mediate information to the vasomotor centre in the brainstem. This causes deactivation of sympathetic vasoconstrictor fibres and activation of vagal nerve fibres eliciting vasodilatation and decrease in heart rate, cardiac output, and blood pressure. Acute decrease in blood pressure causes activation of efferent SNS via baroreceptors (Blanck and Lee 2000). The nucleus solitarius is the primary central synapse for baroreceptor-mediated reflexes and is an important relay station for peripheral information destined for hypothalamic sympathetic control centres. The nucleus solitarius also projects directly to the intermediolateral nucleus in the spinal cord, the common pathway for preganglionic sympathetic outflow (Blanck and Lee 2000).

Rapid physiological changes in blood pressure occur through the activity of the SNS. Regulatory mechanisms for rapid pressure control consist mainly of very rapidly acting nervous and hormonal mechanisms. The noradrenaline (NOR)-adrenaline (ADR) vasoconstrictor system is a part of the sympathetic mechanism for arterial pressure control. Stimulation of the SNS causes a release of ADR and NOR from the adrenal medulla into the circulating blood, and direct nervous excitation of the blood vessels and the heart. ADR and NOR have throughout the body almost the same effect as direct sympathetic stimulation; their effect lasts up to one or two minutes after cessation of stimulation. NOR stimulates alpha-receptors resulting in increased total peripheral resistance and thereby elevates the arterial pressure. ADR mainly stimulates the beta-receptors and thus increases cardiac contractility, heart rate, and cardiac output more than NOR (Moss and Renz 2000). NOR is also a neurotransmitter in the sympathetic nerve endings. Sympathetic stimulation causes release of the NOR from the sympathetic nerve endings, but the amount is very small and its clinical importance in relation to cardiovascular stimulation is probably slight (Derbyshire and Smith 1984).

B.2.2. Cardiovascular and catecholamine responses

Laryngoscopy and intubation cause a strong cardiovascular and catecholamine (CA) response, which subsequently increases the risk of morbidity and mortality especially for patients with coronary artery disease, hypertension, pre-eclampsia, and cerebrovascular disorders (Prys-Roberts 1984, Thomson 1989, Kovac 1996). Increases in HR and acute hypertension may deleteriously affect myocardial oxygen supply and consumption (Kovac 1996, Roizen 2000). The response is

mediated via the SNS. Plasma CAs show similar changes whether samples are obtained from central venous, peripheral venous or arterial lines (Derbyshire et al 1983). The major stimulus to cardiovascular response during and after laryngoscopy followed by intubation is claimed to be the force exerted by the laryngoscope blade on the base of the tongue or by lifting the epiglottis. When laryngoscopy with intubation was compared to laryngoscopy without intubation, the former did not cause an additional increase in cardiovascular or CA parameters; only HR was further increased (Shribman et al 1987, Cros et al 1991). A reduced stimulus to the oropharynx triggered by laryngoscopy has decreased the cardiovascular response (Kautto 1983, Hawkyard et al 1992, McCoy et al 1995, Kitamura et al 2001). Direct laryngoscopy causes a longer lasting stimulus to the pharynx and more potent changes in cardiovascular and CA response than conventional laryngoscopy and intubation (Cros et al 1991). On the other hand, in effective doses finding studies, laryngoscopy without intubation has clearly been a slighter stimulus than laryngoscopy with intubation (Zbinden et al 1994a, Kazama et al 1997). It appears that the maximal increase in blood pressure occurs with laryngoscopy, but the maximal increase in HR occurs with laryngoscopy followed by endotracheal intubation. The number of techniques of hemodynamic modification is many, but the method may be less important than the final result (Thomson 1989).

B.2.3. Attenuation of the cardiovascular and catecholamine responses

The cardiovascular response may be attenuated by lidocaine, by alpha-2-adrenergic agonists, by vaso-active drugs (vasodilators, calcium channel blocker, and beta-adrenergic blockers), or by increasing the depth of anaesthesia (volatile or IV anaesthetics). However, the most frequently used agents to attenuate cardiovascular and CA response to laryngoscopy and intubation are opioids (Kovac 1996).

Lidocaine has been administered in aerosol form, by laryngotracheal spray, or intravenously in an attempt to attenuate cardiovascular response to laryngoscopy and intubation. Inhaled lidocaine was found to be effective (Sklar et al 1992) and ineffective (Laurito et al 1988) in attenuating the cardiovascular response to laryngoscopy and intubation. In another study combination of laryngotracheal lidocaine spray and IV lidocaine 1.5 mg/kg was found effective in attenuating the cardiovascular response to laryngoscopy and intubation (Stoelting 1977). Lidocaine 1 mg/kg IV appeared to improve intubation conditions with alfentanil (Stevens et al 1997) but did not attenuate (2 mg/kg) the cardiovascular response to laryngoscopy and intubation without an opioid (Pathak et al 1990). There are studies showing lidocaine 1.5 mg/kg IV to be ineffective (Miller and Warren

1990) and effective (Splinter and Cervenko 1989) depending on the time of administration before tracheal intubation. It can be said that the effectiveness of lidocaine to attenuate cardiovascular response to laryngoscopy and intubation is controversial.

Alpha-2-agonists are sympatholytic and stimulate the presynaptic alpha-2-adrenoreceptors, thereby inhibiting the release of noradrenaline and renin. They also inhibit central neural transmission in the dorsal horn (Moss and Renz 2000). Clonidine has been shown to reduce anaesthetic requirements, to improve hemodynamics, and to reduce plasma CAs during anaesthesia (Flacke et al 1987, Howie et al 1996). Dexmedetomidine, a selective alpha-2-adrenoreceptor agonist, also reduces anaesthetic requirements during anaesthesia and attenuates response to laryngoscopy and intubation (Aantaa et al 1990, Aho et al 1992, Jaakola et al 1992).

A direct-acting vasodilator, sodium nitroprusside, decreases blood pressure by reducing peripheral vascular resistance and venous return, while nitro-glycerine causes mainly venodilation. Vasodilators attenuate the rise of blood pressure but not of HR induced by laryngoscopy and intubation (Kovac 1996). Like direct vasodilators, calcium channel blockers attenuate the rise of blood pressure but not of HR induced by laryngoscopy and intubation (Kovac 1996). Furthermore, diltiazem slows elimination of midazolam and alfentanil and may delay tracheal extubation after large doses of these anaesthetic adjuncts (Ahonen et al 1996). Beta-adrenergic receptor blockers have been shown to prevent cardiovascular responses to laryngoscopy and intubation (Prys-Roberts et al 1973). Labetalol, a non-selective alpha- and beta-blocker, has been shown to attenuate cardiovascular response to laryngoscopy and intubation (Leslie et al 1989), especially in patients with pre-eclampsia (Ramanathan et al 1988). Esmolol, a short-acting beta-2-adrenergic receptor-blocking agent, attenuates cardiovascular response as well as alfentanil, but not the CA response to laryngoscopy and intubation (Miller et al 1991, Johansen et al 1998, Maguire et al 2001b). The HR response to the superimposed effect of the operating laryngoscope during laryngomicroscopy was attenuated by esmolol but the blood pressure response was not (Korpinen et al 1997).

The adrenergic response to noxious stimulus can also be blocked by volatile anaesthetics; for this purpose the concept of MAC_{BAR} (minimum alveolar concentration to block the adrenergic response) of volatile anaesthetics has been proposed (Roizen et al 1981). MAC_{BAR} for laryngoscopy and intubation is twice or more higher than MAC for skin incision. However, volatile agents as sole drugs unreliably suppress the cardiovascular response to laryngoscopy and intubation (Yasuda et al 1991, Zbinden et al 1994b); only halothane may be better than other volatile agents in blunting the cardiovascular response to laryngoscopy and intubation (Kautto and Saarnivaara 1983).

Ketamine causes central sympathetic stimulation and increases HR and blood pressure after administration. Cardiovascular responses further increases after tracheal intubation and a significant CA response follow (Gutzke et al 1989, Raza et al 1989, Katz et al 1998). These cardiovascular responses of ketamine during induction of anaesthesia and tracheal intubation can be abolished by opioids (Raza et al 1989, Katz et al 1998).

Propofol and thiopental

Propofol attenuates more efficiently than thiopental the cardiovascular response to tracheal intubation and the subsequent increase of CAs whether using bolus doses (Harris et al 1988, Lingren et al 1993) or infusion regimens (Kashtan et al 1990). On the other hand, the CA response to laryngoscopy and intubation was better attenuated with propofol than with thiopental but there were no difference in the cardiovascular response (Brossy et al 1994). In one study propofol attenuated more efficiently than thiopental heart rate and NOR response to laryngoscopy and intubation but not the arterial pressure response (Coley et al 1989); the reason for this unusual reaction may be that they gave fentanyl before induction of anaesthesia. Increasing plasma concentrations of propofol reduce intraoperative analgesic requirements (Smith et al 1994, Vuyk et al 1995b). This can be related to an assumed analgesic action of propofol at the spinal level (Briggs et al 1982, Uchida et al 1995) and direct central sympatholytic or vagotonic actions (Cullen et al 1987). On the other hand, both propofol and thiopental have been shown to be neutral or hypo-algesic, and to inhibit spinal nociceptive transmission (Jewett et al 1992, Wilder-Smith et al 1995). Propofol attenuates reflex sympathetic responses to hypotension at high doses but reflex responses are preserved with low doses; reflex HR (vagal) responses to hypertensive stimulus are well preserved (Ebert and Muzi 1994). In contrast, thiopental reduces tonic sympathetic nerve activity and nearly abolishes the reflex increase in sympathetic activity that occurs during systemic hypotension. Despite of these effects, laryngoscopy and tracheal intubation during thiopental anaesthesia results in profound increases of sympathetic neural outflow (Ebert et al 1990). The better attenuation of the responses seen after propofol compared to thiopental may also be explained by greater depression of laryngeal reflexes as documented in good laryngeal mask insertion or intubation conditions after propofol alone (Keaveny and Knell 1988, Brown et al 1991), a greater relaxation of vocal cords (Barker et al 1992), or a longer lasting hypotensive effect (Mulier et al 1991). Furthermore, it has been shown that the lack of motor response to noxious stimulus is not an accurate predictor of the ability of an agent to depress hemodynamic reaction (Zbinden et al 1994b, Kazama et al 1997).

To summarize, the above-cited studies show that doses of propofol or thiopental sufficient to induce anaesthesia (losses of eyelash reflex or obeying verbal command) alone do not adequately block the cardiovascular or CA response to laryngoscopy followed by intubation.

Opioids

Opioids have been shown to attenuate cardiovascular and CA responses to laryngoscopy and intubation effectively, but in some studies they have failed to do so (Cros et al 1991). Fentanyl has been effective with increasing doses (Kautto 1982, Giesecke et al 1988, Kazama et al 1997). Alfentanil has been effective in attenuating cardiovascular and CA responses to laryngoscopy and intubation (Crawford et al 1987, Scheinin et al 1989, Saarnivaara and Klemola 1991, Miller et al 1993). Alfentanil in dose of 10 μg/kg efficiently attenuated the cardiovascular response to tracheal intubation in elderly patients (Kirby et al 1988). Fentanyl or alfentanil in a dose ratio of 1:13 (Hynynen et al 1986) and fentanyl or sufentanil in a dose ratio of 7:1 (Thomson et al 1987) have produced similar hemodynamic profiles and clinical courses in patients undergoing coronary artery surgery. TIVA with propofol combined with alfentanil, fentanyl, or sufentanil in a dose ratio of 100:10:1 produced similar cardiovascular stability, but in patients receiving fentanyl the trachea was extubated on an average of 2-3 h later than in those receiving sufentanil or alfentanil (Ahonen et al 2000a). Recovery of patients undergoing minimally invasive coronary artery surgery is significantly shorter and more predictable after TIVA with remifentanil-propofol than with alfentanil-propofol (Ahonen et al 2000b). Alfentanil has been found to attenuate similarly to remifentanil the cardiovascular response to laryngoscopy and intubation (Klemola et al 2000, Maguire et al 2001a, Habib et al 2002), but in another study remifentanil was better than alfentanil (Wiel et al 2003).

Sufentanil has been similar to fentanyl in attenuating hemodynamic and CA responses to surgical stimulation (Kietzmann et al 1991). Sufentanil and remifentanil after midazolam premedication resulted in a similar and clinically acceptable effectiveness in blunting the cardiovascular changes during anaesthesia (Thomson et al 2000, Casati et al 2001). During major abdominal surgery, remifentanil appears to offer superior intra-operative hemodynamic stability during stressful surgical events compared with alfentanil, but the incidence of intra-operative hypotension and bradycardia was higher in the remifentanil group (Schüttler et al 1997). Remifentanil can be very useful for attenuation of brief but noxious stimuli because it has a rapid onset and offset of action. Remifentanil has been used with higher infusion rate or bolus dose before and during laryngoscopy and intubation and reduced infusion thereafter (Philip et al 1997, Hall et al 2000). Remifentanil offers excellent hemodynamic control for brief, intense outpatient procedures

performed in high-risk patients (Mackey et al 2000). Remifentanil infusion also produced better cardiovascular stability than fentanyl boluses during rigid bronchoscopy (Prakash et al 2001). Compared to other opioids, remifentanil can more reliably suppress autonomic, hemodynamic, and somatic responses to noxious stimulation and allows the most predictable and rapid trouble-free emergence from anaesthesia (Patel and Spencer 1996).

Remifentanil attenuated better than alfentanil the cardiovascular response to the longer lasting stimulus of the base of the tongue and the pharynx caused by laryngeal microscopic procedures (Pandazi et al 2003). In children, fentanyl seemed to provide a more stable hemodynamic profile prior to laryngoscopy and tracheal intubation when compared to remifentanil (Abdallah et al 2002). In obese patients, fentanyl, alfentanil, and remifentanil at equipotent doses attenuated cardiovascular response to tracheal intubation similarly (Salihoglu et al 2002). In another study, sufentanil and remifentanil were similar in controlling hemodynamics during carotid surgery but remifentanil was better during tracheal intubation (Mouren et al 2001).

The most commonly used dose of remifentanil at induction of anaesthesia that has produced best results in attenuating cardiovascular and CA response to intubation and surgery is 0.5-1.0 μg/kg bolus followed by 0.5 μg/kg/min infusion before tracheal intubation and thereafter about 0.25 μg/kg/min adjusted to clinical signs (Hogue et al 1996, Thompson et al 1998, Hall et al 2000). For the same purposes, alfentanil has been used at a bolus of 20 μg/kg followed by 2 μg/kg/min infusion, which is then reduced to 1 μg/kg/min, respectively (Philip et al 1997).

B.3. Clinical measures of adequate anaesthesia

B.3.1. Physiology and neuroanatomy of the clinical measuring points

Measures of hypnosis

Pupillary light reflex: The irido-constrictor fibres originate in the nucleus of third cranial nerve in the midbrain. Entering the third nerve, they run to the ciliary ganglion and the circular muscle of the iris. If one eye is exposed to light, a constriction of both pupils normally occurs, i.e. a direct and consensual reaction. It is not an all-or-none reaction. An impairment of the reaction becomes evident as a reduction of its normal amplitude. Loss of the reaction of the pupil to light is a result of a lesion involving the reflex pathway at some point. Paralysis of the irido-constrictor fibres either in the nucleus of the third nerve or in the course of the nerve itself causes dilatation of the pupil that fails

to react to light and accommodation (Mason and Kandel 1991). On the afferent side, the reflex runs via the visual pathways to the superior colliculus. From there, pathways run to the irido-constrictor part of the third nucleus on both sides, thereby enabling the light stimulus entering one eye to evoke a contraction of both pupils. For this reason, a lesion that impairs conduction in one optic nerve will diminish or abolish the reaction of both pupils to light. A lesion in the neighbourhood of the cerebral aqueduct of Sylvius may have the same effect, usually bilaterally, while, as stated above, a lesion involving the third nerve at any point in its course may interrupt the efferent pathway for the reflex to the ipsilateral eye (Mason and Kandel 1991). The pupillary light reflex is tested by allocating a flashlight to one eye and observing both pupils for constriction. More precisely, the pupillary light reflex can be quantified by using an infrared pupillometer (Belani et al 1993). The pupillary reflex dilatation, as a response to noxious stimulus, is primarily a sympathetic reflex (Yang et al 2003).

Corneal reflex: The cornea has a dense sensory innervation. The nerve supply to the cornea is derived from the first branch of the fifth cranial nerve (trigeminal nerve). Normally the sensations that can be evoked by corneal stimulation are pain, touch and pressure. The afferents of the corneal reflex are Aδ-fibres. The reflex circuit descends through the spinal trigeminal tract and enters a polysynaptic chain of interneurons in the lateral reticular formation and finally projects to the facial motoneurons bilaterally (Ongerboer de Wisser 1983). Differences exist between corneal and blink reflexes (Berardelli et al 1985); they do not share the same interneurons. The corneal reflex is relayed through fewer synapses and there are indications that the circuit of corneal reflex is specifically nociceptive (Cruccu et al 1991). The corneal reflex habituates less than the blink reflex, which may be due to fewer synapses and less modulation by cortical activity. It is one of the principal reflexes mediated by the trigeminal nerve and is tested by applying a wisp of cotton wool to the cornea. The corneal reflex can also be evoked by electrical stimulation using special electrodes (Mourisse et al 2003). A stimulus applied to one eye normally causes blinking of both eyes. Loss of the reaction of the cornea to touch is the result of a lesion involving the reflex pathway at some point. If the corneal sensibility is diminished, this response will be reduced, or may be absent. Weakness of the orbicularis oculi muscle will cause diminution or loss of the corneal reflex on the side stimulated even though corneal sensibility is normal, but normal blinking will occur on the opposite side. Disappearance of the corneal reflex represents the same level of sedation as the R2 component of the blink reflex (see below) as measured by the OAA/S scale (Mourisse et al 2003).

Eyelash reflex (R2 reflex): The human blink reflex has three components (R1, R2, and R3). The R1 component has short latency, is one sided, and is not clinically visible. The circuit is intrapontine and consists of 2-3 interneurons. The R2 component is the clinically visible reflex, is more

prolonged, bilateral, and causes actual contraction of the orbicularis oculi muscle. The R3 component has the longest latency, is bilateral, and occurs only after strong stimulation. The R3 circuit may be nociceptive (Cruccu et al 1991). The blink reflex (R2) is mediated by Aβ-fibres. The reflex circuit descends through the spinal trigeminal tract and enters a polysynaptic chain of interneurons in the lateral reticular formation and finally projects to the facial motoneurons bilaterally. The suppression of the blink reflex is related to its polysynaptic circuit through the reticular formation, where GABA and benzodiazepine receptors are coupled. Corticoreticular projections are also believed to play a role (Ongerboer de Wisser 1983). The eyelash reflex is tested by brushing the eyelashes with a moving object (e.g. a finger). The blink reflex can also be evoked by electrical stimulation of the supraorbital nerve (Mourisse et al 2003). The stimulus applied to one eye normally causes blinking of both eyes. Loss of the reaction of the eyelash to touch is the result of a lesion involving the reflex pathway at some point. If eyelid sensibility is diminished this response will be reduced, or may be absent. Weakness of the orbicularis oculi muscle will cause diminution or loss of the eyelash reflex on the side stimulated even though eyelid sensibility is normal, but normal blinking will occur on the opposite side. A normal blink reflex is dependent on normal neuromuscular transmission; i.e. muscle relaxants abolish the blink reflex. The components of the blink reflex have different sensitivity to electrical stimulus during different levels of sedation as measured by OAA/S scale (Mourisse et al 2003).

Loss of counting involves higher central areas and is not related to any spinal reflexes such as eyelash, corneal, and pupillary light reflexes. The patient is asked to count slowly (a verbal task) as long as he can from the start of injection/infusion of the hypnotic drug; he is not repeatedly asked to count and will not hear anything. Loss of counting has been shown represent a shallower level of anaesthesia than loss of eyelash reflex or loss of obeying verbal command (de Grood et al 1985, Dunnet et al 1994).

Syringe dropping, as counting, affects more central functions compared to eye reflexes. Patient is asked to hold a syringe from its hub (mostly 20-ml syringes) between the thumb and forefinger for as long as he is able (a motor task). Again, nobody repeatedly asks him to do so. Syringe dropping has been shown to represent a shallower level of anaesthesia than loss of eyelash reflex (Leslie et al 1996).

Loss of obeying verbal command affects also central functions. The patient is asked to "squeeze my hand" or "open your eyes" at 10-20 s intervals from the start of injection/infusion of the hypnotic drug. The patient must first hear the request (the eighth cranial nerve), understand the request (the cortex), the cortex must give a command for the hand to squeeze, and finally, the hand

carries out the request. Because of the above-mentioned long chain of activity, the obeying of verbal command is a more complicated task than holding the syringe or counting. It has been shown that loss of response to verbal command and loss of eyelash reflex represent a similar level of anaesthesia (Newton et al 1990).

Measures of analgesia

Pain and avoidance reaction: The sensory afferent fibres in the peripheral nerves are the axons of the ganglion cells of the spinal dorsal root ganglia or the corresponding ganglia of the sensory cranial nerves. Pain fibres in the peripheral nerves are A-δ- and C-fibres. They conduct mechanical, thermal, and chemical pain impulses. They enter the posterior horn of the spinal cord through the dorsal root of the spinal nerve (Bevan 1999). There they communicate (synapse) with dorsal root cells, projection neurons, and excitatory or inhibitory interneurons. Projection neurons transfer pain information to the higher parts of the CNS. Excitatory interneurons transfer nociception to the projection neurons, to other interneurones, or to the motor neurons that supply spinal reflexes. The most important parts of the dorsal horn in pain transmission are lamina I and V. From the dorsal horn the pain fibres cross the midline, enter the anterolateral column of the spinal cord, and turn upward constituting the spinothalamic tract ending in several different nuclei of the medulla and thalamus. Spinoreticular fibres are also important in pain transmission and they rise with spinothalamic fibres in the anterolateral part of the spinal cord to the formatio reticularis and further to the medial nuclei of the thalamus. From the thalamus, pain fibres rise to the cerebral cortex where pain is perceived and affect is added (Craig and Dostrovsky 1999). The movement reaction to a noxious stimulus is mainly a spinal reflex (Rampil et al 1993), but in addition to action at the spinal level, anaesthetics can diminish the transmission of noxious input to the brain (Antognini et al 2000).

An electrical tetanic stimulation may be the most commonly used pain stimulus. It is applied via self-adhesive or needle electrodes to the lower or upper limb. It is considered as abolished when purposeful somatic movement has ceased as reaction to stimulation. The advantage is that it can be standardized and repeated, and the disadvantage is that it also stimulates sensory fibres and is not purely noxious (Tran et al 2002). The electrical tetanic stimulation is a useful alternative to skin incision as it can be repeated and motor responses to both the tetanic stimulation as well as to the skin incision are abolished with similar plasma concentration of propofol and end tidal isoflurane concentration (Zbinden et al 1994a, Kazama et al 1997).

A pain *stimulus to the nasal cavity* is mediated by the first division of the trigeminal nerve; branches of the nasociliary nerve supply the septum and the lateral wall of the nasal cavity. The sensory fibres from the trigeminal nerve involved in the appreciation of mechanical or thermal pain or touch enter the spinal tract and nucleus of trigeminal nerve. From the nucleus of trigeminal nerve relay fibres cross the midline to the opposite side of the medulla forming the trigeminothalamic tract that is associated with the spinothalamic tract in the pons. All these sensory pathways pass upwards to the posterior part of the ventral nucleus of the thalamus. From there they run to the cerebral cortex of the postcentral gyrus, and partly to the precentral gyrus (Craig and Dostrovsky 1999).

Laryngoscopy and intubation: Laryngoscopy causes a strong pressure to the base of the tongue and stretches pharyngeal structures. Fibres for sensibility of the posterior part of the tongue, the tonsils, and the pharynx are supplied by the ninth cranial nerve (glossopharyngeal). A portion of the afferent fibres from the pharynx is carried by the tenth cranial nerve (vagus). The sensory and motor fibres of the trachea are carried by the vagus nerve. The motor fibres arise from nucleus ambiguous, which is an elongation of the grey matter situated deep in the medulla. The motor fibres are distributed through the glossopharyngeal, vagus, and accessory nerves to the muscles of the palate, pharynx, and larynx. The terminal branches of the vagus nerve innervate all the muscles of the larynx except for the cricothyroid muscle (external laryngeal branch of the vagus). The internal laryngeal branch is the principal sensory nerve of the larynx (Role and Kelly 1991). Thus, the glossopharyngeal nerve mediates the sensory stimulus of the laryngoscopy and the vagus nerve mediates that of the intubation. They mediate the sensory information to the pons and from there the reflexive avoidance reaction results.

In summary, the avoidance reaction to pain is mainly spinal (brain stem) reflex where afferent pain pathways communicate with motor neurons at the spinal or medullar level causing movement of the head, trunk, hand, or foot. Modulation of pain happens in the thalamus, formatio reticularis and cortex.

Other measures

The sensory fibres that perceive impulses concerned with the appreciation of *vibration*, posture and passive movements are thick A-α- and A-β-fibres. They enter the spinal cord with pain fibres through the dorsal root. There they pass upwards in the posterior column of the same side, moving gradually towards the midline constituting the fasciculus gracilis (lower limb) and fasciculus cuneatus (upper limb). They terminate in the medulla in the nuclei gracilis and cuneatus. From these nuclei the second fibres cross to the opposite side in the sensory decussation, after which they

continue as the medial lemniscus and pass upwards to the thalamus. The medial lemniscus is joined in the pons by the fibres from the principal sensory nucleus of the trigeminal nerve. From the thalamus, fibres run to the cerebral cortex of the postcentral gyrus, and partly to the precentral gyrus (Martin and Jessell 1991). Vibration stimulus induces EEG bursts during BSP level of isoflurane anaesthesia in humans (Yli-Hankala et al 1993). Vibrotactile stimulation also elicits a significant increase of the regional cerebral blood flow in the thalamus and in several cortical regions; propofol reduces the increase of the cerebral blood flow induced by vibrotactile stimulation in a dose dependent manner first at the cortex level and later at the thalamus level (Bonhomme et al 2001).

Sense of smell: The filaments of the olfactory nerve (the first cranial nerve) carry impulses from smell receptors in the nasal mucosa to the olfactory bulb, from which the olfactory tract conveys them along the floor of the anterior fossa of the skull to the olfactory area of the cerebral cortex in the neighbourhood of the uncinate gyrus (Dodd and Castellucci 1991). As a result, when smell is used as a measure of unconsciousness, the chain of action starts with instillation of the substance to a nostril so the patient/animal may perceive the smell in the olfactory cortex, then the cortex gives the command for an evasive movement, and finally, the patient obeys the command. Odorized air blown into a nostril elicits a gamma wave response bilaterally in the dentate gyrus and shows that the hippocampus plays a primary role in an olfacto-motor mechanism (Vanderwolf 2001). Therefore the avoidance reaction to an unpleasant smell is more a cortical function than for example that for tail clamping. Part of the evasive movement to smell can be conducted via irritation of sensory fibres of the trigeminal nerve branches in the nasal mucosa.

B.3.2. Clinical measuring points in anaesthesia monitoring

Hypnotic and analgesic measuring points determine the doses and concentrations of anaesthetic agent at which patients are both unconscious and pain free.

B.3.2.1. Hypnosis

Dropping a syringe and loss of the eyelash reflex have been widely used as simple indicators of LOC (Jacobs and Reves 1993). With increasing levels of anaesthetic medication, loss of reaction to verbal command (LVC) appeared simultaneously with or a bit later than loss of the eyelash reflex, both followed at a deeper level by loss of the corneal reflex (Schwilden et al 1985). Using EEG median power frequency (MPF) and propofol infusion ED_{50} and ED_{95} values of propofol for the

suppression of response to verbal command were similar to the values for the suppression of the eyelash reflex (Forrest et al 1994). However, ED_{95} of propofol and thiopental for loss of the eyelash reflex was somewhat higher than ED_{95} for LVC (Naguib et al 1992). EC_{50} and EC_{95} values of propofol for LVC were higher than those for loss of the eyelash reflex (Vuyk et al 1992). Additional different EC_{50} values of propofol for LVC have been reported (Vuyk et al 1992; higher, Forrest et al 1994; lower). ED_{50} and ED_{95} of propofol for LVC and eyelash reflex did not differ significantly and loss of the corneal reflex was not achieved even at doses that abolished reaction to supraorbital pain (Dunnet et al 1994). On the other hand, with midazolam the corneal reflex disappears before the patient is unconscious (Mourisse et al 2003). It has been reported that loss of the eyelash reflex and pupillary light reflex correspond to a deeper level of anaesthetic medication than syringe dropping, and to a similar or deeper level than LVC (Forrest et al 1994, Leslie et al 1996). Ablation of reflex responses has been shown to occur below the level of the cortex unrelated to the state of consciousness (Rampil et al 1993, Rampil and King 1996). Monitoring of blink and corneal reflexes generally could probably measure the suppression of reflex activity (Mourisse et al 2003). Recently, LVC has been used mostly to test LOC (Zbinden et al 1994a, Kazama et al 1997, Iselin-Chaves 2000).

It might be concluded from the above-cited studies that the loss of response to verbal command, loss of pupillary light reflex, and loss of the eyelash reflex are equal for estimation of LOC during induction of anaesthesia. Syringe drop and loss of counting obviously represents levels of sedation. More studies are needed to assign loss of the corneal reflex in its appropriate place. As ablation of reflex responses occurs below the level of the cortex, measures of brain stem or spinal cord function might perform better in predicting movement response to noxious stimuli than EEG parameters (BIS, SEF95) (Leslie et al 1996).

In animals loss of the righting reflex has been used as a measure of LOC; i.e. loss of ability to keep the sternal recumbent position when the operating table is tilted 20^{o} laterally.

B.3.2.2. Analgesia

It has been shown that laryngoscopy without intubation is as strong a stimulus as tetanic stimulation (10 s, 50Hz, 50mA) or skin incision (slightly stronger) and is a stronger stimulus than trapezius muscle squeeze, but the strongest stimulus is laryngoscopy with intubation (Zbinden et al 1994a). In another study EC_{50} of propofol was the same at loss of response to tetanic stimulation (10 s, 50Hz, 80 mA), laryngoscopy, or skin incision; again, laryngoscopy with intubation was the strongest

stimulus (Kazama et al 1997). ED_{50} and ED_{95} of propofol for loss of the reaction to supraorbital pain did not produce loss of corneal reflex (Dunnet et al 1994). The pupillary reflex dilatation has revealed a more dramatic response to painful electrical stimulation than did hemodynamic indicators (Larson et al 1993, Leslie et al 1996), but there were no significant differences in performance between effect-site concentration and Bispectral Index, 95% spectral edge frequency, pupillary reflex amplitude, or systolic arterial blood pressure (Leslie et al 1996). The pupillary reflex dilatation as a response to noxious stimulus is primarily a sympathetic reflex but it requires a supraspinal component for completion (Yang et al 2003). Recently, it was shown that the decrease in pupil response to a noxious stimulus was a better measurement of the progressive increase of the target effect-site concentration of remifentanil than hemodynamic measurements (Barvais et al 2003).

It has been reported that loss of corneal reflex, loss of reaction to trapezius muscle squeeze, and loss of response to skin incision all defined the same depth of thiopental anaesthesia (Becker 1978, Becker and Tonnesen 1978). In another study the EC_{50} of thiopental for tetanic stimulation (10s, 50Hz, 50mA) was slightly lower than EC_{50} for trapezius muscle squeeze, the EC_{50} for laryngoscopy was higher, and the highest EC_{50} was for laryngoscopy followed by intubation (Hung et al 1992). Vuyk et al (1993) also found that laryngoscopy with intubation was the strongest stimulus, but opening of the peritoneum was nearly as strong; these responses were better attenuated with alfentanil-propofol than with alfentanil-nitrous oxide anaesthesia**.**

A conclusion that may be drawn is that it seems that loss of response to trapezius muscle squeeze, electrical tetanic stimulation, and skin incision are equal in estimating loss of movement reaction to noxious stimulus. Therefore, tetanic stimulation can be used as an alternative to skin incision when studying differences of anaesthetic drug action on pain stimulus. Furthermore, tetanic stimulation can be standardized and repeated whereas standardizing skin incision or laryngoscopy with intubation is more complicated. Also, laser stimulation (heat) has been used as a noxious stimulus (Petersen-Felix et al 1996) and can also be standardized. However, special and expensive equipment is needed whereas equipment for tetanic stimulation is inexpensive (muscle relaxant monitor). One advantage of laser stimulation is that it enables the selective stimulation of pain fibres (Tran et al 2002), whereas electrical tetanic stimulation irritates both pain (Aδ, C) and sensory (Aβ) fibres.

In animals, the most frequently used analgesic measuring point is tail clamping where an alligator clip or haemostat is applied to the tail and moved back and forth (Drummond 1985, Rorarius et al 1993). Tail clamping has been represented as the most noxious stimulation that is

clinically reproducible and not excessively traumatic in animals (Eger et al 1965). Electrical stimulation has been proposed as a substitute for tail clamping; stimulation of 15 V with needle electrodes in the tail and tail clamping produced comparable results (Laster et al 1993). Also, laser stimulation can be used in animals (Danneman et al 1994).

B.3.2.3. Electroencephalography (EEG)

EEG is a method of recording changes of electrical potentials in the brain. The recordings are usually made using electrodes applied to the scalp. The spontaneous electrical activity of the brain consists of potential variations, which are called waveforms. These waveforms are registered as potential differences between two EEG electrodes. The frequencies of the EEG waves are highly variable. The frequencies are traditionally divided into different bands: delta (< 4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (> 13 Hz) (Black et al 2000). The field from which waves arise must be close to the electrode and large enough to be seen in the EEG. All EEG waves arise in the cortex of the brain. Functions of the deeper parts of the brain can be estimated only indirectly from their synchronous effects to the EEG. However, all brain potentials do not become evident in the surface of the head. The cortex of the brain is heavily folded (gyri) causing a large part of the cortex to be too far away from the surface of the head resulting in difficulties in its registration (Black et al 2000).

Although the EEG is not, in and of itself, a clinically useful measure of adequate anaesthetic medication, it offers several experimental advantages over clinical measures of drug effect. The EEG is a nearly instantaneous and continuous measuring device that provides an objective and reproducible measure of drug effect. The benefits of using the EEG are specifically that it tells us of the time course of clinically important anaesthetic drug effects and about the relative potency of the drugs. The EEG predicts a more rapid and evanescent effect from a bolus of remifentanil and alfentanil compared with fentanyl or sufentanil. The EEG changes correlate with the observed time course of effect of these drugs in the operating room for such effects as ventilatory depression, sedation, and analgesia (Egan et al 1996).

IV anaesthetics generally have biphasic effects on the EEG, as manifested first by an increase of alpha and beta activity followed by an increase of delta activity and decrease of alpha and beta activity. Propofol and thiopental, when given as a bolus or infusion first produce increased alpha and beta activity of the EEG, then theta and delta activity is increased (Hung et al 1992, Veselis et al

1992, Kuizenga et al 2001); at higher doses BSP is achieved, and finally total suppression of EEG is seen using both drugs (Hung et al 1992, Illievich et al 1993).

Alfentanil and remifentanil are not reliable in producing unconsciousness but they do produce changes in the raw EEG. The changes are identical to all potent μ-agonists and consist of decreasing frequency and increasing amplitude of the raw EEG waves, culminating eventually in pronounced delta-wave activity at maximal drug effect but opioids do not induce BSP (Scott et al 1985, Scott et al 1991, Egan et al 1996). Alfentanil and remifentanil produce similar rapid onset of EEG peak effect when administered in sufficient doses indicating fast equilibrium between plasma and effect-site concentrations (Egan et al 1996). Fentanyl exhibits slower equilibrium time (Scott et al 1985).

B.3.2.3.1. Burst suppression pattern (BSP)

BSP represents a very abnormal cortical activity, where 95% of cortical cells are silent during suppression (Steriade et al 1994). Obviously, at least cerebral cortex is incapable of participating in information processing such as remembering or other cognitive processing in this situation, i.e. the patient is deeply unconscious. Different anaesthetics produce morphologically very different BSPs (Akrawi et al 1996, Watts et al 1999, Jäntti et al 2002) indicative of their different mechanisms of action. In healthy brain, BSP is induced only by high concentrations of anaesthetics (Hung et al 1992, Illievich et al 1993, Hoffman and Edelman 1995). Inhaled anaesthetics induce BSP at approximately 1.5 MAC (Hoffman and Edelman 1995, Watts et al 1999). Thiopental and propofol induce BSP at concentration of approximately 30-40 μg/ml (Hung et al 1992) and 8-9 μg/ml (lllievich et al 1993), respectively. Thiopental and propofol induce BSP near the EC_{50} of suppression of a noxious stimulus (Hung et al 1992, Shanks et al 1993, Kazama et al 1997). A higher EC_{50} of propofol without adjuvant drugs for suppression of reaction to skin incision has been reported (Smith et al 1994). The EC_{50} of suppression of a noxious stimulus for IV anaesthetics has been used as an equivalent to 1 MAC of inhaled anaesthetics. If this is granted, the above-mentioned studies show that at BSP level, patients are at different levels of anaesthetic medication with inhaled than with IV anaesthetics but at the same level with propofol and thiopental. During BSP induced by inhaled anaesthetics, vibration, auditory, visual, or somatosensory stimuli can evoke bursts (Yli-Hankala et al 1993, Hartikainen et al 1995), but this does not happen during IV anaesthesia.

Tracheal intubation performed during BSP induced by etomidate produced minimal changes in cardiovascular reactions and in intracranial pressure (Modica and Tempelhoff 1992). Propofol

infused at a rate sufficient to suppress the EEG does not depress the heart or excessively prolong emergence from anaesthesia after cardiopulmonary bypass and deep hypothermic circulatory arrest (Stone et al 1996).

C. PURPOSE OF THE STUDY

1. To evaluate propofol, thiopental, and ketamine infusion anaesthesia in rabbits and to find ED_{50} and EC_{50} at hypnotic and analgesic end-points in rabbits (I).

2. To compare the cardiovascular and catecholamine responses to tracheal intubation with propofol or thiopental after bolus and infusion doses (II, III), and the superimposed noxious stimulus of prolonged laryngoscopy during laryngomicroscopy (II).

3. To test the hypothesis, that using an objective measure of depth of anaesthesia like BSP instead of clinical signs would help to decide, whether there is a difference between thiopental and propofol in their ability to suppress the cardiovascular and catecholamine response to laryngoscopy with intubation (III).

4. To determine the effective doses and concentrations of propofol and thiopental with and without remifentanil (IV) at hypnotic, analgesic, and EEG-end-points (III, IV).

5. To determine the concentrations of thiopental and propofol at BSP (III, IV), to describe the differences of BSP with thiopental and propofol IV anaesthesia, and to develop an algorithm for automatic detection of BSP (V).

D. MATERIAL AND METHODS

D.1. Patients and experimental animals

The designs of our studies were approved either by the Ethics Committee of South Karelia Central Hospital, the Tampere University Hospital, or by the Ethics Committee for studies on laboratory animals of the University of Tampere Medical School. Informed written consent was obtained from all patients.

One hundred and forty-three healthy (ASA I-II) patients (54 male, 89 female, mean age 42 yr, range 18-64 yr) participated in the studies. Seven patients with incomplete data were excluded from the final analysis. The experimental animal study (I) included 9 New Zealand White rabbits. Study I was carried out at the Department of Biomedical Sciences of the University of Tampere Medical School. Study II was performed in Tampere University Hospital, and all other studies at the Department of Anaesthesia, South Karelia Central Hospital. The signal processing of study V was carried out at the Information Processing Laboratory of Oulu University. Mathematical and signal processing methods of study V are not included in this thesis. All studies were randomized (Table 1).

D.1.1. Experimental animals

Nine New Zealand White male rabbits were used in study I. All rabbits were in good health and examined by a veterinarian before the start of the study. They were housed individually in stainless steel cages and had free access to standard rabbit pellets and tap water until the induction of anaesthesia.

D.1.1.1. Rabbit anaesthesia

No premedication was used. Each rabbit served as its own control and was given propofol, thiopental or ketamine in a randomized fashion with an interval of at least 7 days. Reactions to ammonia vapour instillation and tail clamping were tested in different sessions. During ammonia vapour sessions as well as in tail clamping session's loss and return of the righting reflex was recorded. Thus each rabbit was anaesthetized six times. After local anaesthesia to the basis of the ear, the central auricular artery and a marginal ear vein were cannulated with 22-gauge needles that

were fixed to the ear with adhesive tapes. Anaesthesia was induced with an infusion of the study drug at 30 ml/h using a syringe pump (Braun Infusomat, Medical Braun, Melsungen, Germany). The infusion rate had been chosen to provide a slowly increasing plasma level of the anaesthetic drugs. The concentrations of the drugs were 25 mg/ml for thiopental, 10 mg/ml for propofol, and 20 mg/ml for ketamine. The rabbits breathed spontaneously during the study. Supramaximal stimuli were applied to the rabbits at 20 s intervals after they had lost the righting reflex. The infusion was stopped at loss of reaction to the supramaximal stimulus. After the recovery of the righting reflex the animal was decannulated and brought back to its cage.

Table 1. Study designs, subjects, and tested end-points in different studies.

Study	Study design	Number of subjects	Subjects	Tested end-points
I	Randomized, no premedication	9	Rabbits	Righting reflex, Ammonia vapour, Tail clamping
II	Randomized, premedicated	20 (four excluded)	Patients	Tracheal intubation, Prolonged noxious stimulus to the pharynx
III	Randomized, no premedication	60 (two excluded)	Patients	Eyelash, pupillary reflex, Burst suppression of EEG Tracheal intubation,
IV	Randomized and blinded, premedicated	45	Patients	Counting, Verbal command, Tetanic stimulation, Burst suppression of EEG
V	Randomized, no premedication	18 (one excluded)	Patients	Burst suppression of EEG

D.1.2. Surgical patients

A mixture of promethazine 0.7 mg/kg and pethidine 0.7 mg/kg was used as intramuscular premedication in study II and glycopyrronium 4 μg/kg was given before induction of anaesthesia. No premedication or anticholinergics were used in studies III and V. Patients were premedicated with oral diazepam 0.1 mg/kg in study IV but no anticholinergics were used. All intubations were done with Macintosh blades.

D.1.2.1. Anaesthesia methods

Study II. Twenty patients scheduled for elective laryngomicroscopy were studied. Patients were randomly allocated by selection of sealed envelopes to one of two groups of 10 patients each: propofol or thiopental. An arterial line was inserted for monitoring and drawing of blood samples. Alfentanil 17.5 μg/kg was given 1 min before induction of anaesthesia with propofol 2 mg/kg or thiopental 5 mg/kg. The bolus was followed by a fixed rate infusion of propofol 12 mg/kg/h or thiopental 18 mg/kg/h until the end of the operation. Suxamethonium 1 mg/kg was used to facilitate tracheal intubation with a special double lumen plastic catheter. One lumen of the catheter was connected to the jet ventilator while the other served as a monitoring line. Muscle relaxation was maintained with an infusion of suxamethonium 8-64 mg/min according to the activity of the laryngeal muscles as observed by monitoring the airway pressure curve and by the surgeon's assessment. Ventilation throughout the procedure was with 100% oxygen at 20 breaths/min. The surgical procedure began 5 min after tracheal intubation. Arterial blood samples (5 ml) for ADR and NOR determinations were collected, and heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressure were recorded simultaneously at 1) baseline, 2) 1 min and 3) 5 min after tracheal intubation, and 4) immediately, 5) 2.5 min, 6) 5 min and 7) 10 min after insertion of the operating laryngoscope (OL), and 8) immediately, 9) 2.5 min and 10) 5 min after removal of OL, and 11) immediately and 12) 5 min after arrival in the recovery room, and 13) when patients had been estimated as fully awake.

Study III. Sixty patients scheduled for elective surgical procedures were studied. Patients were randomly allocated by selection of sealed envelopes to one of four groups of 15 patients each: propofol bolus, thiopental bolus, propofol infusion, or thiopental infusion. An arterial line was inserted for monitoring and drawing of blood samples. Anaesthesia was induced in the bolus groups

either with propofol 2.5 mg/kg or thiopental 5 mg/kg injected over 20 s, and additional doses of propofol 0.5 mg/kg or thiopental 1 mg/kg were given at 30 s intervals until loss of eyelash and pupillary light reflexes. In the infusion groups, anaesthesia was induced either by infusion of propofol 30 mg/kg/h or thiopental 75 mg/kg/h until burst suppression was achieved. The EEG was monitored using a Neuropak 8 (Nihon Kohden, Japan) evoked potential measuring system. After onset of BSP, the infusion of propofol was decreased to 20 mg/kg/h and that of thiopental to 37.5 mg/kg/h. The aim was to maintain the BSP (2-5 s suppressions between bursts) until the trachea was intubated. If mean blood pressure decreased below 60 mmHg, 3 mg of ethylphenylephrin (Effortil®, Boehringer, Germany) was given IV. One minute after the last bolus dose or one minute after the onset of BSP, rocuronium 0.6 mg/kg was used to facilitate tracheal intubation. Duration of intubation was recorded. After intubation in the BSP groups, the lungs were ventilated with 30% oxygen in air and anaesthesia was continued with propofol 15 mg/kg/h or thiopental 25 mg/kg/h for 5 minutes. Thereafter anaesthesia was continued with 65% nitrous oxide in oxygen, fentanyl, and isoflurane, which was also the maintenance in the bolus groups. Arterial blood samples for ADR and NOR determinations were collected 1) at baseline, 2) before tracheal intubation, and 3) 1 min, 4) 2 min and 5) 5 min after tracheal intubation. HR, SAP and DAP were registered continuously and recorded 1) on the ward, 2) before induction of anaesthesia, 3) lowest after induction, 4) pre-intubation, and 5) highest, 6) 30 s, 7) 1 min, 8) 2 min and 9) 5 min after tracheal intubation. Arterial blood samples for propofol and thiopental determinations in the infusion groups were collected 1) 5 min after infusion started, 2) at the onset of BSP, 3) 1 min after intubation, 4) at the end of infusion, and 10, 40 and 120 min after infusion was stopped with propofol, and 20, 60 and 240 min with thiopental, respectively.

Study IV. Forty-five patients scheduled for elective surgical procedures were studied. Patients were randomly allocated by selection of sealed envelopes to one of three groups of 15 patients each: placebo, low dose remifentanil, or high dose remifentanil. All patients received a bolus of 0.05 ml/kg over 15 s followed by an infusion of 1.5 ml/kg/h of the study drug via a syringe pump (Perfusor, Braun Melsungen, Germany). In the placebo group, the fluid was physiologic saline. In the low dose group the concentration of remifentanil was 5 μg/ml and in the high dose group 20 μg/ml, respectively. Patients and the investigating anaesthetist were blinded to the identity of the fluids. One minute after the start of infusion of the study drug anaesthesia was induced by intravenous infusion of propofol at a rate of 30 mg/kg/h until the onset of BSP. Patients were asked to evaluate infusion pain at the infusion site (no pain, mild, moderate, or severe pain). The EEG was

monitored using the EEG module of an S/5 anaesthesia monitor (Datex-Ohmeda, Espoo, Finland). After onset of BSP the infusion rate of propofol was decreased to 18 mg/kg/h and rocuronium 0.6 mg/kg was given to facilitate tracheal intubation. The purpose was to maintain the EEG at BSP level (2-5 s suppression between bursts) to the end of the infusion. If mean blood pressure decreased below 60 mmHg, 3 mg of ethylphenylephrin was given IV. After tracheal intubation patients' lungs were ventilated with 30% oxygen in air and anaesthesia was continued with infusion of the study drug at 1.5 ml/kg/h and propofol 18 mg/kg/h for at least five minutes. Four end-points were recorded 1) loss of counting, 2) loss of obeying verbal command, 3) loss of reaction to tetanic electrical stimulation, and 4) the onset of BSP. Time, cumulative propofol dose, venous plasma concentration of propofol, and BIS values were recorded at the attainment of each end-point. ED_{50} and EC_{50} of propofol were calculated for each end-point. Venous blood samples from a large antecubital vein (on the non-infusion arm), were collected for propofol determinations at the attainment of each end-point and just before tracheal intubation and at the end of propofol infusion.

Study V. Eighteen patients scheduled for elective surgical procedures were studied. Patients were randomly allocated by selection of sealed envelopes to one of two groups of 9 patients each: propofol or thiopental. Anaesthesia was induced either with infusion of propofol 30 mg/kg/h or with thiopental 75 mg/kg/h. The EEG was monitored using a Neuropak 8 (Nihon Kohden, Japan) evoked potential measuring system. When BSP was detected, the infusion rate was decreased to 20 mg/kg/h with propofol and to 37.5 mg/kg/h with thiopental. Infusion rate was maintained unchanged for five minutes. The aim was to maintain BSP until the end of the study. Patients were given rocuronium 0.6 mg/kg to facilitate tracheal intubation. After tracheal intubation, the propofol infusion rate was decreased to 15 mg/kg/h and that of thiopental to 25 mg/kg/h. Infusion of anaesthetics was discontinued five minutes after tracheal intubation. Anaesthesia was continued with isoflurane and fentanyl as needed.

D.2. Trial designs

The design of all human studies was open and randomized (table I) except for study IV, which was double blind and placebo controlled. Exclusion criteria were body mass index (BMI) >30, arterial hypertension, diabetes, cardiovascular or neurological diseases, and usage of CNS targeted drugs. The rabbit study (I) was performed in an open, randomized, and crossover manner.

D.2.1. Objectives of the studies

Study I. The purpose of the study was to investigate the relationships between infusion dose, plasma concentration, and effect of intravenous anaesthetics in rabbits. Therefore, the effects of a steady infusion of propofol, thiopental, and ketamine on the loss of the righting reflex, loss of reaction to tail clamping as an example of a peripheral pain stimulus, and loss of reaction to intranostril insufflation of ammonia vapour as an example of a CNS stimulus were investigated**.** Plasma concentrations of norketamine and dehydronorketamine, the metabolites of ketamine were also measured.

Study II. The aim of the study was to investigate cardiovascular and catecholamine response to laryngoscopy followed by tracheal intubation, and to the longer-lasting stimulus of laryngoscopy for endolaryngeal procedures. TIVA and jet ventilation for laryngomicroscopy offer an opportunity to study the effect of, first, jet ventilation, a strong tracheal stimulus, and second, the superimposed stimulus of long-lasting laryngoscopy. The cardiovascular response and changes of CAs were monitored during TIVA using either thiopental or propofol in two groups of patients undergoing laryngomicroscopy.

Study III. The aim of the study was to test the differences of variance of recorded parameters by investigating plasma CA and hemodynamic responses to tracheal intubation during BSP induced by steady infusion, the "more objective" approach, and after bolus doses until loss of reflexes, the "clinical" approach, with either propofol or thiopental. In addition, the plasma concentrations of 3, 4-dihydroxyphenylethylenglycol (DHPG), an intracellular metabolite of norepinephrine, and arterial plasma concentrations of propofol and thiopental were measured to estimate their concentrations at BSP.

Study IV. The purpose of the study was to evaluate the effect of remifentanil – given before induction of anaesthesia – on propofol requirements, plasma concentrations, and BIS values at hypnotic, analgesic, and EEG end-points. The end-points were loss of counting, loss of obeying a verbal command, loss of reaction to painful tetanic stimulation, and onset of BSP.

Study V. The object of the study was to investigate BSP characteristics of propofol and thiopental, and the reliability of segmentation and classification methods to automatically detect BSP induced by propofol or thiopental.

D.2.2. Clinical measuring points

D.2.2.1. Rabbits

In the rabbits, loss of the righting reflex was used as a hypnotic end-point, loss of reaction to intranostril insufflation of ammonia vapour as an example of a CNS end-point, and tail clamping as an example of a peripheral pain end-point.

Righting reflex. Loss and reoccurrence of the ability to keep the sternal recumbent position when the operating table was tilted laterally 20^{o}.

Instillation of ammonia vapour: A plastic cannula was inserted into the antrum of one nostril. The cannula was connected to a three-way stopcock, which gave access to a wall outlet oxygen line and to a glass syringe of 10 ml filled with ammonia vapour. Saturated ammonia vapour was obtained from a glass bottle half filled with ammonia solution 25% (Merck, Darmstadt, Germany). A flow of 0.5 l/min of oxygen was applied from the loss of righting reflex until the animal began to return to consciousness. As a stimulus, 2 ml of ammonia vapour was injected into the oxygen flow every 20 s. The reaction to intranostril ammonia vapour was considered absent when there were no general movements and no movements of the nose at two consecutive testing. The drug infusion was stopped, but ammonia vapour insufflations continued as described until the reoccurrence of purposeful movements at two consecutive testing.

Tail clamping. The proximal third of the rabbit's tail was shaved when unconscious. The claws of a DeBakey haemostat no. 3 were softened with two layers of adhesive band and were marked 4 cm from the tip. The marked site of the haemostat was clamped to the first ratchet position on the tail 1.0 - 2.0 cm distal from the tail's root. Pain was induced by moving the haemostat longitudinally on the tail for 5 s at approximately 1 Hz. The stimulus began at 20 s intervals after rabbits had lost their righting reflex. The reaction to tail clamping was considered absent when there were no purposeful movements at two consecutive testing. A purposeful movement meant at least a moderate escape reaction, but not changes of breathing patterns, stiffening, coughing or swallowing. The drug infusion was stopped, but tail clamping continued as described until reoccurrence of purposeful movements at two consecutive testing.

D.2.2.2. Surgical patients

In the human studies loss of counting (IV), loss of pupillary light reflex (III), loss of eyelash reflex (III), and obedience to verbal command (IV) were used as hypnotic end-points. Analgesic end-points were loss of purposeful reaction to electrical tetanic stimulation (IV), laryngoscopy and intubation (II, III), and the superimposed stimulus of direct laryngoscopy used in laryngomicroscopy (II). EEG end-point was the onset of burst suppression pattern (III, IV, V).

Hypnosis (Loss of consciousness = LOC): Eyelash reflex was tested by touching the eyelash with a moving forefinger. The reflex was estimated to be abolished if there was no blinking of the lids. Pupillary light reflex was tested by allocating a flashlight to one eye. An abolished pupillary reflex meant a small pupil with no visible reaction to light. Loss of counting was tested by asking the patient to count continuously from the start of the infusion of propofol. It was stated, "abolished" when the patient stopped counting spontaneously, patients were not asked to continue counting. Loss of obeying verbal command was tested by asking the patient loudly to "squeeze my hand", which was continued at 15 s intervals. It was estimated as negative when the patient did not squeeze the anaesthetist's hand on request.

Analgesia: Loss of reaction to tetanic stimulation was started at 30 s intervals after LOC and consisted of 3 s bursts of 50 Hz and 60 mA applied via self-adhesive electrodes to the ulnar nerve at the wrist. It was considered as abolished when purposeful somatic movement ceased as reaction to stimulation. Laryngoscopy followed by tracheal intubation was evaluated and registered by measuring the subsequent cardiovascular and CA response. Furthermore, the superimposed stimulus was investigated by intratracheal jet ventilation and prolonged direct laryngoscopy with the straight Kleinsasser laryngoscope.

Electroencephalography (EEG): Burst suppression pattern (BSP) was used as an EEG end-point. The EEG was evaluated visually. The onset of BSP was stated when 2-4 s of EEG suppression between bursts had been noted. Cardiovascular and CA response to tracheal intubation during BSP was measured (III). Off-line analysis of BSP induced by propofol and thiopental was performed in study V.

D.2.3. Anaesthesia monitoring

In study II an Anaesthesia and Brain Activity Monitor (ABM^{TM}, Datex, Espoo, Finland) was used. Cardiovascular parameters were printed at 10 s intervals on a paper chart recorder. A monitor

providing electrocardiogram, invasive (arterial line) or non-invasive blood pressure, heart rate, end tidal CO_2, peripheral oxygen saturation, peripheral and endonasal body temperatures, and EEG (S/5^{TM}, Datex-Ohmeda, Espoo, Finland) was used as an anaesthesia monitor in studies III, IV, and V. The anaesthesia data of study III was collected to the hard disk of a portable personal computer. The electrocardiogram, systolic and diastolic arterial pressure, heart rate, end-tidal CO2, peripheral oxygen saturation, and neuromuscular block were monitored in all human studies. Peripheral and endonasal body temperatures were monitored in study III. Arterial blood gas analyses were taken just before, at the end of the procedure, and after full recovery (II).

D.2.4. EEG monitoring

The EEG was recorded using a Neuropak 8 (Nihon Kohden, Japan) evoked potential measuring system in the studies III and V. The EEG signal was obtained from a pair of silver cup electrodes. The electrode impedance was kept <5 kΩ. Electrodes were Cz and A1 in study III, and Fpz and C3 in study V. In study V the EEG data was collected on the hard disk of the Neuropak 8 monitor and copied to a portable personal computer for off-line analysis. The sampling frequency was 1000Hz. The EEG was evaluated visually in study III.

In study IV, a one channel EEG was monitored using the EEG module of the S/5 monitor. The EEG signal was obtained from a pair of gold-coated cup electrodes. Electrodes were Fz and T3. Electrode impedance was kept <5 kΩ. The EEG was evaluated visually.

An Aspect 1050 monitor (version 1.21, BIS algorithm 3.3, Aspect Medical Systems Inc., Natick; MA, USA) was used to monitor the BIS in study IV.

D.2.5. Cardiovascular measurements

Cardiovascular and other data during anaesthesia was recorded using the S/5 monitor in all human studies with the exception of study II where the ABM-monitor was used. SAP and DAP were measured from an arterial line in studies II and III and non-invasively (NIBP) in studies IV and V. From the ABM-monitor, the averages of arterial blood pressure and HR were printed at 10 s intervals on a graphic recorder. From the S/5 monitor, anaesthesia data was collected on the hard disk of a portable personal computer at 10 s intervals.

D.2.6. Catecholamine measurements and analysis

Plasma CA analysis was performed in the Institute for Biomedical Science of Tampere University during study II, and in the Department of Pharmacology of Turku University during study III.

In study II, arterial blood samples (5 ml) for ADR and NOR determinations were collected into EDTA tubes and maintained at 0 ^{o}C in an ice bath. After plasma separation, the samples were stored at -20 ^{o}C until analyzed by high-performance liquid chromatography (HPLC) using electrochemical detection with dihydroxybenzylamine as an internal standard (Goldstein et al 1981). The inter and within-batch coefficients of variations for ADR and NOR were between 7 - 10% in a concentration range from 0.7 to 6.0 pmol/ml, while for ADR concentrations below 0.5 pmol/ml the variation rose from 11% (0.5 pmol/ml) to 40% (0.15 pmol/ml). Thus the detection limit of determination was 0.20 - 0.25 pmol/ml.

In study III, arterial blood samples (9 ml) for catecholamine determinations were collected into prechilled EDTA tubes and maintained at 0 ^{o}C in an ice bath. Transfer to the laboratory was within 10 minutes where the samples were immediately centrifuged at 0 ^{o}C and stored at -70 ^{o}C until analyzed by HPLC with coulometric electrochemical detection (Scheinin et al 1991). ADR, NOR, and DHPG interassay coefficients of variation were 11.8% (mean 0.24 nM; n=10), 8.2% (mean 1.17 nM; n=10), and 9.1% (mean 4.84 nM; n=10) with quantitation limits of 0.05, 0.05, and 0.5 nM, respectively.

D.2.7. Analysis of plasma concentrations of intravenous anaesthetics

Plasma thiopental analysis was performed in the Department of Chemistry of Tampere University Hospital in studies I and III. Plasma propofol analysis was performed in the Department of Clinical Pharmacology of Helsinki University in studies I and IV, and in the Department of Chemistry of Tampere University Hospital in study III. Plasma ketamine, norketamine, and dehydronorketamine analysis was performed in the Department of Mental Health and Alcohol Research of the National Public Health Institute in Helsinki.

In study I, arterial blood samples (1 ml) for plasma propofol and thiopental determinations were drawn into Eppendorf tubes, the samples were centrifuged and the plasma was stored at -20 ^{o}C until analyzed by HPLC methods (Parviainen et al 1984, Servin et al 1988). The lower limit of detection was 3 ng/ml for propofol and 0.3 μg/ml for thiopental with intra-assay coefficients of variation 5%

and 4%, respectively. Plasma ketamine, norketamine, and dehydronorketamine were measured using gas chromatography as heptafluorobutyric acid anhydride (HFBA) derivatives. 200 µl of the sample were buffered with 1 ml of 0.5 M $NaHCO_3$ and extracted with 5 ml of toluene containing nortriptyline (5 µl/ml) as an internal standard. After mixing and centrifugation, the organic layer was changed into a clean tube and 2 µl of HFBA in 1 ml of $NaHCO_3$ was added. After mixing and centrifuging, the inorganic phase was discarded and the toluene layer was transferred to another tube, evaporated into dryness, and the residue dissolved with 150 µg of ethanol. Two µl of the elute were then injected into an HP 5990 gas chromatograph (Hewlett Packard, Avondale, PA, USA) equipped with HP nitrogen phosphorus/electron capture detector. The column used for separation was 30 m by 0.318 mm DB-17 (50% phenyl- and 50% methylpolysiloxane; film thickness: 0.25 µm) packed column (J & W Scientific, Falsom, CA, USA), the temperature of which was programmed to 150-300 ^{o}C at 15 ^{o}C/min. Intraday variations, expressed as coefficients of variation for 6 successive analyses were 3.7, 7.4 and 6.1 % for 15.3 ng/ml of ketamine, 1.6 ng/ml of norketamine and 1.6 ng/ml of dehydronorketamine, respectively.

In study III, arterial blood for propofol and thiopental determinations were collected into EDTA tubes and transferred within 30 minutes to the laboratory where plasma was separated and stored at -20 ^{o}C until analyzed by HPLC methods (Parviainen et al 1984, Plummer 1998). Propofol and thiopental intra-assay coefficients of variation were 5% and 4% with quantitation limits of 3 ng/ml and 0.3 µg/ml, respectively.

In study IV, venous blood samples for propofol determinations were collected into EDTA tubes and transferred to the laboratory within 20 minutes. Plasma was separated immediately and stored at -20 ^{o}C until analyzed by HPLC methods (Plummer 1998). The intra-assay coefficient of variation was 5% and quantitation limit 3 ng/ml.

D.3. Statistical methods

Statistical computations were done in the School of Public Health of the University of Tampere in studies II and III.

In all studies, the statistics were based on the analysis of variance for repeated measures for different continuous variables. Duncan's test was used as a post hoc test in study I, and Tukey's procedure in studies III and IV. For demographic, anaesthesia, and other uncontinuous data one-way analysis of variance was used, and the Mann-Withney U-test was used for demographic and

anaesthesia data in study II. In study II, the baseline was used as a covariate and the Huynh-Feldt approximation (Bryant and Gillings 1985) was used when indicated by the sphericity test where $p < 0.10$ was regarded as significant, because the test is extremely powerful. In study III, Levene's test (Hair et al 1998) was used to compare the equality of the variances, Wilcoxon's signed ranks test was used for within group differences before and after tracheal intubation, and the Solo Power Analysis software was used for power calculations to detect a 20% difference between means at a two-sided significance level of 0.05. In study IV, the power analysis showed that a sample size of 15 patients per group would have 90% power at the 5% significance level to identify a reduction of 25% in propofol dose requirement. The computation was carried out using SPSS for Windows (version 6.1 [I] and version 10.1 [III]) software (SPSS inc., Chicago, USA) except in study IV where the GraphPad Prism (version 3.02) software (GraphPad Software Inc., San Diego, USA) was used. Results are presented as mean (SD) and 95% confidence limits (CL_{95}), unless otherwise specified; $P < 0.05$ was considered to be statistically significant.

E. RESULTS

In respect to the physical characteristics, all groups were comparable to each other.

E.1. Responses at different measuring points

Cardiovascular and CA responses to tracheal intubation (II, III) and during laryngomicroscopy (II) were compared between propofol and thiopental. In study II, patients first received an alfentanil bolus, and then either propofol bolus and steady infusion or thiopental bolus and steady infusion. In study III, patients received either bolus of propofol or thiopental until loss of eyelash and pupillary light reflex or infusion of propofol or thiopental until the onset of BSP before tracheal intubation.

E.1.1. Cardiovascular responses

There were no significant differences in baseline values between groups (II, III). Alfentanil 17.5 μg/kg given about 3 min before tracheal intubation abolished the SAP and DAP responses but not the HR response (II). Even at the BSP level of propofol or thiopental infusion, the cardiovascular response to tracheal intubation was significant when compared to values before intubation. The response was also significant compared to baseline values in the thiopental BSP group and in both loss of reflexes groups, but not in the propofol BSP group where there was no significant increase in SAP or DAP (III). After insertion of the operating laryngoscope (II) there was a significant cardiovascular response in both the propofol and the thiopental group, and SAP and DAP remained above the baseline values during the whole procedure. With thiopental, SAP responded to insertion of the operating laryngoscope more intensively than with propofol but there were no other significant differences between the groups as shown by the other cardiovascular parameters (DAP, HR).

After bolus doses of thiopental (III) the cardiovascular response (SAP, DAP, HR) to tracheal intubation was the most intense when compared to all other groups ($p<0.05$). After bolus doses titrated to loss of reflexes, the cardiovascular responses to tracheal intubation were more pronounced with thiopental than with propofol ($p<0.05$) but during BSP, only DAP increased significantly in the thiopental group compared to the propofol group ($p<0.05$) although SAP tended to be higher in the thiopental group ($p=0.08$). Especially in the BSP groups, cardiovascular responses were very short-lived after tracheal intubation, 10-20 s, and would have been missed even with intermittent

registration at 30 s after tracheal intubation. Overall, the cardiovascular response to tracheal intubation was less pronounced in the BSP groups compared to the bolus groups (III).

Levene's test for differences of variance (III) between the combined (propofol and thiopental) bolus and BSP groups in the cardiovascular response to tracheal intubation showed significant differences in 13 of the tested 24 pairs (Table 2); in 6 pairs, significance was due to the smaller variance in the BSP group in both pairs (in favour of our hypothesis), in 5 pairs due to the BSP group in one pair, and no difference in the other pair, and in 2 pairs the difference was in the BSP group in one of the pairs and in bolus group in the other pair (Table 2).

Table 2. Results of Levene's test (p-values) for differences of variance in cardiovascular values between combined (propofol and thiopental) bolus and burst suppression (BSP) groups in study III. Bold underlined represents significance due to smaller variance in BSP group in both pairs, bold in BSP group in one pair and no difference in the other pair, and italics in BSP group in one pair and in bolus group in the other pair.

Time points	Systolic arterial pressure	Diastolic arterial pressure	Heart rate
Arrival	0.814	0.512	0.298
Lowest after induction	**0.042**	0.218	0.14
Pre-intubation	**0.002**	0.90	**0.026**
Highest after intubation	0.261	0.488	**0.018**
30 s after intubation	*0.003*	**0.033**	0.145
1 min after intubation	*0.009*	0.19	0.09
2 min after intubation	**0.002**	**0.008**	0.33
3 min after intubation	**0.002**	**0.033**	0.791
5 min after intubation	**0.000**	**0.014**	0.77
Count of $p<0.05$	7	4	2

E.1.2. Plasma catecholamines

Arterial ADR decreased significantly after intubation and during five minutes of jet ventilation without stimuli in both groups compared to the baseline values, but values just before intubation were not measured (II). Arterial ADR increased significantly immediately after insertion of the operating laryngoscope in the thiopental group and to some extent in the propofol group, and remained higher in the thiopental group compared to the propofol group during and after anaesthesia (II). Arterial NOR remained stable in both groups after intubation and during five minutes of jet ventilation compared to the baseline values. Arterial NOR increased significantly in both groups after insertion of the operating laryngoscope and remained elevated thereafter throughout the whole observation period without differences between groups (II).

In the bolus groups, propofol attenuated the plasma CA response to tracheal intubation more efficiently than thiopental, but neither of them totally blocked the plasma NOR response to intubation (III). During BSP there were no significant increases in plasma ADR concentrations after tracheal intubation. Propofol attenuated more efficiently the NOR response to tracheal intubation than thiopental in all groups, in fact it was nearly totally blocked during BSP induced by propofol (III).

In study III, a significant difference for the variances of the catecholamine response to tracheal intubation was found between the combined (propofol and thiopental) bolus and BSP groups in only two of 15 possible instances (table 3).

Table 3. Levene's Test of Equality of Error variances for catecholamines (p-values).

Time Points	Adrenaline	Noradrenaline	DHPG
Baseline	0.382	0.645	0.647
1 min before Intubation	0.087	0.371	0.882
1 min after Intubation	**0.044**	0.518	0.771
2 min after Intubation	**0.014**	0.639	0.686
5 min after Intubation	0.070	0.348	0.579

DHPG = 3, 4-dihydroxyphenylethylenglycol

E.2. Effective doses

In rabbits, ED_{50} and ED_{95} of a steady infusion of propofol, thiopental, and ketamine for the loss of the righting reflex, loss of reaction to tail clamping, and loss of reaction to intranostril insufflations of ammonia vapour were defined (I). In humans, ED_{50} and ED_{95} of a steady infusion of propofol and thiopental for loss of consciousness (III, IV), loss of response to noxious stimulus (IV), and onset of BSP (III, IV) were defined with two different infusion doses of remifentanil (IV), and without remifentanil (III, IV). Furthermore ED_{50} and ED_{95} of propofol and thiopental on LOC were defined after bolus doses (III).

In the rabbits, ED_{50} and ED_{95} at loss of righting reflex, reaction to ammonia vapour, and reaction to tail clamping with propofol, thiopental and ketamine are presented in Table 4.

Table 4. ED_{50} and ED_{95} (CL_{95}) values (mg/kg) of propofol, thiopental, and ketamine at various end-points in rabbits during the infusion of the study drugs (I).

End-points	Propofol 300 mg/h	Thiopental 750 mg/h	Ketamine 600 mg/h
Loss of righting reflex			
ED_{50}	4.3 (3.7-4.9)	7.7 (6.8-8.6)	5.2 (4.5-5.9)
ED_{95}	6.0 (5.4-6.6)	10.4 (9.5-11.3)	7.6 (6.8-8.3)
Loss of reaction to ammonia vapour			
ED_{50}	11.6 (8.4-14.7)	17.6 (15.0-20.3)	18.9 (11.8-26.0)
ED_{95}	16.9 (13.7-20.1)	21.6 (19.0-24.3)	38.5 (31.4-45.6)
Loss of reaction to tail clamping			
ED_{50}	18.6 (16.0-21.1)	27.2 (24.4-30.0)	72.6 (49.9-95.3)
ED_{95}	25.1 (22.5-27.7)	32.8 (30.1-35.5)	124.5 (101.8-147.2)

ED_{50} and ED_{95} of propofol and thiopental without premedication at loss of eyelid and pupillary light reflexes after bolus doses, and at the onset of BSP after infusion of 30 mg/kg/h and 75 mg/kg/h are presented in Table 5 (III). ED_{50} and ED_{95} of propofol with and without remifentanil for loss of obeying verbal command, loss of reaction to tetanic stimulation, and at the onset of BSP after infusion of 30 mg/kg/h with oral diazepam 0.1 mg/kg premedication are presented in Table 5 (IV). ED_{50} and ED_{95} for loss of pain reaction did not differ significantly from BSP inducing dose in the saline group (IV). Remifentanil decreased the propofol dose at the end-points LOC, loss of pain reaction, and at BSP by about 20-30%, 50-60%, and 25-30%, respectively, and decreased by about the same extent the times to reach end-points (IV). Thus, BSP was induced with propofol infusion at about a 25-30% smaller dose when diazepam premedication or remifentanil infusion was added.

Table 5. ED_{50} and ED_{95} (CL_{95}) values (mg/kg) of propofol and thiopental at various end-points in diazepam 0.1 mg/kg premedicated (P) and non-premedicated (N) patients with or without remifentanil infusion (III, IV).

End-points	Propofol bolus or infusion (N)	Saline + Propofol 30 mg/kg/h (P)	Remifentanil 7.5 μg/kg/h + Propofol 30 mg/kg/h (P)	Remifentanil 30 μg/kg/h + Propofol 30 mg/kg/h (P)	Thiopental bolus or infusion (N)
Loss of consciousness, Test model	Loss of eyelid and pupillary light reflexes	Loss of verbal command	Loss of verbal command	Loss of verbal command	Loss of eyelid and pupillary light reflexes
ED_{50}	2.8 (2.6-2.9)	1.6 (1.5-1.7) #	1.3 (1.1-1.5)	1.2 (1.1-1.3) *	5.2 (4.9-5.4)
ED_{95}	3.1 (2.9-3.2)	2.0 (1.9-2.2) #	2.1 (1.9-2.3)	1.4 (1.3-1.5) *	6.1 (5.9-6.3)
Loss of reaction to tetanic stimulation					
ED_{50}		3.3 (2.9-3.6)	1.8 (1.4-2.0) *	1.5 (1.4-1.6) *	
ED_{95}		4.2 (3.8-4.5)	2.9 (2.6-3.2) *	1.7 (1.6-1.8) *	
The onset of BSP	Inf (30 mg/kg/h)				Inf (75 mg/kg/h)
ED_{50}	5.0 (4.4-5.6)	3.8 (3.3-4.3) #	2.6 (2.2-3.1) *	2.8 (2.6-3.1) *	11.3 (10.0-12.6)
ED_{95}	6.9 (6.3-7.5)	5.3 (4.8-5.8) #	4.6 (4.1-5.1) *	3.7 (3.4-3.9) *	15.4 (14.1-16.7)

* = $p<0.05$ compared to saline (P) group; # = $p<0.05$ compared to propofol (N) group;

BSP = burst suppression pattern; Inf = infusion rate

E.3. Effective concentrations

In rabbits, EC_{50} and EC_{95} of a steady infusion of propofol, thiopental, and ketamine for the loss of the righting reflex, loss of reaction to tail clamping, and loss of reaction to intranostril insufflations of ammonia vapour were defined (I). In humans, EC_{50} and EC_{95} of a steady infusion of propofol and thiopental for loss of consciousness (IV), loss of response to noxious stimulus (IV), and onset of BSP (III, IV) were defined with two different infusion doses of remifentanil (IV), and without remifentanil (III, IV).

In the rabbits EC_{50} and EC_{95} at loss of righting reflex, reaction to ammonia vapour, and reaction to tail clamp with propofol, thiopental, and ketamine are presented in Table 6.

Table 6. EC_{50} and EC_{95} (CL_{95}) values (μg/ml) of propofol, thiopental, and ketamine at various end-points in rabbits during the infusion of the study drugs (I).

End-points	Propofol	Thiopental	Ketamine
Loss of righting reflex			
EC_{50}	3.86 (3.31-4.41)	51.1 (43.8-58.4)	14.2 (12.4-16.0)
EC_{95}	4.79 (4.24-5.34)	81.3 (74.0-88.6)	17.4 (15.6-19.2)
Loss of reaction to ammonia vapour			
EC_{50}	4.91 (3.68-6.14)	69.0 (56.8-81.2)	23.9 (18.5-29.3)
EC_{95}	7.68 (6.45-8.91)	87.5 (75.0-100.0)	34.8 (29.4-40.2)
Loss of reaction to tail clamping			
EC_{50}	8.32 (7.14-9.50)	98.0 (81.8-114.2)	21.4 (14.2-28.6)
EC_{95}	9.77 (8.59-10.96)	130.9 (114.7-147.1)	39.8 (32.6-47.0)

Venous EC_{50} and EC_{95} values for propofol after infusion of 30 mg/kg/h with diazepam 0.1 mg/kg premedication and with or without remifentanil infusion at LOC, loss of pain reaction, and onset of BSP are presented in Table 7. Remifentanil reduced EC_{50} for LOC and loss of pain reaction about 50-70%, but EC_{50} for BSP was unchanged. Arterial EC_{50} and EC_{95} for infusions of propofol (30 mg/kg/h) and thiopental (75 mg/kg/h) at BSP without premedication are presented in Table 7. Arterial and venous EC_{50} of propofol differed significantly at the onset of BSP but EC_{95} did not (Table 7).

Table 7. EC_{50} and EC_{95} (CL_{95}) values (μg/ml) after infusion of propofol and thiopental at various end-points in diazepam 0.1 mg/kg premedicated (P) and non-premedicated (N) patients (III, IV).

End-points	Propofol (arterial) (N)	Saline+ Propofol 30 mg/kg/h (P)	Remifentanil 7.5 μg/kg/h + Propofol 30 mg/kg/h (P)	Remifentanil 30 μg/kg/h + Propofol 30 mg/kg/h (P)	Thiopental (arterial) (N)
Loss of consciousness					
EC_{50}		3.33 (2.54-4.12)	1.61* (0.51-2.71)	1.04 * (0.37-1.73)	
EC_{95}		5.70 (4.91-6.49)	6.52 (5.42-7.52)	3.91 * (3.24-4.58)	
Loss of reaction to tetanic stimulation					
EC_{50}		6.15 (4.87-7.43)	3.31 * (2.19-4.43)	2.90 * (1.83-3.97)	
EC_{95}		10.79 (9.51-12.07)	7.08 * (5.96-8.20)	6.85 * (5.78-7.92)	
Onset of BSP					
EC_{50}	9.65 (9.03-10.27)	7.55 # (6.34-8.76)	7.47 # (6.12-8.82)	6.59 # (5.98-7.97)	31.60 (27.46-35.74)
EC_{95}	10.82 (10.20-11.44)	10.93 (9.71-12.14)	11.10 (10.75-12.45)	10.77 (9.39-12.15)	42.78 (38.64-46.92)
Steady state BSP					
EC_{50}	7.13 (6.49-7.77)	6.78 (5.97-7.60)	7.70 (6.65-8.75)	8.00 (6.94-9.06)	27.85 (23.96-31.74)
EC_{95}	9.48 (8.84-10.12)	10.17 (9.35-10.99)	10.67 (9.62-11.72)	10.56 (9.50-11.62)	38.12 (34.23-42.01)

BSP = burst suppression pattern; * = $p<0.05$ compared to the saline group; # = $p<0.05$ compared to the propofol (arterial) group

E.4. EEG and BIS

A typical evolution of EEG patterns is seen both with propofol and thiopental. This consists of an increase in fast activity, then an increase in slow activity and finally burst suppression (III, IV, V).

In study IV, BIS values between remifentanil groups did not differ significantly at any end-point. BIS values did not change significantly in the remifentanil groups from baseline to loss of counting as they did in the saline group. BIS values changed significantly in all groups from loss of counting to loss of obeying verbal command (LVC), and further to loss of reaction to tetanic stimulation. BIS values did not change significantly from loss of pain reaction to BSP in the saline group but they did in the remifentanil groups. Differences between groups appeared in loss of response to tetanic stimulation and BSP end-points, which were achieved with higher BIS values in the remifentanil groups than in the saline group (Table 8).

Table 8. BIS values and percentage changes (compared to saline group) at different end-points.

Time-points	Saline + Propofol 30 mg/kg/h	Remifentanil 7.5 µg/kg/h + Propofol 30 mg/kg/h	Remifentanil 30 µg/kg/h + Propofol 30 mg/kg/h
Baseline	95 (93-97)	97 (93-100) +2%	94 (93-96) -1%
Loss of counting	87 (83-91)	89 (87-91) +2%	90 (84-96) +3%
Loss of verbal command	73 (64-81)	80 (75-85) +10%	77 (72-82) +5%
Loss of pain reaction	35 (31-39)	55 (48-63) * +57%	60 (53-67) * +71%
Onset of BSP	32 (28-35)	41 (37-45) * +28%	38 (33-43) * +19%

Values are median (=BIS_{50}) (CL_{95}), BSP= Burst suppression pattern of the EEG.

* = $p < 0.05$ compared with saline group.

Times to reach BSP end-points did not differ significantly between propofol and thiopental with the infusion regimen (III). BSP could be maintained in all patients (III, IV, V) before tracheal intubation, but some patients (III, V) did not preserve BSP at the end of propofol infusion when the infusion was decreased to 15 mg/kg/h 5 min before the end of the study. In the thiopental group with the infusion regimen, all patients preserved BSP.

In study V, the propofol anaesthesia data for a total of 80 minutes of BSP was comprised of bursts (41.7%), suppressions (22.3%), and artefacts (35.9%). In the thiopental anaesthesia data for a total of 80 minutes of BSP, the percentages were: 34.9% bursts, 22.8% suppressions, and 42.3% artefacts. The data included a large number of artefacts because of the mask ventilation before the insertion of the tracheal tube, the insertion of the tracheal tube itself, and the connection to a ventilator after insertion of the tracheal tube. All these actions lead to head movements and resulted in artefacts. Thus, during anaesthesia there are long periods of artefacts making detection of artefacts very important during EEG monitoring.

During BSP, the bursts consisted of parietal negative slow wave or a series of slow waves (V). On top of this, 10 Hz mixed frequency activity is seen. In addition, 13 – 15 Hz spindles resembling the sleep spindles are seen with propofol, and these are either on the bursts or during suppression. Furthermore, negative sharp waves are seen sometimes at the onset of bursts. These typical patterns are presented in figure 1. Notice that the bursts do not fulfil the requirement of stationarity or Gaussian distribution, and therefore calculation of power spectrum and parameters such as spectral edge during burst suppression are not mathematically correct (Miller et al BJA 2004). The segmentation and classification method presented in study V worked well and showed that BSP detection could be automated. It also accurately detected artefacts.

E.5. Other results

Alfentanil bolus of 17.5 μg/kg (II) and high dose remifentanil infusion 0.5 μg/kg/min (IV) totally abolished the injection pain of propofol at the infusion site. The low dose remifentanil infusion 0.125 μg/kg/min was ineffective in abolishing the infusion pain of propofol (IV). Recovery was prolonged significantly with thiopental compared to propofol, but there was no significant difference in blood gas values between groups (II). Eight patients in the propofol bolus group and 7 patients in the thiopental bolus group needed one extra bolus to abolish reflexes; additional boluses were not needed (III). Tracheal intubation times did not differ between groups (III).

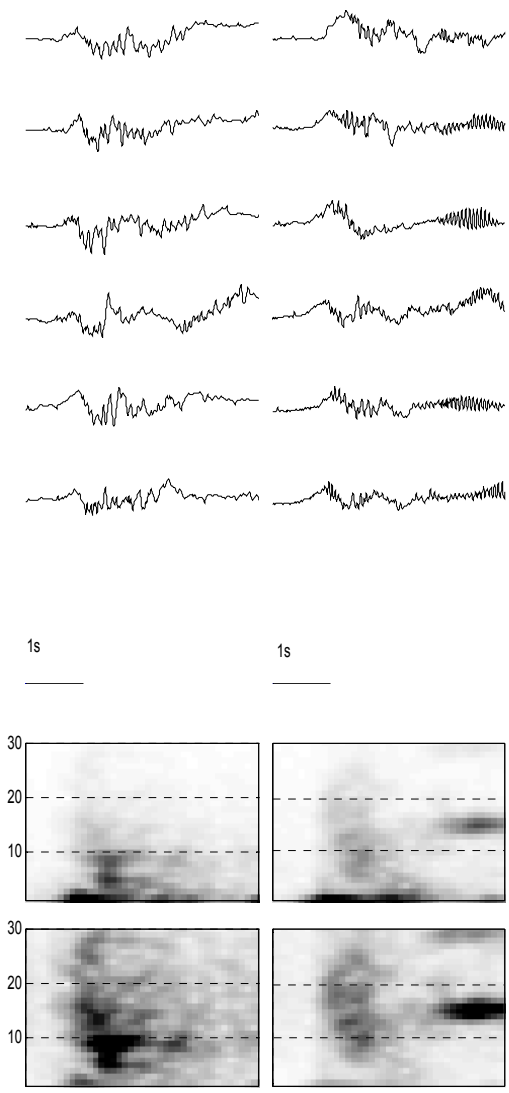

Figure 1. Propofol (right) and thiopental (left) burst suppression patterns during anaesthesia (V). On the bottom of the picture two corresponding spectrograms for each column are seen. The upper one represents the amplitude spectra versus time, and the lower one the amplitudes are divided by 1/f for illustrative purposes to enhance the high frequency contents.

F. DISCUSSION

F.1. General aspects

Movement reaction to noxious stimuli, classically skin incision, is used as a measurement of the depth of anaesthesia. Tail clamping was used in rabbits and electrical stimulation instead of skin incision was used as noxious stimulus in human patients. However, tail clamping, like skin incision, is not a pure pain stimulus; tactile receptors are also activated and the latter information is transmitted through sensory Aβ−fibres. Nor is electrical stimulation, on the other hand, a purely noxious stimulus as it also causes vibrotactile stimulation. The use of laser stimulation is the only way to achieve a rather pure pain stimulus (Tran et al 2002). Anaesthetics affect not only cortical function but also spinal reflexes to a different degree; for example, isoflurane affects the spinal cord and spinal reflexes more than propofol or thiopental (Zhou et al 1997, Kertz et al 2001, Antognini et al 2002). Therefore hypnosis, analgesia, function of spinal reflexes, and muscle relaxation must be considered specifically instead of speaking generally about the "depth of anaesthesia".

A constant supramaximal stimulus is essential for the determination of the analgesic potency of an anaesthetic drug (Quasha et al 1980). It has been proposed that tetanic stimulation of the magnitude of 65-70 mA, 100-Hz, and lasting 10 s, is supramaximal (Hornbein et al 1982). This study used 60 mA, 50 Hz, and 3 s stimulation (IV); the intensity of the stimulus was nearly the same, but the duration was shorter. Higher (80 mA and 50 Hz, Kazama et al 1997) and lower (50 mA and 50 Hz, Zbinden et al 1994a, Zbinden et al 1994b) intensity of electrical stimuli have been used. We think that this study's and others use of non-supramaximal electrical stimulation may still be used as a reliable substitute for skin incision.

Pre-treatment with barbiturate or with ketamine increases the metabolism of ketamine (Livingstone and Waterman 1978, Woolf and Adams 1987). Pre-treatment with barbiturate or ketamine might increase the metabolism of propofol as well, because propofol is mainly metabolized in the liver (Simons et al 1991). The different sessions in our study were carried out at intervals of at least 7 days to minimize a possible influence on the results of the induction of liver enzymes (I). If induction of liver enzymes were persistent, this would be balanced out by the randomization of the administration of the study drugs.

In study I, plasma concentrations of propofol and thiopental increased steeply during the whole infusion period, but those of ketamine remained almost unchanged from the loss of reaction to ammonia vapour to loss of reaction to tail clamping (Table 6). Thus, accumulation of ketamine

happened, but plasma concentrations increased very slowly compared to propofol or thiopental. The reason for this might be that with the infusion regimen the steady-state concentration of ketamine had already been achieved when the first sample was taken, but not that of propofol or thiopental. It has been shown with propofol in rats, that end-points can be achieved with smaller dosages when slower infusion rates are used, but with too slow rates of infusion, higher doses again become necessary (Larsson et al 1994).

The duration to loss of reaction to tail clamping, loss of reaction to ammonia vapour, and awakening times were significantly longer with ketamine than with propofol or thiopental (I). Of these end-points, tail clamping measures the function of the spinal reflex arch, whereas smelling and awakening depend on the function of the CNS. In healthy adults, alteration of qualitative consciousness starts at a bolus dose of 0.2 mg/kg of ketamine, pain is abolished after 0.5 mg/kg, but surgical anaesthesia, i.e. sufficient depression of quantitative consciousness, requires at least 2 mg/kg; at the latter stage, spinal arch reflexes still function. Thus, in the rabbits the same order of events was seen as in the humans: depression of spinal arch reflexes with ketamine appears at concentrations equal to or higher than those needed for total depression of cortical function. There is the possibility that using a pure pain stimulus instead of tail clamping would have provided a different picture of the analgesic potency of ketamine and its metabolites in rabbits.

In study II, a rather small number of patients (8 + 8) were studied and no power analysis was used before the study; thus the data does not permit us to draw definite conclusions. The small number of patients was one reason why we used powerful statistical procedures; i.e. baseline covariates and Huynh-Feldt approximation, but when the results of study III were added, the results were more reliable when cardiovascular and catecholamine responses to tracheal intubation were compared with propofol and thiopental.

In study IV, loss of response to tetanic stimulation in the remifentanil groups would have been achieved earlier, and at lower propofol doses and concentrations (and higher BIS values) when taking into account that reaction to the first tetanic stimulation was seen in 8 patients in the low remifentanil group and in 3 patients from the high dose remifentanil groups, compared to all patients in the saline group. This was one weakness of study IV. Another weakness was that steady-state concentrations of propofol were not used; venous concentrations from the study were not comparable to other studies where steady-state concentrations were used. We designed our study protocol to resemble clinical practice. The only nearly steady-state concentration of propofol in study IV was the time-point when the infusion was stopped (infusion of 18 mg/kg/h was continued about 10 min). The BSP steady-state concentration of propofol in study IV was slightly lower than

the concentrations at BSP in the study of Illievich et al (1993) but the same as in study III. The reason for this may be that we used venous instead of arterial concentrations. Ultimately, groups in study IV were comparable to each other because they were treated similarly and percentage changes in plasma concentrations of propofol might be put into clinical practice.

If opioids have synergic action on hypnotic drugs but no influence on BIS values, co-administration of a hypnotic drug and an opioid would result in faster achieving of end-points, especially analgesic, with lower doses and plasma concentrations of hypnotics and with higher BIS values than with hypnotics alone. However, the results of research done on the influence of opioids on propofol doses, concentrations, and BIS values at hypnotic and analgesic end-points are conflicting. Iselin-Chaves et al (1998) reported that without painful stimulation, LOC and BIS revealed no interaction between propofol and alfentanil; Guignard et al (2000) reported similar results with propofol and remifentanil. On the other hand, during a steady target-controlled infusion of propofol, increasing infusion rates of remifentanil reduced BIS (Strachan and Edwards 2000). Mi et al (1999) found that LOC and inhibition of noxious stimulus were present at higher BIS values and lower propofol doses with the combination of propofol and fentanyl than with propofol alone. Recently, LOC was observed at a mean BIS value of 46, and a mean effect-site propofol concentration of 3.5 μg/ml with a target controlled infusion of propofol. After LOC, remifentanil was infused progressively to change the concentration from 1 ng/ml to 5 ng/ml; BIS remained unchanged (Barvais et al 2003).

In study IV, the patients of the remifentanil groups lost response to tetanic stimulation and achieved BSP end-point with higher BIS values than those of saline group; however, there was no difference at the LOC end-point (Table 8). BIS is a univariate index that includes data from several different anaesthetics and tries to use information from several different processes to produce a monotonous function of the change from continuous EEG to suppression. During the induction of anaesthesia, BIS values and plasma concentrations of propofol change very quickly. The BIS version we used in study IV is 30 s delayed (Høymork et al 2001) compared to the state of the patient. Thus, timing of BIS-registration and blood sampling are very critical and hard to standardise. Høymork et al (2001) were also unable to correlate BIS with the measured levels of anaesthetic drugs during stable level of anaesthetic medication. Furthermore, BIS values in the range of 30-50 are not a sensitive indicator of different effect levels, and BIS also has limitations at BSP level of anaesthesia (Bruhn et al 2001). Therefore, the conflicting results of BIS values in study IV and the above-mentioned studies might have been due to methodological limitations.

In order to study the behaviour of different commercial indices we should have the original wide-band EEG, process the individual components separately, and analyze their contribution to the final index. Simultaneous study of the topography of the EEG as well as evoked potentials and event related potentials should yield important insight into cerebral function. Integration with other research methods and basic neurophysiology such as sleep research and epileptology should finally help us to understand what we really are measuring with these indices – and what is not measured.

F.2. Cardiovascular and catecholamine responses

Measurement methods

The reliability of the result of catecholamine measurements (II, III) depends not only on the determination technique but also on blood sampling and processing. For example, the duration of sample storage and temperature are important. That is why we collected samples into prechilled EDTA tubes and maintained them at 0 ^{O}C in an ice bath before separation of plasma. The storage temperature was -20 ^{O}C in study II and – 70 ^{O}C in study III until analyzed by HPLC methods. The sampling site might have an effect on results because NOR is metabolized in the lungs and the biological half-life of plasma CAs is about 2 min. On the other hand, there have not been very large differences in CA concentrations and responses in the studies where different sampling sites have been used (Gin et al 1993, Lindgren et al 1993, Brossy et al 1994). We used an arterial line for blood sampling. In study II we used HPLC method of Goldstein et al (1981); its detection limit is about 0.2 nM for CAs. In study III we used the HPLC method of Scheinin et al (1991); its detection limit is 0.05nM for CAs. However, in study II the plasma concentrations of ADR and NOR were mostly in the limits of 0.2-4.0 nM: only ADR concentrations after induction of anaesthesia before insertion of the operating laryngoscope were below 0.2 nM in some patients. To conclude, our sampling and storage were equal and appropriate but the method of CA determination was more accurate in study III than in study II.

The reliability of the result of propofol and thiopental measurements (I, III, IV) depends not so critically on the blood sampling and processing as the CA results. Measurements of propofol and thiopental plasma concentrations were accurate and are described in former studies (Parviainen et al 1984, Plummer 1998); their quantitation limits were 3 ng/ml and 0.3 μg/ml with interassay coefficients of variations 5% and 4%, respectively. Gas chromatographic analysis of ketamine,

norketamine, and dehydronorketamine (I) has not been used before and its intra-day variations were small 3.7, 7.4, and 6.1%, respectively. Thus, it seems to be an accurate method.

Responses

In study III, the results did not support the hypothesis that a well-defined BSP would cause smaller variances of mean values in cardiovascular or plasma CA responses to tracheal intubation than the loss-of-reflexes anaesthesia; they do not explain why attenuation of catecholamine and hemodynamic responses to tracheal intubation is better in both BSP groups compared with the loss of reflexes groups. The differences of the hemodynamic responses to tracheal intubation between bolus and BSP groups may be explained by two different mechanisms (III). First, with bolus doses there is a relatively high contribution of direct depression of the cardiovascular system because of high peak concentrations. Second, during drug infusion, such high peak concentrations are not achieved and depression of the CNS becomes more prominent. Some of the differences between bolus doses and an infusion regimen may be related to the half-life of equilibrium between blood and effect site.

Study II showed that cardiovascular response to tracheal intubation is attenuated well with alfentanil pre-treatment and this is in accordance with previous studies (Crawford et al 1987, Saarnivaara and Klemola 1991). The cardiovascular and CA response after insertion of the operating laryngoscope reflects different alfentanil concentrations, as we did not gave further doses of alfentanil. Neither propofol nor thiopental could attenuate well the hemodynamic or CA response to insertion of the operating laryngoscope, but propofol did attenuate them slightly better than thiopental. The cardiovascular and CA responses possibly correlate with the higher forces applied to the base of the tongue by the straight operating laryngoscope as the forces applied during laryngoscopy have been implicated as factors involved in the cardiovascular response to tracheal intubation (Schribman et al 1987, Hassan et al 1991, McCoy et al 1995, Kitamura et al 2001). It has been shown that opioids attenuate well the hemodynamic or CA response to insertion of the operating laryngoscope (Pandazi et al 2003). The better attenuation of the NOR response with propofol than with thiopental in study III was not seen in study II. The reason may be found in different levels of anaesthetic medication, as we did not monitor EEG changes in study II. The reason for no differences in HR reaction between propofol and thiopental may be partly due to glycopyrrolate that was given to both groups in study II before the induction of anaesthesia.

In bolus groups (III), propofol attenuated more efficiently plasma ADR response to tracheal intubation than thiopental, but neither of them totally blocked plasma NOR response to tracheal

intubation, which is in accordance with previous studies (Gin et al 1993, Lindgren et al 1993, Brossy et al 1994). During BSP propofol almost totally blocked the NOR response to tracheal intubation whereas thiopental did not. In our BSP group (III), cardiovascular response was seen after tracheal intubation with propofol, which was insignificant except for HR. The better attenuation of the hemodynamic response to intubation seen after propofol than thiopental may be partly due to a stronger effect on pharyngeal and laryngeal mechanoreceptors as documented in good intubation conditions after propofol alone (Keaveny and Knell 1988, Barker et al 1992), a specific peripheral effect (Yamazaki et al 2002), or a longer lasting hypotensive effect (Mulier et al 1991). Propofol also decreases sympathetic activity but only in the unstimulated state (Ebert and Muzi 1994). Sympathetic outflow does not necessarily increase uniformly to all tissues. Stimuli producing increased sympathetic neural traffic to muscle and skin may not be associated with increased HR or MAP (Sellgren et al 1990); this may confound attempts to correlate changes in plasma CA concentrations and changes in HR or MAP in response to noxious stimuli.

Opioids attenuate the responses to noxious stimuli, but even large doses of opioids used for patients undergoing coronary artery bypass grafting surgery, including fentanyl at doses up to 100 μg/kg, did not reliably prevent an increase of heart rate or blood pressure in response to tracheal intubation or sternotomy (Wynands et al 1983, Hynynen et al 1986, Philbin et al 1990). Much lower doses of opioids are needed to attenuate the responses to noxious stimuli when a hypnotic agent is added (Parsons et al 1994). It seems that both hypnotic and analgesic agents are needed to attenuate responses to tracheal intubation.

Different sampling sites have been used as a possible explanation for different results regarding the CA response to tracheal intubation. However, the explanation seems to be improbable as our results are in accordance with previous studies where sampling was from a central venous line (Lindgren et al 1993), a peripheral line (Gin et al 1993), and an arterial line (Brossy et al 1994). In study III, we confirmed that serum levels of norepinephrine's metabolite DHPG do not change when NOR is changing (Scheinin et al 1991). Thus, it seems useless to monitor DHPG levels in future similar studies.

F.3. Anaesthetic efficacy of IV anaesthetics

One weakness of our (III, IV) studies was that we did not use steady-state concentrations and another that we measured venous plasma concentrations of propofol (IV); venous concentrations of propofol differ significantly from those of arterial concentrations (Wang et al 1994, Zheng et al

2000). Premedication with the benzodiazepine midazolam reduced propofol requirements at hypnotic and analgesic end-point (Wilder-Smith et al 2001). With drug infusion, end-points are attained at smaller doses than with bolus doses (Stokes and Hutton 1991, Peacock et al 1992, Avram et al 1993). The smaller doses at LOC in study IV compared with study III are obviously result of infusion induction of anaesthesia and premedication with diazepam, but premedication and infusion do not explain similar plasma concentrations at BSP in studies III and IV (see below).

Propofol doses (ED_{50} and ED_{95}) at the BSP end-point in study IV were significantly different from those of study III, but of the drug concentrations, only EC_{50} was significantly smaller in study IV than in study III. Differences in plasma concentration of propofol can be explained by venous (IV) and arterial (III) sampling and by not having been at steady state during sampling. The propofol concentrations (III, IV) did not differ significantly between each other10 min after attainment of BSP with same infusion rate (20 mg/kg/h). Plasma concentrations of propofol during BSP seem to be similar regardless of anaesthetic adjuvant used; Stone et al (1996) induced anaesthesia with midazolam, thiopental and fentanyl and administered isoflurane in nitrous oxide and oxygen throughout the procedure, but plasma concentration of propofol at BSP was the same as in our studies (III, IV). Cheng et al (1996) induced BSP with propofol without premedication at a mean dose of 5.7 mg/kg, which is in accordance with our study III. After premedication with midazolam, Illievich et al (1993) gave an initial bolus of propofol 1 mg/kg followed by an infusion of 20 mg/kg/h for 30 minutes. They achieved BSP with a mean dose of 6.2 mg/kg (bolus + infusion) vs. our 3.9 mg/kg in study IV (diazepam premedication + infusion only). The difference in this study's results may be due to bolus and infusion (Illievich et al. 1993) vs. infusion (IV), and to a different definition of BSP; they regarded BSP to be present after 4 s of suppression whereas we regarded BSP to be present after 2-4 s of suppression between bursts. Furthermore, we used higher infusion rate (30 mg/kg/h). Again, plasma propofol concentrations were the same at the attainment of BSP. The addition of remifentanil in two different doses caused significantly faster attainment of end-points, and at lower doses of propofol compared to the saline group (IV).

The infusion dose, plasma concentrations, and effects of propofol, thiopental, and ketamine have not been studied systematically in rabbits previously (I). All our rabbits survived the infusion anaesthesia with different anaesthetics. In a previous study (Peeters et al 1988) where surgical anaesthesia was achieved with nearly the same doses of thiopental as in study I, five of the six rabbits underwent sustained respiratory arrest. Peeters et al (1988) used bolus doses, whereas we used infusion of thiopental. It seems that infusion anaesthesia is better tolerated in rabbits than anaesthesia with repeated bolus doses, which has also been shown in humans (Stokes and Hutton

1991). We showed that norketamine and dehydronorketamine are important metabolites of ketamine in rabbits, as they are in humans (I). Interestingly, plasma concentrations of propofol at loss of reaction to tail clamping and at reappearance of righting reflex were nearly same as during sufficient surgical anaesthesia (measured by purposeful movement to painful stimulus) and awakening concentrations in humans, respectively (Davidson et al 1993, Wessen et al 1993)

F.4. EEG and BIS

The effects of anaesthetic drugs on the EEG have been known for over 50 years. Several monitors which graphically present these changes in compressed, easy to red form have been on the market, but only recently when Aspect in their BIS monitor reduced the information to one single number, the BIS-index, did a breakthrough occur in monitoring the effects of anaesthetics with the EEG (Sebel et al 1997). The BIS index utilizes multivariate analysis and a selection of spectral, bispectral and time domain measures. The actual contribution of bispectral information has been questioned (Miller et al 2004). Another approach was the Entropy module introduced by DATEX (Viertiö-Oja et al 2004). It measures spectral entropy by applying Shannon's function to the power spectrum derived with Fourier transform. It therefore measures how much the slow activity resembles pure sinusoidal waveform, i.e. contrary to what is claimed, it does not evaluate the general predictability or regularity of the signal. Furthermore, it measures EMG of frontalis muscle as did its predecessor, the ABM-monitor (Edmonds and Paloheimo 1985), and burst suppression. Other commercial equipment such as Narcotrend (Kreuer et al 2003) or SNAP (Willmann et al 2002) also mainly rely on spectral power estimates; phase as well as pattern information is not used except for burst suppression detection.

The above-mentioned indices work with different anaesthetics and certain index values can be roughly used as estimates of the level of anaesthetic medication as the indices change monotonically with increasing drug concentrations (Sebel et al 1997, Bruhn et al 2000b). The indices are only intended to estimate the hypnotic component of anaesthesia, not muscle relaxation or reflexes. Being derived from the brain's cortex, the indices are not good at predicting movement of the patient in response to pain. BSP is a sign of intermittent suppression of majority of cortical cells (Steriade et al 1994), indicating that the cortex is not capable of functioning normally. There is not a single report suggesting memory of events at this level of anaesthesia. While this level is unnecessary deep for most routine surgery, short suppressions are frequently seen during induction of anaesthesia with bolus doses. The pattern is easy to detect with little practice, and therefore could be a very useful

indicator of the appropriate point for, for instance, intubation with minimal risk of catecholamine activation. Therefore, we chose the BSP of the EEG, the level of which is easily defined as suppression durations between bursts (III, IV). Automatic detection of BSP (V) might increase its value for research, but the results of study III shows that cardiovascular reflexes are still highly variable apart from loss of CA response with propofol at BSP level.

The pharmacokinetic profile of thiopental is not ideal for infusion anaesthesia. Additionally, thiopental has been claimed to be worse than propofol in attenuating the cardiovascular and CA responses to intubation. These conclusions have been made from studies where the depth of anaesthesia was controlled by analysis of clinical signs. We hypothesized that more precise information might be obtained about differences in reaction to tracheal intubation between propofol and thiopental when unconsciousness is controlled by aid of the BSP. Thiopental is an old and standard anaesthetic, and it is still widely used. Our study III was not intended to provide new margins for a cardiovascular safety of intubation. We excluded patients at risk from our study population. We hoped to find a better tool for studies comparing induction agents at tracheal intubation. We found that at BSP level, thiopental attenuated the hemodynamic response to intubation nearly as well as propofol, but propofol better attenuated the CA response.

The biphasic effect of propofol and thiopental on the EEG is one reason for the imperfect prediction of the EEG parameters. Initially an increase of fast activity occurs, with an increase in power in the beta range (propofol blood concentration: 1-2 μg/ml) (Seifert et al 1993); increase of slow activity, and finally burst suppression follow. There is a problem, therefore, interpreting the meaning of a particular value of an EEG indicator (Bührer et al 1992), because one indicator value may result from two different plasma concentrations.

It has been reported that during isoflurane anaesthesia, median frequency and spectral edge frequency based indices may produce illogical values during the BSP (Thomsen and Prior 1996). That phenomenon can be solved by reliable BSP detection. The BIS is a univariate index that combines several disparate descriptors of the EEG into a single value and it is not without problems in detecting BSP or unconsciousness; at the beginning of BSP, BIS does not indicate an increased anaesthetic drug effect (Bruhn et al 2000a, Bruhn et al 2001); and with rapidly changing drug concentrations during the induction of anaesthesia, BIS could not be correlated to the moment of loss of consciousness (Kuizenga et al 2001). Different anaesthetics produce very different burst suppression patterns (Akrawi et al 1996, Watts et al 1999, Jäntti et al 2002), indicating their different mechanisms of action. It is obvious that differences in EEG and BSP with different anaesthetics have an effect on BIS monitoring. If one would produce a separate algorithm for each

anaesthetic, the BIS would be more accurate. Our measure of depth of anaesthesia (III, IV) was a certain level of BSP (2-5 s suppressions between bursts) or loss of reflexes (III). When one anaesthetic drug is employed**,** BSP starts at a BIS level around 40 (Bruhn et al 2000a, Ludbrook et al 2002); at that level the patient is deeply unconscious. Approximate entropy, a measure of signal complexity and regularity, quantifies EEG changes during anaesthesia and classifies correctly the occurrence of BSP as increasing anaesthetic drug effect, but EEG median frequency or spectral edge frequency 95 without burst compensation do not (Bruhn et al 2000c, Bruhn et al 2001).

We conclude that these EEG-based indices are useful in research only when changes can be explained with changes in the original EEG; for instance, increase of fast or slow activity or onset of burst suppression. Particularly, we must then carefully confirm that when univariate indices are used, whether BIS, spectral edge, median frequency, or spectral entropy etc, their calculation is sound; i.e. the EEG used for spectral estimate is stationary, for example. Calculation of power spectrum during burst suppression, for instance, is not mathematically correct, as can be seen from Fig 1, which demonstrates the non-stationarity of the signal. Studies of the topography of EEG, as well as evoked and event-related potentials, should yield important insight in the cerebral function.

F.5. Clinical implications

In rabbits we showed that propofol, thiopental, and ketamine are poor analgesics when used alone in cases where tail clamping is used as the pain stimulus. During non-noxious diagnostic procedures, propofol seemed to be the best choice because recovery was rapid and breathing pattern was well preserved during infusion. During painful surgical procedures, additional analgesics are obviously necessary and study I provides guidelines for effective doses and concentrations for hypnotic and CNS end-points.

In studies II and III it was clearly shown that propofol attenuates better the CA response to tracheal intubation than thiopental, but neither of them totally blocked cardiovascular response. We hypothesized that more precise information might be obtained on the reaction to tracheal intubation when unconsciousness was controlled by aid of the BSP, but cardiovascular reflexes were still highly variable at BSP level apart from loss of catecholamine response with propofol. However, we found that at BSP level, thiopental attenuated the hemodynamic response to intubation nearly as well as propofol. We think that when unconsciousness is measured more objectively than by loss of reflexes, e.g. using BSP, more accurate information may be received about different responses and actions of anaesthetic drugs.

Our results demonstrate that the BIS value at BSP onset is variable and depends on the presence of opioid, among other factors. BIS depends on a variety of processes; i.e. oscillations in the EEG. BSP is another very different nonlinear oscillation, which is partly independent of the other processes. Our results demonstrate that alfentanil and remifentanil at higher doses are effective in reducing injection pain at the propofol infusion site. Loss of verbal command was better than loss of counting to measure loss of consciousness during anaesthesia induction, because all except one patient in high dose remifentanil group reacted to verbal command after loss of counting (IV). Remifentanil given before steady infusion of propofol significantly reduces propofol doses and shortens the times to reach hypnotic, analgesic, and EEG end-points. Effects of the combination of remifentanil and propofol on BIS values at analgesic and EEG end-points were logical, but were illogical at hypnotic end-point (IV).

We analyzed BSP differences between propofol and thiopental and showed that BSP can be detected automatically with our method (V). This automatic detection is useful when comparing different anaesthetics at certain EEG effect level. It is also useful when BSP level of anaesthesia is needed.

SUMMARY AND CONCLUSIONS

In this study, differences, effective doses, and concentrations of propofol and thiopental in hypnotic, analgesic, and EEG end-point were evaluated. Nine New Zealand White rabbits, and 143 patients scheduled for elective surgical procedures were studied. Infusions of propofol and thiopental were used in all studies (I-V); bolus doses were used as an induction of anaesthesia in study II before the infusion of the anaesthetic agent started. Furthermore, in study III there was two bolus groups (loss of reflexes) as controls. In addition to propofol and thiopental, ketamine was used in study I.

1. A comparison of ketamine, propofol, and thiopental in rabbits revealed propofol to be the best choice during non-noxious diagnostic procedures because recovery was rapid and breathing patterns were well preserved during infusion. Recovery was prolonged after thiopental and ketamine. Effective doses and concentrations for hypnotic and analgesic end-points were defined. The main metabolites of ketamine in rabbits were norketamine and dihydronorketamine.

2. Alfentanil 17.5 μg/kg given 2 min before tracheal intubation with propofol 2.0 mg/kg or thiopental 5 mg/kg, followed by infusion attenuated arterial pressure response but not heart rate response (II). Neither infusion of propofol (12 mg/kg/h) nor infusion of thiopental (18 mg/kg/h) could attenuate the cardiovascular or catecholamine response to the insertion of the operating laryngoscope 10 min after alfentanil bolus (II). The response of SAP and ADR was more pronounced with thiopental (II).

According to the present study, propofol better attenuates the catecholamine response to tracheal intubation than thiopental (II, III), especially the NOR response (III). This partially explains the differences in cardiovascular responses to tracheal intubation between propofol and thiopental. In fact, CA response to tracheal intubation was almost totally blocked during burst suppression pattern (BSP) of EEG induced by propofol. It is obvious that neither propofol nor thiopental alone can totally block the cardiovascular response to tracheal intubation. This shows that mechanical stimuli from the larynx and the base of the tongue are important in mediating the cardiovascular responses to tracheal intubation.

3. Our hypothesis that more precise information might be obtained on the reaction to tracheal intubation when unconsciousness is controlled by aid of the BSP instead of clinical signs was not supported. Levene's test showed insignificant differences of variance between BSP level anaesthesia compared with loss of reflexes level anaesthesia (III). Cardiovascular reflexes were still highly variable at BSP level except for the loss of catecholamine response with propofol. However, we did find that at BSP level, thiopental attenuated the hemodynamic response to intubation nearly as well as propofol (III).

4. The effective doses of thiopental at hypnotic and EEG end-points were determined (III). Remifentanil infusion started before the infusion of propofol significantly reduced times and doses of propofol at the attainment of hypnotic, analgesic and BSP end-points (IV). Remifentanil also affects the BIS value at BSP onset level. However, when remifentanil was present, plasma concentrations of propofol were not reduced at BSP end-point as they were in hypnotic and analgesic end-points (IV). These results suggest that remifentanil is kinetically useful for loss of consciousness because it accelerates the hypnotic onset of propofol.

5. The arterial concentrations of thiopental and propofol at the onset of BSP were determined (III, IV). Propofol and thiopental have certain similarities in burst suppression pattern of EEG, but differences exist especially in the terminal parts of the bursts (V). During BSP induced by propofol 13-15 Hz spindle oscillations are seen both during bursts and suppressions. These oscillations are also present at a continuous suppression level. Different anaesthetics produce different BSPs indicating their different mechanisms of action. An algorithm for automatic detection of BSP was developed (V). Automatic detection is useful when comparing different anaesthetics at certain EEG effect level and when BSP level of anaesthesia is needed.

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ORIGINAL COMMUNICATIONS