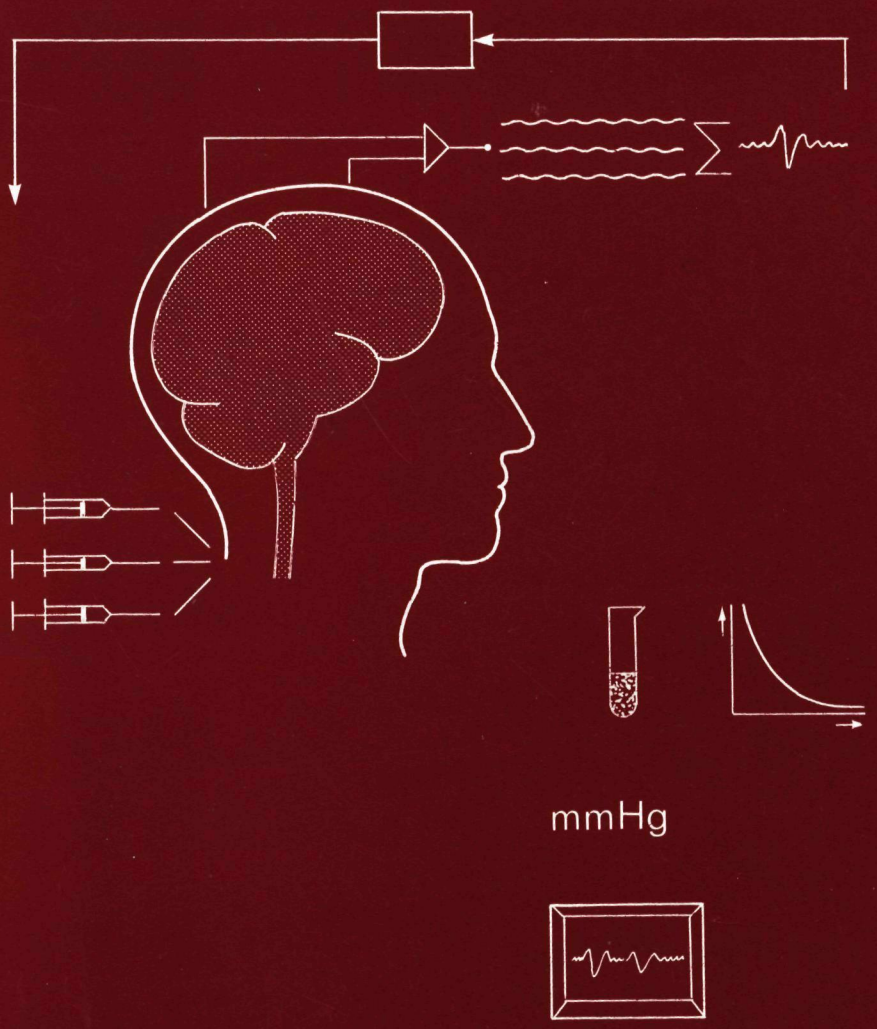
DEPTH OF INTRAVENOUS ANESTHESIA

clinical signs against farmacokinetic and neurophysiological parameters



Herman Bernard Hendrik van Beem

DEPTH OF INTRAVENOUS ANESTHESIA

CLINICAL SIGNS AGAINST FARMACOKINETIC AND NEUROPHYSIOLOGICAL PARAMETERS

Cover design Cees Nicolasen

DEPTH OF INTRAVENOUS ANESTHESIA

CLINICAL SIGNS AGAINST FARMACOKINETIC AND NEUROPHYSIOLOGICAL PARAMETERS

Een wetenschappelijke proeve op het gebied van de

MEDISCHE WETENSCHAPPEN

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Katholieke Universiteit Nijmegen,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op
dinsdag 19 januari 1993
des namiddags te 3.30 uur precies

door

Herman Bernard Hendrik van Beem
geboren op 5 november 1943 te 's-Gravenhage

Promotores: Prof Dr. J.F. Crul
Prof. Dr. S.L.H. Notermans

To my Parents
To Corry, Roald, Robin

The following papers form chapters 3,4,5:

Chapter 3: HBH van Beem, H Meulman, A VanPeer. Clinical experience with a fixed rate of alfentanil infusion. European Journal of Anaesthesiology 1987;Supplement 1:31-34.

Chapter 4: H van Beem, A VanPeer, R Gasparini, R Woestenborghs, J Heykants, H Noorduin, J van Egmond and J Crul. Alfentanil pharmacokinetics during and after a fixed rate infusion. British Journal of Anaesthesia 1989;62:610-615.

Chapter 5: H van Beem, A Koopman-van Gemert, H Kruls, SLH Notermans. Spinal monitoring during vertebral column surgery under continuous alfentanil infusion. European Journal of Anaesthesiology 1992;9:287-291.

CONTENTS

CHAPTER 1

INTRODUCTION AND AIMS OF THE STUDY

INTRODUCTION

During the administration of an anesthetic the anesthesiologist constantly has to make decisions about the dosage of a number of potent drugs. As a basis for these decisions ideally the anesthesiologist should be able to constantly compare desired effect with observed effect. The desired effect means an unconscious patient without awareness and either conscious or subconscious recall and who will wake up quickly after cessation of the administration of anesthetic drugs. However the assessment of consciousness or awareness during anesthesia is still an unresolved problem.

In recent years drugs for use during anesthesia with high receptor specificity have become available. These drugs are short acting and are relatively free of side effects. They have brought within reach the separate production of some of the requirements of anesthesia, i.e. analgesia, unconsciousness and muscle relaxation. For these reasons anesthesia by continuous infusion is gaining increasing popularity [1]. In this thesis intravenous anesthetic drugs are investigated. Both a potent short acting analgesic -alfentanil- and a short acting hypnotic -propofol- are studied. Anesthetic depth in inhalation anesthesia has always been monitored by observing clinical signs such as sweating, tear formation and the cardiovascular parameters blood pressure and pulse rate. Because of the relative lack of side effects, these signs, however, are not reliable during intravenous anesthesia, particularly during light levels. Therefore to avoid too light anesthesia with the possibility of awareness during intravenous anesthesia additional techniques for monitoring of anesthetic depth are needed. We chose to

investigate the use of two types of neurophysiologic monitoring: SomatoSensory Evoked Potentials and EEG. We expected modulation of the conduction along sensory pathways by the analgesic to become detectable in the SomatoSensory Evoked Potentials. The effects of the hypnotic drug on spontaneous activity of the brain were expected to show in the frequency content of the EEG signal.

AIMS

We define the aims of this study as follows.

1. Exploration of two intravenous anesthetic drugs. By testing a pure analgesic and a pure hypnotic in separate experiments, we try to show the clinical usefulness of both drugs in future intravenous techniques. This part of the work will give some answers to the question how well these drugs fulfil the criteria of steady state intravenous anesthesia.

2. Testing the possibilities of using Neurophysiological monitoring for the assessment of anesthetic depth during these two types of intravenous anesthesia.

3. Efforts to correlate three elements in the determination of anesthetic depth during intravenous infusion of these drugs: clinical signs, neurophysiological changes and plasma concentration.

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CHAPTER 2

LITERATURE

HISTORY

Techniques of general anesthesia

From the first days of anesthesia until early in the twentieth century general anesthesia was produced by inhalation of a volatile anesthetic as a "mono anesthetic" -usually ether or chloroform. The advent of the barbiturates marked a gradual change towards anesthetic techniques which included intravenous drugs. As early as 1938 the favourable interaction of Nitrous Oxide and barbiturates was recognised [1]. Also the importance of combining barbiturates with analgesics was stressed and nitrous oxide and pethidine were recommended in a number of papers [2],[3]. Gradual evolution of these concepts have led to the development of five groups of general anesthetic techniques.

1 Intravenous induction with a hypnotic -which sole effect is to produce unconsciousness- or an inhalation induction followed by maintenance with inhalation agents. This technique is commonly known as "Inhalation anesthesia"
2 Intravenous induction with a hypnotic followed by a combination of a potent analgesic and a high dose of a neuroleptic. These techniques are known under the name of "Neurolept anesthesia"
3 Intravenous induction with a hypnotic followed by a combination of intravenous analgesics, neuromuscular relaxants and sometimes small doses of benzodiazepines or neuroleptics supported by artificial ventilation with Nitrous Oxide in Oxygen. This is the most widely used form of "Intravenous anesthesia"

4 Induction and maintenance of anesthesia by high dose opioids, usually in combination with a benzodiazepine or nitrous oxide. These techniques are commonly called "Narcotic anesthesia".

5 Intravenous induction with a hypnotic and analgesic, followed by the same hypnotic, an analgesic and a neuromuscular relaxant, all given exclusively intravenously. These techniques are grouped under the name "Total Intravenous Anesthesia".

ad1 Inhalation anesthesia is not a subject in this thesis.

ad2 These techniques originate from the 'lytic cocktail' described by Laborit and Hugenard in 1954 [4] [5]. This type of anesthetic technique is called "Neurolept". The term Neurolept to indicate the combination of potent analgesic and neuroleptic (or tranquillizer) drugs was first described by de Castro and Mundeleer in 1959 [6]. Initially the name Neurolept Analgesia was used to indicate that patients were not necessarily unconscious, but gradually this term has been used almost indiscriminately with Neurolept Anesthesia, and the subtle difference between the neuroleptic and anesthetic states has disappeared.

ad3 These techniques were grouped under the name "Balanced Anesthesia". This term was revived and publicized by Gray and Rees in 1952 [7] from earlier work by Lundy [8].

ad4 The use of morphine as a single anesthetic agent was first described by Lowenstein and co-workers in 1969 [9]. They used it in patients with severe heart disease presenting for cardiac surgery. Although the patients did not show any response to surgical stimulus, a high rate of awareness was reported. These reports led to a search for an improved hypnotic component of the technique by addition of other agents, for example a benzodiazepine as premedicant, or nitrous oxide peroperatively.

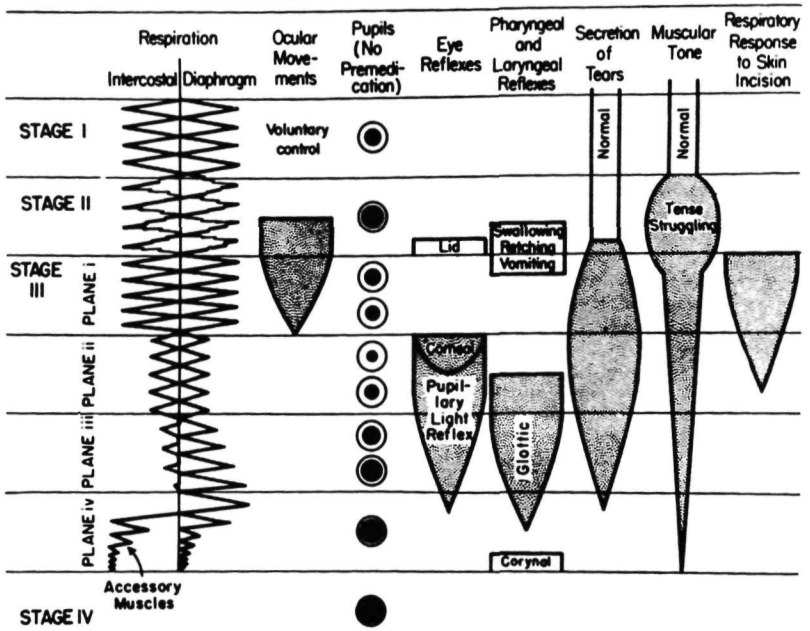
ad5 In Total Intravenous Anesthesia all drugs are given intravenously. Many anesthesiologists consider Total Intravenous Anesthesia as an ideal technique because it allows separate control over

hypnosis, analgesia and muscle relaxation. Also, with proper use of the technique, it allows for faster induction and recovery [10].

Anesthetic depth

Fig. 2.1

Gillespie's modification of Guedel's chart for the signs and stages of anesthesia. From Gillespie NA. The signs of anaesthesia. Anesth Analg Curr Res 1943;22:275. Reproduced with permission.



In the literature no perfect definition of anesthetic depth can be found. Using the effects of ether as a guide Guedel described his concept of stages of general anesthesia around 1937 [11] {Fig.2.1}. With the introduction into anesthesia of muscle relaxants and of intravenous anesthetics the stages of Guedel no longer applied for the following reasons. Neuromuscular relaxants posed a particular problem as seven of the nine components of Guedel's system involved the gradual

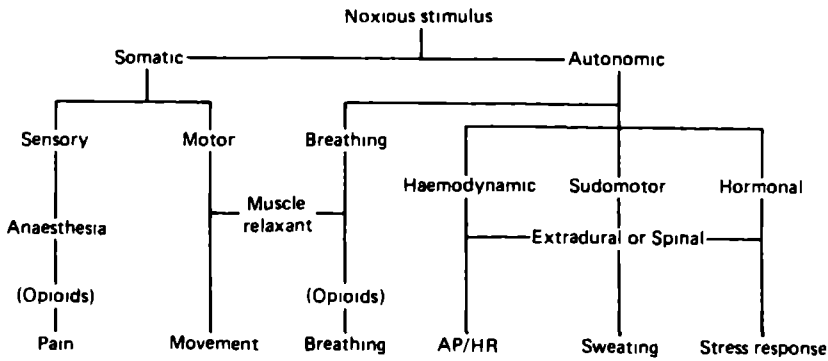
abolition of skeletal muscle activity. Barbiturate induction can produce a state that fulfils the criteria for Guedel's stage 3, yet when a skin incision is made the patient will move as if in stage 2. Woodbridge in 1957 tried to solve this problem by defining the necessary components of general anesthesia [12]. He concluded that anesthesia should consist of the suppression of four components of neuronal activity:

- Sensory (afferent) pathways.
- Motor (efferent) pathways.
- Reflexes (autonomous)
- Mental (state of sleep or unconsciousness).

From these elements he derived the signs that could be interpreted as an indication of insufficient depth. His paper included the first scientific recognition that a rise in pulse rate or blood pressure marks too light an anesthetic depth.

Fig. 2.2

Suppression of responses to noxious stimuli. Ranked from left to right in the order in which they are suppressed by general anaesthetics. From Prys-Roberts C. British Journal of Anaesthesia 1987;59:1342. Reproduced with permission.



In 1987 in an editorial in The British Journal of Anaesthesia Prys Roberts gave a reappraisal of the concept of anesthetic depth [13]. He defined general anesthesia as a state of absence of perception of noxious stimulation as transmitted by the sensory nervous system. According to his theory the other three elements mentioned by Woodbridge are only secondary to the blocking of sensory (afferent) stimulation. Anesthetic depth should then be monitored by observing and or monitoring the various responses to noxious (surgical) stimulation. (Fig.2.2)

PRESENT SITUATION

Intravenous anesthesia

Definition

Intravenous anesthesia is anesthesia produced by intravenously administered drugs, without the use of volatile anesthetics. In this thesis we will make a differentiation between total intravenous anesthesia and intravenous anesthesia. In total intravenous anesthesia the patient is ventilated with an air/oxygen mixture; in intravenous anesthesia the patient is ventilated with a nitrous oxide/oxygen mixture while all other drugs are given intravenously. Nitrous oxide contributes both to the analgesic and the hypnotic effects of the intravenous drugs. The recent development of powerful drugs with a high receptor specificity and favourable pharmacokinetics makes it possible to produce all objectives of general anesthesia by selectively injecting or infusing separate drugs. This is gradually making intravenous anesthesia a clinical reality. The techniques described in this thesis could be seen as recent additions to the group of techniques formerly called balanced anesthesia, now called intravenous anesthesia.

Objectives of general anesthesia

In spite of the new approach by Prys-Roberts, the components of general anesthesia as defined by Woodbridge can still serve as the basis for the development of an intravenous anesthetic technique.

- Analgesia

Providing analgesia is probably the most important task for the anesthesiologist since only with adequate analgesia can both mental suffering from pain and the potentially harmful stress response to surgery be mitigated. In general anesthesia opioids is the group of drugs most frequently used to produce the desired analgesia. For the purpose of intravenous anesthesia the use of an ultra short acting powerful synthetic analgesic allows titration of analgesia to the needs of the individual patient and to the stage of the surgical intervention without prolongation of recovery or postoperative respiratory depression.

- Muscle relaxation

Muscle relaxation serves two important functions. Firstly it prevents reflex muscle contraction upon painful surgical stimulation, making surgical access possible to body cavities especially in the case of abdominal surgery. Secondly it facilitates intubation and artificial ventilation. Through the reduction of sensory input into the reticular formation muscle relaxation may play a role in increasing anesthetic depth. Pancuronium has been shown by Forbes and coworkers to decrease Minimal Alveolar Concentration (=MAC) for Halothane [14]. MAC is the minimal concentration in the alveoly of the lung of an inhalation agent needed to abolish movement in response to surgical incision in 50% of a standard patient population. More research will be needed to show the true nature and the importance of this reduction in MAC with muscle relaxation.

- Autonomic reflex suppression

Tissue damage by surgery or manipulation of internal organs produces reflexes mediated through the autonomous nervous system. In

intravenous anesthesia suppression of these reflexes is produced by the combined effects of sedatives -especially neuroleptic drugs- , hypnotics and analgesics. The addition of specific drugs such as the vagolytics atropine or glycopyrrolate and alpha and beta adrenergic blocking drugs may sometimes be helpful or even necessary.

- Unconsciousness

Unconsciousness in the context of general anesthesia is a state of the central nervous system of reversible suppression of its response to external and internal sensory input. Drugs that have as their main effect to cause unconsciousness are commonly called hypnotics. In intravenous anesthesia unconsciousness is produced and maintained by a combination of effects from various drugs. In the context of total intravenous anesthesia a continuous infusion of a pure hypnotic will produce sleep which is enhanced by sedative effects from narcotic analgesics and or neuroleptics. Alternatively a high dose of a narcotic analgesic will produce heavy sedation or even light sleep which can be deepened by combining it with nitrous oxide or a low dose of a hypnotic. In this type of narcotic sedation the most important receptor involved is the μ opiate receptor, but other receptors including the GABA receptor might also be involved [15],[16].

Drugs to be used in intravenous anesthesia

From the literature some of the properties can be distilled that would be required to make ideally suitable drug components of an intravenous technique.

The 'ideal' narcotic

Based on their experience with morphine as an intravenous anesthetic, Moldenhauer and Hug [17] stated that the ideal narcotic in a narcotic intravenous technique has the following properties:

- Greater specificity and efficacy than that of existing narcotics. This would require higher receptor affinity.
- Analgesia without: respiratory depression, nausea or intestinal cramping.

- Fast onset and short duration of effects. This would allow better control over intensity of analgesia as a change in dose or infusion rate would quickly show its effect.
- Non-addictive, lack of tolerance. This becomes more important when the duration of (continuous) administration increases.

The 'ideal' hypnotic

Based on our own experience in combination with comments given in literature we state as some of the properties an ideal hypnotic should have.

- Fast acting with smooth induction.
  Fast onset of action means a fast induction. Rapid transition to deeper levels of anesthesia usually mean smooth induction with little or no excitatory phenomena. Also an injection or a change in infusion rate is quickly followed by a change in effect thus allowing titration of effect against need. Ideally the effect should start after one circulation time.
- Short acting with fast recovery.
  Short action of an intravenous drug can mean rapid redistribution or a short elimination half life. In both cases the effects of the drug will disappear quickly after termination of an infusion. A short elimination half life is preferable to only rapid redistribution. The reason for this is that for a drug that is purely redistributed, significant elimination from the body continues after recovery of the patient carrying the risk of depression of the central nervous system lasting into the postoperative period.
- Specific without side effects.
  High specificity means that the drug has only one principal action and thus has few other effects. Such a drug will mainly interact with one type of receptor or one group of receptors. This makes the effects of varying doses predictable.

- Metabolites
  Metabolites should have no (hypnotic) effect. With prolonged infusion of the drug the accumulation of metabolites might otherwise prolong hypnotic effect.

Intravenous versus inhalation anesthesia

Side effects
All inhalation anesthetics known to date have side effects particularly on the heart and blood vessels. These side effects are dose dependent meaning that for an increase in anesthetic effect also inevitably these side effects are increased. Recently developed drugs used for intravenous anesthesia have been reported to produce much less side effects on the circulation. Thus in the range of effects normally used these drugs will not neccessarily cause a clinically significant change in circulatory variables.

Recovery
The newer hypnotic drugs have very short elimination half lives. Recovery from intravenous anesthesia can therefore be fast. Especially for propofol short recovery times have been published. In one report the initial distibution half life, $t_{1/2\alpha}$, was calculated at 23.6 min [18]. Also the quality of recovery measured with simple cognitive tests was described as superior, both in adults and in children [19], [20].

Environmental considerations
All inhalation agents in use today are halogenated carbo-hydrates. Whether scavenging of waste gases is used or not, any gases not metabolised by the patient are eventually vented into the atmosphere thus contributing to pollution. With the increasing acceptance of closed or low flow systems this consideration loses some of its importance.

Occupational hazard
When inhalation anesthetics are being used all operation theatre personnel is continuously exposed to low concentrations. Many studies

have shown trace concentrations of nitrous oxide and of volatile anesthetics in the working environment of operating theatre personnel. In one study 5-10 ppm Halothane was found within a 1 meter radius of a semiclosed circle anesthesia circuit [21]. The consequences of this type of exposure to low concentrations are as yet not fully clear. A number of animal studies and some statistical studies in theatre personnel suggest potentially harmful effects [22]. The large number of people exposed to a potential occupational hazard warrants attempts to eliminate all risks. Expensive systems for scavenging can in part solve this problem but exposure will still occur. The use of total intravenous anesthesia would avoid these hazards altogether.

Anesthetic depth

Definition

Although a partly intuitive, partly objective assessment of anesthetic depth is made by the anesthesiologist as part of patient monitoring in every case it is very difficult to give a clear and simple definition of anesthetic depth. Anesthetic depth could be described as the level of depression of all responses to noxious (surgical) stimulation. This needs depression of consciousness, pain perception, muscle responses and autonomic reflexes.
For the purposes of this thesis we will use the following definition:

Anesthetic depth is the degree of suppression of consciousness and responsiveness of the central nervous system to noxious stimulation.

The ideal indicator of anesthetic depth.

According to Sebel [23] a good indicator of anesthetic depth should fulfil the following requirements:

1. It should show graded responses to changing anesthetic depth at all levels from light sedation to deep surgical anesthesia.
2. It should be independent of anesthetic technique and respond to surgical stimulus when anesthesia is inadequate.

3 The indicator should be easily quantified, readily interpreted, and be unaffected by such routine operating theatre interference as electrocautery and other electrical interference.

Anesthetic depth in clinical practice

Muscle response

During light anesthesia without full muscle relaxation movement in response to surgical stimulation is a very important clinical sign of insufficient anesthetic depth. Two types of response are seen according to increasing depth. First at lighter levels there is either a purposeful or an uncoordinated movement of arms or legs. At deeper levels only a tightening of facial musculature "frowning" can be noticed. The use of movement as indicator of depth was further developed by Tunstall and coworkers [24]. Before full curarization of their patients they isolated one forearm from the circulation by inflating a tourniquet. They then prompted the patient verbally to show awareness by movement of the isolated arm. Thus even in the curarized patient movement can be used to indicate inadequate anesthetic depth. Subsequent research has shed doubt on the accuracy of the isolated forearm technique for the detection of awareness [25].

Respiration

When a patient is breathing spontaneously during inhalation anesthesia the pattern of respiration is a very important sign of anesthetic depth. In the lightest planes of anesthesia breathing is irregular, becoming regular and automatic with a fixed inspiration/expiration ratio when anesthesia deepens. At the deepest levels of anesthesia respiration becomes increasingly depressed, finally leading to complete cessation of respiration. In intravenous anesthesia the pattern of breathing is mainly determined by the central effect of hypnotics and opioids. When breathing becomes progressively depressed and the patient has to be ventilated artificially this clinical sign is no longer of use.

Autonomic response

According to Prys-Roberts three types of autonomic response to surgical stimulation play an important role in the determination of anesthetic depth [13]. These are:

1 Haemodynamic. This response is a consequence of sympathetic stimulation leading to peripheral vasoconstriction and direct adrenergic stimulation of the heart. Also the parasympathetic system can show response to surgical stimulation, usually in the form of bradycardia.

2 Sudomotor. This reflex is characterized by sweating. It is produced by sympathetic stimulation.

3 Hormonal. A number of hormones, amongst others catecholamines, insulin and growth hormone are secreted in higher concentration under conditions of surgical stress [26], [27].

The importance of measuring anesthetic depth

Patient Safety

Because in intravenous anesthesia clinical signs as mentioned above are unreliable, there is always the risk that either too light or unnecessary deep levels of anesthesia go unnoticed. Too light an anesthesia may lead to awareness with possibly harmful psychological effects and to a potentially harmful stress response. Too deep a level of anesthesia by drug overdosage gives rise to perioperative side effects and prolonged recovery with undesirable depression of respiration and circulation.

Clinical assessment of anesthetic depth in intravenous anesthesia

Introduction

The drugs used in intravenous anesthesia do not produce the generalised central nervous system depression as the inhalation agents do. For example the use of opioids prevents pupillary dilatation.

Therefore the stages of anesthetic depth as described by Guedel, can not be applied to this type of anesthesia. One of the biggest problems remaining is that no monitoring is known to discriminate completely between effects of the hypnotic and the analgesic. No clear advice can be found in the literature on how to decide which drug to supplement when a patient's response to surgical stimuli is observed.
Clinical observation to assess anesthetic depth in intravenous anesthesia consists of a number of observations meant to estimate the amount of autonomic nervous stimulation and of observation of other signs of response to painful stimulation. Autonomous stimulation can be assessed by measuring changes in blood pressure and heart rate and by looking for sweating and signs of peripheral vasoconstriction. Signs of reaction to pain are movement of extremities, eyebrow movement and lachrymation. All these signs combine to give an overall impression that is in part intuitively interpreted by the experienced anesthesiologist to arrive at an estimate of anesthetic depth.

Circulation

Circulatory side effects are much less with intravenous agents than with inhalation agents. Also effects of intravenous agents on the circulation do not always show a linear dose effect relationship. Therefore depression of blood pressure and/or cardiac output alone cannot be employed for objective determination of the anesthetic depth during intravenous anesthesia.

Muscle response

Neuromuscular relaxants form part of most techniques of general anesthesia. When the capability of the patient to use skeletal muscles changes throughout the procedure, this prevents patient movement to be used as a consistent measure of anesthetic depth.

Respiration

The change in respiratory pattern and respiratory rate produced by narcotic analgesics makes respiration an unreliable parameter for

assessment of anesthetic depth in intravenous anesthesia. Paralysis of respiratory musculature with neuromuscular relaxants as is the case in most intravenous techniques precludes it altogether.

Autonomic response

Autonomic reflex suppression by intravenous drugs and/or the use of autonomous nervous system blocking drugs makes the use of a rise in pulse rate and blood pressure less reliable in the prediction of light levels of anesthesia as reports of awareness during anesthesia have shown [28].

Techniques for monitoring anesthetic depth in intravenous anesthesia

Neurophysiology

Monitoring of anesthetic depth in intravenous anesthesia should take into account the fact that separate drugs are being used to produce the desired effects. The description of the concept of anesthetic depth as defined earlier in this chapter explains why we feel that any type of monitoring should at least consist of tests of depression of consciousness and of pain response. Both drug actions involve the central nervous system. That is why in this thesis we concentrate on techniques of monitoring central nervous system activity for objective assessment of anesthetic depth.

Plasma concentration

Modern hypnotics and analgesics are all drug with good lipid solubility and rapid penetration of the blood-brain barrier. This means that there is a good correlation between drug effect and concentration in the plasma. It would even be more ideal if concentration could be measured at the target receptor, but this is for the time being impossible. The only drawback with the use of plasma concentration as gauge of anesthetic depth is that estimation of drug concentration can only be performed off line, which is a time consuming process. This method finds at present only use as a posteriori check of other on line measurements or

as check of computer prediction in open loop controlled infusion. Developments of immuno essay in combination with ion sensitive field effect transistor techniques might in future offer the possibility of on line plasma concentration measurement [29].

Neurophysiological monitoring

As defined above anesthetic depth is derived from the absence of responses. All responses are elicited through the central nervous system. From there it follows that a monitor of anesthetic depth should measure the suppression of the central nervous system caused by the drugs used.

In clinical neurophysiology techniques for monitoring spontaneous and evoked electrical activity from the central nervous system have been developed. These signals can give an indication of the level of spontaneous or evoked activity of central nervous system structures. For any form of neurophysiological monitoring to be of value as a monitoring tool for anesthetic depth it is necessary that the result be a real time signal and can easily be interpreted by the anesthesiologist. Preferably the result must be in a form that allows for quantitative measurement. It has been the advent of mini- and microcomputers that has made it feasible to perform real time analysis of neurophysiological signals.

We will continue by looking in more detail into the techniques employed in clinical practice.

Types of neurophysiological monitoring

Electroencephalogram

The Electroencephalogram (EEG) is formed by the spontaneous potential changes of neurones in the cerebral cortex recorded by surface electrodes from the scalp. Using the raw EEG signal to measure anesthetic depth presents a problem. The most common form of processing is visual assessment of amplitude, frequency content and change in time of the signal. To perform this kind of evaluation a great deal of expertise is needed. Most important, the raw signal has too high

a content of information to allow on line visual quantification of anesthetic depth. Therefore methods to reduce the complexity of the signal and to simplify the presentation of relevant information contained in the EEG have been developed. These methods are based on data reduction and data compression.

Methods of data reduction

A commonly employed technique of EEG monitoring in the operating room uses two channnels of EEG, one from each hemisfere. This supposes that the changes produced during anesthesia are global, not focal. This means that enlarging the area of brain under a pair of electrodes does not make the information invalid. The amplitude, frequency and time domains are combined and often compressed to derive a visually identifiable tracing that represents electrical activity per lead over a fixed period of time. A clear review of techniques of data reduction was given by Levi et al in 1980 [30]. At present the most important means for data reduction is a mathematical technique called Fast Fourier Transform (FFT). FFT is a computer algorithm for the Fourier power spectrum analysis. It can be performed in microseconds by a microcomputer and calculates the power of all sinus wave components that add up to reproduce the original signal of an epoch of EEG.

Data compression

The resultant data stream from the Fourier Transformation is often further compressed to obtain an image of change over time that can easily and quickly be interpreted. The plot of power against frequency is smoothed and presented in graphical form where the data related to subsequent epochs are plotted with an upward shift. Parts of the previous spectrum that fall behind the next spectra are not plotted according to a hidden line suppression algorithm. A plot results of consecutive EEG epochs where frequencies representing significant power in the raw EEG show up as quasi mountains. Such a plot is

Fig. 2.3

Formation of the compressed spectral array (CSA). From Levy WJ et al Automated EEG processing for intraoperative monitoring. Anesthesiology 1980;53:227. Published with permission.

A Successive Power Spectra.

B Spectra are plotted with small vertical displacement indicating time.

C Hidden line suppression algorithm is employed.

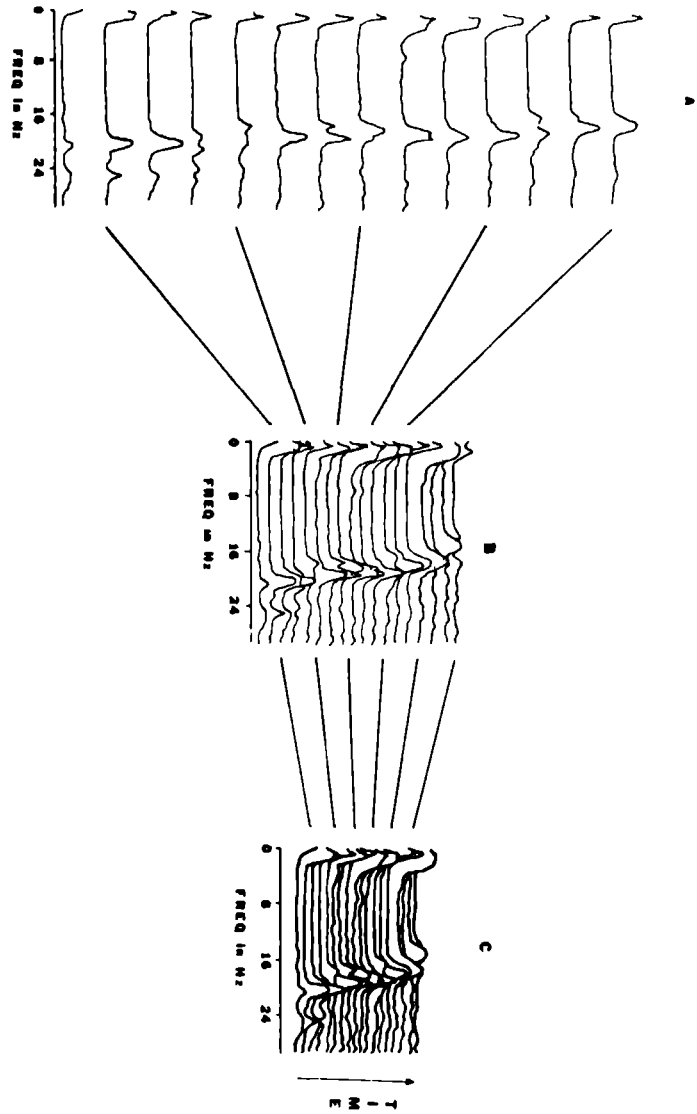
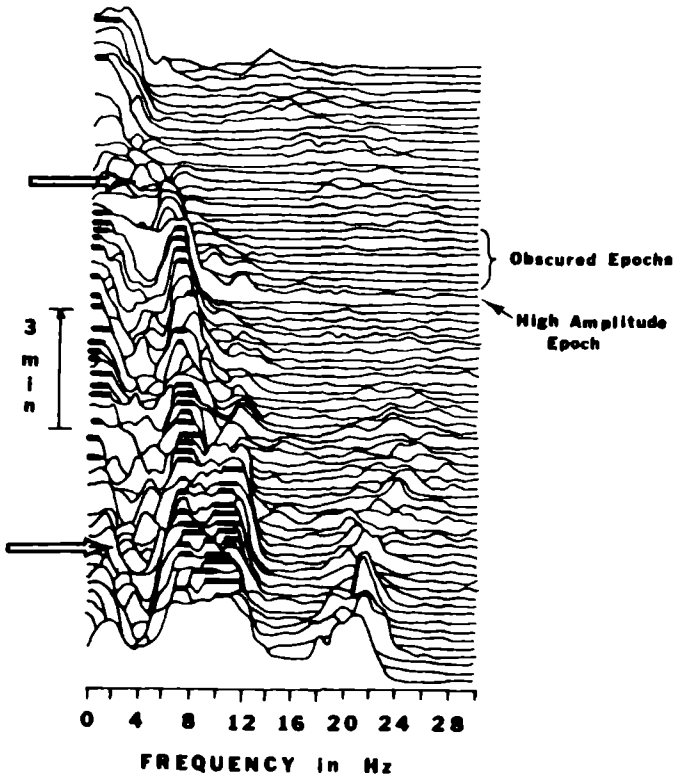


Fig. 2.4

Problems with the linear display of the spectral analysis (CSA).
1) Loss of data. An epoch of high-amplitude acivity is shown obscuring part of the data in subsequent epochs for almost 3 min. Any changes in the 0-7 Hz range of the EEG during this time would not be detectable. In an effort to prevent an even greater loss of data when very high amplitude activity occurs "hills" may be truncated, as indicated by the heavy horizontal lines. Unfortunately, this only changes the nature of the data lost, it does not prevent the loss.
2.) Confusion of time and amplitude. Because time and amplitude of the EEG spectrum are displayed on the same axis, an identifiable baseline is needed to estimate the amplitude. The low-amplitude, high-frequency segment of the epoch often serves as such a baseline; however, in areas such as those identified by the hollow arrows, it may be difficult or impossible to identify the baseline and estimate EEG activity. From Levy WJ. et al Automated EEG processing for intraoperative monitoring. Anesthesiology 1980;53:228. Reproduced with permission.



called a Compressed Spectral Array [30, 7] (Fig.2.3). A disadvantage of this technique is that finer details of previous spectra can become invisible when a dominant peak in the power spectrum develops (Fig.2.4).The resultant compressed spectral array however is very easy for the detection of gross change over time. These techniques are employed by the Pathfinder II EEG Frequency Analysis Program (Nicolet Biomedical Instruments, Madison Wisconsin USA) used for the EEG study described in this thesis.

A recent development in presentation of frequency spectral data is the Power Density Plot. In this plot spectral data are plotted horizontally as dots, where the spacing between dots is varied according to power. This plotting technique avoids some of the drawbacks of the spectral array with hidden line suppression. Also the power density plot can be recorded on a simple dot matrix printer. A way of further data reduction is to extract a single numerical parameter from the frequency spectrum, usually a percentile. This is the frequency below which a given percentage of total measured power lies. The 50 percentile has been described by Stoeckel and Schwilden under the name of Median Frequency [31]. The 90 percentile was amongst others used by Stanski under the name of Spectral Edge Frequency [32], [33].

Changes in the EEG produced by anesthetics

Introduction

A large number of papers have been written about changes in EEG frequency content produced by drugs used in anesthesia. A summary is given below.

Nitrous Oxide

In concentrations below 70% Nitrous Oxide causes little change in the EEG other than some attenuation of alpha activity. With a unipolar frontal electrode mode of recording, fast activity at 30 Hz and above can be seen with N_2O inhalation [34]. The importance of this fast oscillatory activity has yet to be established.

Halogenated volatile agents.

The initial EEG response to halogenated inhalation anesthetics in the absence of N_2O is an increase in amplitude and a shift in mean frequency to 10-20 Hz. In monkeys a shift of high voltage activity from occipital to frontal parts of the skull is seen at about 0.4 MAC. This pattern is probably related to the loss of consciousness [35]. As inspired concentration is increased beyond 1 MAC the EEG is progressively slowed. With Ethrane a convulsive EEG pattern is observed [36]. With deepest levels of Isoflurane anesthesia the EEG first shows burst suppression and subsequently becomes isoelectric [37].

Fentanyl, sufentanil, alfentanil.

The EEG with fentanyl and sufentanil has mostly been studied in conjunction with the high-dose opiate technique employed in cardiac surgery. The overall pattern is a slowing of dominant frequency without much change in general amplitude. The Spectral Edge frequency has been shown to decrease linearly with increasing plasma concentration of alfentanil. There is, however, a significant hysteresis in this relation [38].

Barbiturates

With increasing plasma concentration a characteristic pattern of changes in the EEG can be defined for the barbiturates. This is demonstrated for thiopental in a classical paper by Kiersey and Bickford [39]. They described five patterns with increasing depth of anesthesia. They could not show any influence on these patterns by curare up to a point where expired minute volume was reduced by 50%. The description of the five EEG patterns is reproduced here from the original paper.

"First pattern. This pattern is characterized by high-amplitude, fast spiky activity of mixed frequencies varying between 10 and 30 cycles per second with the predominant frequency near 20 cycles per second.

Second pattern. This pattern is a complex of many frequencies but differs from the preceding because of the presence of predominantly

slower wave forms of very irregular contour and random ocurrence. There is also much variation in voltage, the larger and predominating waves representing close to 150 microvolts. Superimposed on these slower waves and occupying the intervals between them is a much faster activity rather spikey in character and irregular in amplitude. The frequency of this element is near 10 cycles per second and the amplitude is comparable to that seen in the first pattern.

Third pattern. This is characterized by a progressive suppression of cortical activity taking the form of short periods of relative quiescence that separate groups or bursts of waves. These bursts are frequently made up of two distinct elements. The first appears abruptly and consists of a short series of high-voltage waves of a frequency usually found to be near 10 cycles per second and continuing for about one second; the second element follows immediately in the form of two or more slow waves at a frequency of near 2 per second and tailing off into the next suppression phase.

Fourth pattern. The difference between this and the preceding pattern is the duration of the periods of cortical inactivity which are defined as lasting between three and ten seconds.

Fifth pattern. In this pattern periods of inactivity do not appear more frequently than once every ten seconds and there is further reduction in the amplitude of the components which may, for all components, fall below 25 microvolts. The frequency of the waves is the same as that found in the active phases of the preceding pattern."

Experience with thiopental infusions for reduction of elevated intracranial pressure has learned that with the highest plasma concentrations EEG becomes isoelectric.

Propofol

The influence of propofol on the EEG has been studied using various techniques of EEG analysis.

One study employed the Cerebral Function Analyzing Monitor (CFAM). The CFAM calculates on line the relative power in the alpha, beta, delta and theta bands and displays this graphically. With this monitor a significant change in EEG power is only seen at the highest plasma

concentration. At the lighter stages of anesthetic depth there is a decrease in percentage beta activity together with increases in relative theta and delta power [40]. Drug effects can also be observed in the Power Spectrum. The median frequency is one of the indicators that can be used [31].

Conclusion

Not one uniform pattern of EEG change can be defined for all anesthetic drugs. Especially the lighter planes of anesthesia give rise to varying patterns. Deepening unconsciousness invariably leads to lowering of the dominant frequency and the deepest levels of anesthesia produce EEG silence sometimes alternating with bursts of activity "burst suppression".

The EEG represents spontaneous electrical activity from central nervous system structures. Anesthesia as defined above is dependant on (absence of) processing of noxious stimuli in the brain. Therefore from a theoretical point of view evoked electrical activity should provide more information on the influence of anesthetic agents on central nervous system functioning.

Evoked Potentials

An evoked potential is the electrical response from the central nervous system to an externally applied sensory stimulus. Evoked potentials can not be recorded without the help of computing techniques. A response to a single sensory stimulus is not be discernible from the background noise - mostly EEG -. The most common form of improving the signal to noise ratio of an evoked potential is the technique of averaging multiple consecutive responses. In this way those parts of the recorded signal that have a fixed time relation to the stimulus become visible as the random EEG background noise averages out.

Evoked potentials can be triggered from auditory, visual and somatosensory sources in the sensory system. In this thesis emphasis lies on intravenous techniques employing a continuous infusion of an opioid which suppresses perception of pain. We therefore chose to

study SomatoSensory Evoked Potentials concentrating on the transmission of somatosensory stimuli.
In a review of spinal cord monitoring Nash and Brown suggested the need to include the stimulus site, recording site and evoked potential in the nomenclature [41].
In accordance with their suggestion the method of evoked potential recording used in this thesis has been abbreviated as SCEP (SomatoSensory Cortical Evoked Potentials).

The SomatoSensory Evoked Potential

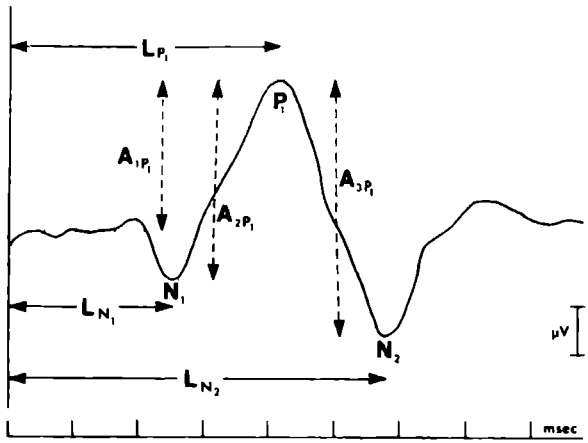
In the SomatoSensory Evoked Potential waveform recorded from the scalp (SCEP) two parts can be distinguished: a rather constant first part called the specific complex which is believed to arise from the projection of sensory activity onto the cerebral cortex and a variable part arising from the spread and subsequent integration of sensory activity across cortical structures.
For evaluation peaks and valleys in the signal are identified and labelled (Fig.2.5). The time from the stimulus to the labelled points is called latency. As a naming convention for points thus identified the label "P" for a positive deflection and "N" for a negative deflection is used followed by either a number indicating the order or the number of microseconds latency as a subscript. The amplitude is measured either for each peak with reference to the line of electrical neutrality or as a peak to peak value.

Influence of anesthesia on Evoked Potentials

Premedication.
Morphine 10 mg intramuscularly or diazepam 10 mg orally were compared in a double blind trial with placebo. There was no difference between drug and placebo in effects on posterior tibial nerve SCEP [42].

Fig. 2.5

How to measure peak latency, peak amplitude, and peak-to-peak amplitude of a transient EP. Peak latency is measured from the stimulus at the beginning of the tracing to the first negative (L_{N1}), first positive (L_{P1}), and second negative (L_{N2}) peak. Peak amplitude is measured from a baseline drawn through a quiet part of the tracing (A_{1P1}). Peak-to-peak amplitude is measured with reference to the preceding (A_{2P1}) or following (A_{3P1}) peak of opposite polarity.
From Spehlmann R. Evoked potential primer. 1985, Butterworth Publishers, Boston. Reproduced with permission.



Inhalation anesthetics

In doses in the clinical range the inhalation agents, halothane, enflurane and isoflurane, all increase latencies and to a lesser extent reduce the amplitude of the SCEP to stimulation of the median nerve [43]. Isoflurane also increases the latency and decreases the amplitude of the Cortical SomatoSensory and Visual Evoked Potentials

[44]. Halothane 0.25-2.0% in combination with nitrous oxide has been reported to increase latency of all components of the SCEP to posterior tibial nerve stimulation. Especially the peaks after P30 were sometimes obliterated. Spinal Monitoring was possible in 91% of patients [45].

Nitrous oxide

Nitrous oxide by itself in concentrations up to 50% decreases the amplitude of SCEP more than 1 MAC of halothane, but has no effect on latency [46]. In one study in cats the effects of nitrous oxide on amplitude of SomatoSensory Evoked Potentials was measured using chronically implanted electrodes in different parts of the brain. The cortical response was reduced by more than 40% with 75% inhaled concentration of nitrous oxide [47].

Narcotics

The opioids can produce changes in latency and amplitude of SCEP [48]. Brain stem components of Auditory Evoked Potential are very robust and show little change over a wide range of dosage [49].

Barbiturates

In dosages up to the point where the EEG becomes isoelectric SomatoSensory and Auditory Evoked Potentials are still measurable. There are dose dependent changes in amplitudes and latencies [50].

Etomidate

In one study using upper extremity SomatoSensory Evoked Potentials etomidate increased latencies of N20 and P23 without alteration of latencies of N10 or N14 and increased the amplitude of P15-N20 and N20-P23 while the amplitude of N10 was unchanged and the amplitude of N14 was decreased [51].

Propofol.

Propofol seems to enhance the amplitude of SomatoSensory Evoked Potentials when compared with the amplitude during nitrous oxide inhalation [52].

Ketamine

Ketamine enhances SomatoSensory Evoked Potential amplitude when preinduction and postinduction values are compared. Addition of nitrous oxide to a ketamine infusion anesthesia reduces amplitude by about 50% [53].

Conclusion

The specific complex of evoked potentials is changed by anesthetics and analgesics. Inhalation anesthetics progressively depress evoked potentials with increasing concentration and can obliterate components of evoked potentials. Especially components with longer latencies are subject to suppression by anesthetic drugs. Nitrous oxide mainly influences amplitude. Opioid analgesics cause a dose dependent change in amplitude and an increase in latency of Cortical SomatoSensory Evoked Potentials.

Brain stem components of the Auditory Evoked Potential are less influenced than evoked potentials originating in higher parts of the brain.

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CLINICAL EXPERIENCE WITH A FIXED RATE OF ALFENTANIL INFUSION

H.B.H. van Beem, H. Meulman and A. VanPeer*

Department of Anaesthesia, University Hospital, Catholic University of Nijmegen, St Radboudziekenhuis, P.B. 9101, NL-6500HB, Nijmegen, The Netherlands and
* Department of Drug Metabolism and Pharmacokinetics, Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse, Belgium

Published in: European Journal of Anaesthesiology
1987;Supplement 1:31-34.

SUMMARY

Twenty-seven patients received an alfentanil loading dose of 100 $\mu g \cdot kg^{-1}$ in two 50 $\mu g \cdot kg^{-1}$ aliquots followed by a fixed rate infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At clinical signs of response to surgical stimulus, an alfentanil dose of 1 mg was added. Patients were ventilated with a N_2O/O_2 mixture. Muscle relaxation was achieved with a vecuronium infusion. No other drugs were given during the procedure. Major orthopaedic or maxillo-facial surgery patients were studied. The duration of infusion was from 2-7 h (mean of 3.9 ± 1.6 h SD). In 25 of 27 cases the anaesthesia was considered adequate and stable. A mean of two additional doses per patient were needed in 25 patients, with a range of zero to four doses in the group. This study supports the view

that after an appropriate loading dose a fixed-rate infusion of alfentanil at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ can be given for up to 7 h to provide satisfactory stable analgesia without undue postoperative ventilatory depression or prolonged recovery in the majority of cases.

Alfentanil, one of the potent modern opioids, has been shown to have a relatively short terminal elimination half-life because of a distribution volume that is five times smaller than fentanyl. It has an onset time of 1-2 min which allows it to be used as a continuous infusion that can be varied and titrated to the clinical effect [1]. From the work published by Ausems and colleagues, there is evidence that a plasma concentration of 200-300 $ng \cdot ml^{-1}$ is adequate in most patients to suppress the response to surgical stimulus from superficial surgical procedures [2]. By using average pharmacokinetic parameters for alfentanil [3], [4] and a two-compartment pharmacokinetic model predictions of plasma concentration for given dosage schemes have been made [5]. In this simulation, an alfentanil 100 $\mu g \cdot kg^{-1}$ loading dose immediately followed by a 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion provided the best approximation to achieve rapidly and then maintain plasma concentrations above approximately 200 $ng \cdot ml^{-1}$. The aim of the present study was to see if such an infusion can be useful in a clinical setting for the provision of background intra-operative analgesia with i.v. single-dose injections being used to treat transient, noxious stimuli.

PATIENTS AND METHODS

Twenty-seven patients gave their verbal consent to take part in the study which was approved by the local ethics committee. Patient characteristics are shown in Table 3.1.

Patients received either no premedication or, if required, diazepam 10 mg by mouth 1 h before the operation. Anaesthesia was induced with an alfentanil loading dose of 50 $\mu g \cdot kg^{-1}$ body weight followed by vecuronium 100 $\mu g \cdot kg^{-1}$ and thiopentone 2 $mg \cdot kg^{-1}$. The patients' trachea were intubated and the lungs ventilated mechanically with an

TABLE 3.1
Patient data.

Number in study	27
Sex (M/F)	18/9
Mean age (yrs)	42 (range 14-81)
Mean weight (kg)	71 (range 50-96)

N_2O/O_2 mixture 70%/30% to an end-tidal CO_2 of 3.5-4.5 kPa. After the initial dose an infusion of alfentanil 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was started. Immediately before the initial skin incision a second bolus of 50 $\mu g \cdot kg^{-1}$ was given, making a total loading dose of 100 $\mu g \cdot kg^{-1}$. An infusion of vecuronium was started and the rate adapted to generate between 50% and 75% twitch depression. Whenever a rise in blood pressure and/or pulse rate of more than 10% above normal for the patient, or any other response to surgical stimulation, was noticed an i.v. dose of alfentanil (1 mg) was administered. Alfentanil and vecuronium were stopped when surgery was expected to end within 20 min.

A 20-gauge teflon cannula was inserted into a radial artery and used for blood pressure monitoring and blood sampling. Blood samples for the measurement of alfentanil plasma concentrations were taken at various times throughout the procedure and recovery phase. Plasma levels were estimated using a radioimmunoassay technique [6]. One hour after the infusion had been stopped, an arterial blood gas estimation was done to quantify the degree of ventilatory depression. For the clinical evaluation of the technique we examined: (1) stability of anaesthesia as indicated by the number of supplementary doses needed; and (2) the speed and quality of recovery. For a pharmacokinetic evaluation plasma concentrations were used to determine the stability of the plasma concentrations at steady state.

The distribution half-life for alfentanil has been defined by various authors as between 9 and 16 min [3], [4], [7]. We therefore took the first sample 40 min past the time of the second loading dose as a definition of the starting point of steady state. We compared the

concentration at this point to the concentration at the time when the infusion was stopped.

RESULTS

Clinical stability

The mean duration of infusion was 3.9 ± 1.5 h (SD) with a range of 1-7 h. Two patients were considered unstable when the use of frequent doses of alfentanil did not maintain blood pressure and/or pulse rate within 10% of normal for that patient. Other signs of autonomic stimulation also remained present. In these two cases an inhalation agent was added to the anaesthetic technique. In the remaining 25 patients a mean of two supplementary doses (range zero to four) were given per patient.

Recovery

In the 25 patients receiving only alfentanil and vecuronium, no reversal drugs were used. All patients were able to answer simple questions within 10 min after N_2O had been stopped (16.7 ± 10.7 min after the end of infusion). Ventilatory frequency at this stage was between 8 and 12 breaths·min^{-1}. Throughout the recovery period ventilatory frequency stayed above eight breaths·min^{-1} and the depth of breathing was judged adequate in all 25 patients. Arterial PCO_2, 1 h after alfentanil infusion had been stopped, showed a mean of 6.07 (± 1.06) kPa. Twenty-three patients did not request analgesics within the first hour of recovery. The incidence of vomiting during the first hour of recovery was 100%, much higher than expected.

Plasma concentration

Mean concentration at the starting point of steady state was 307 (±110) ng·ml^{-1}. Mean concentration just before the end of infusion was 284 (±103) ng·ml^{-1}. This difference was not statistically significant ($P>0.05$).

DISCUSSION

Synthetic opioids such as alfentanil have little effect on the circulation over a wide range of plasma levels. Except for ventilatory depression, muscle rigidity, bradycardia and nausea/vomiting, they have few other side effects. This can make a general anaesthetic technique with a drug like alfentanil preferable to the use of inhalational agents in a number of cases. With the pharmacokinetic properties of alfentanil, a fixed-rate, continuous infusion technique should provide the anaesthetist with the advantages of a stable opioid effect and still allow a rapid recovery time. Such a regimen would, in principle, resemble the use of longer acting opioid analgesics since after establishing the infusion one would only need to treat responses to surgical stimuli with a single dose of alfentanil, which will have effect within 1-2 min.

We took as our starting point a theoretical prediction of the alfentanil loading dose and maintenance infusion rate needed to attain a desired steady-state plasma concentration of 200 $ng \cdot ml^{-1}$ [5]. Redistribution of the loading dose that was given in two 50 $\mu g \cdot kg^{-1}$ increments will result in the lowest plasma concentration occurring about 45 min after the second loading dose. We took this as the point to assess the steady-state alfentanil plasma concentratiion. Had any accumulation been present in our patients this would have shown up in the comparison we made between plasma concentration at this point and the concentration at the end of infusion.

A remarkable observation was the relative stress-free, painless recovery period. This contrasts with our earlier experience with fentanyl for this type of surgery, where, much more frequently, analgesics had to be given within the first minutes after recovery. In this study no drugs with anti-emetic properties were given. Also, nasogastric tubes were not inserted in spite of some prolonged surgery. These factors might account for the unexpectedly high rate of nausea and vomiting we observed. Later experience indicates that the use of low-dose droperidol may prevent nausea without clinically prolonging recovery.

We claim that with the alfentanil dosages used in the study one might expect to achieve a stable level of intra-operative analgesia in 90% or more of all cases with an acceptable rate of recovery and very little risk

of post-operative respiratory depression. In a small percentage of patients the combination of this dosage of alfentanil and N_2O may not be sufficient to obtain the desired stability of analgesia.

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ALFENTANIL PHARMACOKINETICS DURING AND AFTER A FIXED RATE INFUSION

Evaluation of the effects of dose, duration of infusion, age and body weight.

H. van Beem*, A. VanPeer$, R. Gasparini$, R. Woestenborghs$, J. Heykants$, H. Noorduin#, J. van Egmond* and J. Crul*

* Department of Anaesthesia, University of Nijmegen, The Netherlands.
$ Department of drug metabolism and Pharmacokinetics and
# Department of Clinical Research and Development, Janssen Pharmaceutica, Beerse Belgium.

Published in: British Journal of Anaesthesia 1989;62:610-615

SUMMARY

Twenty-nine patients (age range 14-81 yr) undergoing orthopaedic surgery were administered 100 $\mu g \cdot kg^{-1}$ alfentanil given as two i.v. boluses and followed by a fixed rate infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 44-445 minutes. Additional 1 mg bolus doses of alfentanil were administered as required. Plasma samples were assayed for alfentanil using radioimmunoassay. Pharmacokinetic parameters were estimated by a model-independent approach and by curve-fitting. Regression analysis showed no statistical relationship between T½ß, Cl or Vd and the duration of the infusion, total dose or body weight. We found no

significant correlation between age and T½ß of alfentanil for patients younger than 40 yr. For patients older than 40 yr, T½ß increased linearly with age. There was no significant decrease in Cl with age although the lower values for clearance (100-200 ml·min^{-1}) were generally found in subjects older than 60 yr. The present study demonstrated that a 100 µg·kg^{-1} loading dose and a 1 µg·kg^{-1}·min^{-1} infusion may be appropriate for analgesia in general surgical procedures.

INTRODUCTION

Most information on the pharmacokinetics of alfentanil has been obtained after a single bolus injection to patients under general anesthesia [1-7]. Maitre [8] used data from four of those studies to calculate a set of average population pharmacokinetic parameters for alfentanil after a bolus injection using the NONMEM computer program [9], [10]. Sex, body weight and particularly age were noted to be factors affecting the disposition of alfentanil in the normal population of surgical patients without liver or renal function impairment.

There are only few detailed pharmacokinetic studies of a continuous infusion of alfentanil, despite the clinical importance of this technique [11-13]. Both Fragen and colleagues [11] and Shafer, Sung and White [12] used a 2-compartmental model in their kinetic analysis, whereas Reitz and coworkers [13] applied a model-independent approach. The pharmacokinetic parameters for alfentanil given by i.v. infusion were similar to those after a single bolus injection, but there were also some conflicting data. Based on a diminished clearance found in 2 of 11 patients Reitz [13] claimed that the clearance of alfentanil decreased linearly with duration of infusion. Shafer [12] on the other hand did not find such a correlation. These conflicting findings may be a result of the small numbers of patients included in these studies. Only a few subjects older than 60 yr were included. We have therefore investigated a larger and population, using infusions of longer duration.

Using computer predictions based on averaged kinetic parameters, Noorduin and collegues [14] examined infusion regimens aimed at providing adequate peroperative analgesia whilst avoiding postoperative respiratory depression. Their recommendation for surgery under general anaesthesia was: a fixed rate maintenance infusion of alfentanil 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ preceded by a loading bolus injection of 100 $\mu g \cdot kg^{-1}$. This should give a therapeutically adequate plasma concentration, at steady state, of 300 $ng \cdot ml^{-1}$ [15]. The present study was designed to evaluate these predictions in a patient population with the widest acceptable age range and duration of major peripheral surgery.

PATIENTS AND METHODS

Twenty-nine patients (19 female) gave verbal consent to participate in the study, which was approved by the local ethics committee. All patients were ASA I or II without impairment of hepatic or renal function and were scheduled for orthopaedic surgery (Table 4.1). Mean age was 42 yr (range 14-81), mean weight 70 kg (range 50-96), mean duration of infusion 228 minutes (range 44-445). Mean total dose of alfentanil was 24.8 (range 10.1-45.3) mg.

Patients received either no premedication or diazepam 10 mg by mouth 1 hour before surgery. Anaesthesia was induced with an i.v. bolus of alfentanil 50 $\mu g \cdot kg^{-1}$, vecuronium 100 $\mu g \cdot kg^{-1}$ and thiopentone 2 $mg \cdot kg^{-1}$. After tracheal intubation, the lungs were ventilated mechanically with 70% nitrous oxide in oxygen to an end-tidal carbon dioxide partial pressure of 3.5-4.5 kPa. An i.v. infusion of alfentanil 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was started immediately after the initial 50 $\mu g \cdot kg^{-1}$ bolus of alfentanil. A second 50 $\mu g \cdot kg^{-1}$ alfentanil bolus was administered i.v. immediately before incision, in most cases approximately 30 minutes after the first bolus. An infusion of vecuronium was started and the infusion rate was adapted to give single twitch depression of 50-75%. An additional bolus of alfentanil 1 mg was given if an increase in arterial pressure or heart rate of more than 10% greater than baseline occurred or if the patient responded in other ways to surgical stimulation. The infusions of alfentanil and vecuronium were stopped

Table 4.1
Patient data.

Patient number	Sex	Age (yr)	Weight (kg)	Duration of infusion (min)	Total dose (mg)
1	F	70	90	241	33.1
2	F	74	68	173	20.3
3	M	32	92	107	18.8
4	M	64	61	230	22.4
5	F	15	80	284	33.5
6	F	18	55	129	13.5
7	M	71	96	178	22.6
8	F	36	56	353	29.1
9	F	58	73	131	17.8
10	F	80	75	220	20.0
11	F	58	61	216	21.5
12	F	81	80	230	27.4
13	M	33	70	44	10.1
14	M	24	92	356	44.8
15	F	48	65	133	15.4
16	F	31	73	150	18.6
17	M	24	78	398	41.4
18	F	31	56	321	29.3
19	F	26	63	237	21.8
20	F	33	75	390	45.3
21	M	15	65	101	12.9
22	M	19	58	347	27.2
23	F	14	50	287	24.3
24	M	26	80	445	45.2
25	M	41	72	173	21.4
26	F	32	70	176	26.0
27	F	42	56	183	16.7
28	F	50	50	192	17.6
29	F	59	72	175	19.9
mean		42	70	228	24.8
min		14	50	44	10.1
max		81	96	445	45.3

approximately 20 min before the end of the operation.
Blood samples were obtained from a twenty gauge Teflon cannula inserted into a radial artery, immediately before the first bolus injection of alfentanil and at 5, 10, 20, 30, 45, 60 and every subsequent 30 min during the infusion; further immediately before and 3 and 5 minutes after each supplementary bolus; and finally 3, 10, 30, 60 and every subsequent 60 min for 8 h after cessation of the infusion.

Analysis

Concentrations of alfentanil in plasma were measured by a specific radioimmunoassay [16]. The detection limit of the assay was 1 $ng \cdot ml^{-1}$ plasma. The accuracy and reproducibility of the radioimmunoassay were within 5%. Pharmacokinetic parameters were calculated by two methods: model-independent approach (MI) and curve fitting (FIT) using standard one-, two- or three-compartment analysis.
In the model-independent approach, the terminal half-life ($T_{½ß}$) and the pharmacokinetic parameters based on the area under the plasma concentration-time curve were calculated. $T_{½ß}$ was obtained as $0.693/ß$ where ß is the slope of the terminal log-linear plasma concentration-time data. The total area under the plasma concentration-time curve ($AUC_{0-\infty}$) was estimated as $AUC_{0-\infty} = AUC_{0-t} + C_{t/ß}$ where AUC_{0-t} was obtained using trapezoidal summation to the last plasma concentration (C_t).
All plasma concentration-time curves of alfentanil were fitted to a standard multiexponential equation for a set of i.v. bolus doses and a continuous infusion [17]. Compartmental volume (Vc), α, ß and k_{21} were obtained using extended least-squares nonlinear regression (ELSFIT) [18]. The appropriate compartmental model was selected by evaluation of the standard errors on the parameter estimates, scatterplots of the residuals between experimental and predicted plasma data and the maximum likelihood function. All other pharmacokinetic parameters were derived using standard methods [17].
The relationships between the relevant pharmacokinetic parameters and variables such as infusion duration, total dose, age and body weight were investigated by linear regression analysis [19].

The estimated steady state concentration (the plasma concentration that would have been reached if the infusion had continued long enough for steady state to be attained) was calculated with the formula: Concentration = Infusion rate / Clearance.

RESULTS

Pharmacokinetic analysis

The pharmacokinetic parameters obtained by the model-independent approach and by curve-fitting are listed in Tables 4.2 and 4.3, and the two-sided 95% confidence intervals (t x SEM) for the mean absolute differences between both methods expressed as a percentage of MI are 2-5% for Cl and 8-15% for T½ß and Vd area (Table 4.4).

The time course of the alfentanil plasma concentration was fitted to a two-compartmental model in 26 patients. The plasma concentration data of 3 patients (Nos 4, 7 and 18) could not be fitted adequately by any compartmental model. We were able to show in the 26 patients whose data could be fitted by both methods that there was no relevant difference between parameters found with our curve-fitting method and those found using a model-independent analysis.

Table 4.2
Pharmacokinetic parameters derived by model independent approach.

Patient number	T½β (min)	Cl ($ml \cdot min^{-1}$)	Vdarea (l)
1	115	197	32.8
2	155	107	23.9
3	72	401	41.5
4	226	99	32.2
5	80	272	31.3
6	78	194	21.8
7	156	446	100.6
8	94	321	43.7
9	144	171	35.6
10	134	172	33.3
11	78	329	37.2
12	185	198	52.7
13	66	382	36.4
14	70	457	46.3
15	92	332	44.1
16	90	305	39.6
17	79	268	30.4
18	99	181	25.9
19	135	231	45.0
20	94	197	29.8
21	90	218	28.2
22	90	258	33.5
23	77	245	27.2
24	91	178	23.5
25	114	297	48.9
26	96	440	61.1
27	56	362	29.5
28	112	340	54.9
29	102	396	58.5
Mean	106	276	39.5
SD	38	101	15.9

Table 4.3
Pharmacokinetic parameters derived by curve-fitting.

Pat nr	t½α min	t½β min	k10 min^{-1}	k12 min^{-1}	k21 min^{-1}	Vc l	Vd_{ss} l	Vd_{area} l	Cl $ml \cdot min^{-1}$
1	8.9	132	.025	.042	.016	7.67	27.2	36.4	191
2	6.8	193	.019	.068	.019	5.15	23.3	27.5	99
3	9.9	77	.038	.024	.016	10.13	25.1	43.0	385
4	---	---	----	----	----	-----	----	----	---
5	10.3	83	.024	.028	.024	11.78	25.8	33.5	280
6	6.8	80	.030	.051	.029	6.27	17.2	21.9	191
7	---	---	----	----	----	-----	----	----	---
8	12.4	94	.029	.020	.014	10.92	26.4	43.4	321
9	2.0	122	.046	.265	.043	4.11	29.6	33.6	191
10	13.9	151	.015	.024	.015	11.25	29.5	37.6	173
11	8.8	96	.031	.036	.018	10.27	30.6	43.7	316
12	15.2	229	.014	.025	.010	13.62	47.3	61.8	187
13	14.1	69	.026	.014	.019	15.96	28.1	42.0	421
14	13.8	72	.027	.015	.018	17.15	31.4	47.5	456
15	12.0	70	.025	.020	.023	13.26	24.6	33.3	332
16	19.8	106	.020	.010	.011	15.11	28.5	47.4	309
17	4.6	77	.054	.082	.025	5.14	21.9	31.2	280
18	---	---	----	----	----	-----	----	----	---
19	18.5	140	.021	.012	.009	11.58	28.0	49.9	248
20	21.1	111	.018	.010	.011	11.23	20.7	32.5	203
21	22.8	95	.014	.008	.016	15.55	23.4	30.2	220
22	25.7	97	.018	.006	.011	14.73	22.2	36.5	262
23	22.3	92	.022	.006	.011	11.47	17.9	33.3	251
24	8.7	96	.027	.039	.021	6.53	18.3	24.3	176
25	4.5	83	.055	.084	.023	5.50	25.2	36.2	304
26	7.4	92	.047	.039	.015	9.69	35.0	60.6	456
27	2.4	55	.076	.173	.047	4.85	22.6	29.1	368
28	6.5	131	.059	.043	.010	6.10	33.5	67.6	358
29	12.4	106	.033	.018	.011	11.99	31.8	60.6	395
Mn	12.0	106	.031	.045	.019	10.27	26.7	40.2	284
SD	6.5	39	.016	.057	.009	3.89	6.3	12.0	95

Table 4.4
Comparison of pharmacokinetic approaches.
Mean difference and mean absolute difference between the Model Independent (MI) and the curve fitting (FIT) approaches expressed as a percentage of MI value.

$$100x\frac{1}{N}\sum_{I=1}^{N}\frac{MI-FIT}{MI} \qquad 100x\frac{1}{N}\sum_{I=1}^{N}\frac{|MI-FIT|}{MI}$$

Parameter	Mean difference (95% conf. lim. = 2 x SEM)	Mean absolute difference (95% conf. lim. = 2 x SEM)
t½β (min)	-5.5 (-10.9; -0.1)	11.3 (7.8; 14.8)
Cl ($ml \cdot min^{-1}$)	-1.3 (-3.1; 0.5)	3.3 (2.0; 4.6)
Vd_{area} (l)	-6.4 (-11.4; -1.4)	10.9 (7.5; 14.3)

N=26

There was a wide variation in T½β values which ranged from 56 to 226 min. The highest values were mostly found in the age group older than 60 yr.

Effects of dose or duration of the infusion
The duration of the infusions ranged from 44 to 445 min. Total dose ranged from 10.1 to 45.3 mg. There was no significant correlation between the pharmacokinetic parameters (T½β, Cl ,Vc, Vd_{ss}, Vd_{area}) and the duration of the infusion, or with the total dose including all supplementary i.v. bolus doses.

Effects of body weight
There was also no significant relationship between clearance or volume of distribution and body weight.

Effects of age

Vdss was significantly enlarged with increasing age (P=0.003). Clearance did not correlate significantly with age (P=0.16). Age had a linear effect on T½ß in the patients older than 40 yr (P=0.0006). A correlation was not shown in the patients younger than 40 yr (P=0.74).

Steady state concentration

The mean estimated steady state concentration was 293 (SD 132) ng·ml $^{-1}$ (range 147-636 ng·ml $^{-1}$).

DISCUSSION

Our kinetic parameters correlate well with values obtained in earlier studies after a single dose [1-7] or an infusion [11-13]. The average T½ß was in the order of 2 h and Cl was approximately 4 ml·kg $^{-1}$·min $^{-1}$ in young to middle-age subjects. In the present study, 26 patients were fitted to a two-compartmental model and 3 patients could not be fitted adequately to any compartmental model.

Plasma concentrations after a single bolus injection can usually be fitted to a two-compartmental [3-5] or to a three-compartmental model [1],[2]. However it is well known that after cessation of an infusion the initial, fast distribution phase is reduced and is discriminated less easily in the total plasma concentration-time profile. This could explain why a three-compartmental model did not improve the fit over a two-compartmental analysis in the present study or in any other infusion study of alfentanil [12],[13]. Shafer, Sung and White [12] found no correlation between clearance and duration of infusion and reported also that the pharmacokinetics were independent of the maintenance infusion rate (0.25-1.3 µg·kg $^{-1}$·min $^{-1}$), duration of the infusion (59-385 min), body weight (40-113 kg), age (18-59 yr), sex or type of surgery (superficial or intra-abdominal). In contrast Reitz and collegues [13] claimed there is a decrease in clearance and a prolonged half-life with increasing duration of surgery. Visual inspection of their published data reveals no correlation in the nine patients undergoing surgery for less than 150 min and an increase in T½ß and a decrease of Cl in

only 2 patients with surgery lasting for 212- and 335 min respectively. The present study shows that the pharmacokinetics of alfentanil given by i.v. infusion are independent of the duration of the infusion (in the case of our study ranging from 44-445 min) and the total dose given (10.1-45.3 mg). Consequently, our data and those of Shafer do not confirm the conclusion drawn by Reitz.

A factor known to change the disposition of alfentanil is age. Helmers [4] found prolonged T½ß and reduced clearance of alfentanil after a single bolus dose in the elderly. In addition, the population pharmacokinetic analysis by Maitre on single-dose data [8], which included the Helmers data from elderly patients, revealed age-related reductions in clearance and a slower redistribution from the deep compartment. With an alfentanil infusion Shafer's group [12] found no correlation between age and pharmacokinetic parameters, but it has to be stressed that the ages of their patients ranged from 18 to 59 yr. Scott and Stanski [20] reported increased T½ß with age but they did not find clearance values significantly affected by age. It should be noted that a very short infusion of alfentanil 1500 $\mu g \cdot min^{-1}$ was given for about 5 min and these data should be considered rather as a slowly given bolus than as a continuous infusion. Our findings are similar to those of Scott and Stanski [20], with T½ß increased significantly in subjects older than 55 yr, but no significant linear correlation between clearance and age. One reason for the lack of correlation with clearance is probably that this tends to be more variable during a continuous infusion in long-term surgery than after a single bolus injection.

Both the loading dose and maintenance infusion rate in this study were calculated on the basis of body weight as is conventional practice. The population pharmacokinetic analysis after a single bolus dose by Maitre revealed a significant effect of body weight on the volume of distribution of the central compartment but not on clearance. In our study, plasma clearance and volumes of distribution (Vdss and Vdarea) did not correlate significantly with body weight.

According to the findings of Ausems and colleagues [15], for adequate pain relief the concentration at steady state should be in the order of 300 $ng \cdot ml^{-1}$. The mean value of the calculated alfentanil steady-state

concentration in our study averaged 293 ng·ml^{-1} It indicates that the proposed 100 µg·kg^{-1} loading dose and an infusion of 1 µg·kg^{-1} min^{-1} might be considered as an appropriate regimen for analgesia in general surgical procedures As in the present study, transient periods of inadequate analgesia (indicated by hypertension and tachycardia) may be treated by the use of additional iv bolus doses of alfentanil 1 mg.

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CHAPTER 5

SPINAL MONITORING DURING VERTEBRAL COLUMN SURGERY UNDER CONTINUOUS ALFENTANIL INFUSION

H. Van Beem*, A. Koopman-van Gemert*, H. Kruls#, S.L.H. Notermans$

*Institute of Anesthesiology
#Department of Orthopedics
$Department of Neurology
Nijmegen Academic Hospital, St. Radboudziekenhuis Nijmegen, Holland.

Published in: European Journal of Anaesthesiology 1992;9:287-291

SUMMARY

An anaesthetic technique for surgical procedures on the vertebral column is described consisting of a continuous infusion of a short acting opioid, alfentanil, and a muscle relaxant, vecuronium, in combination with ventilation using a nitrous oxide/oxygen mixture. It is shown that the two standard forms of spinal monitoring: wake-up testing and somatosensory cortical evoked potentials can be employed effectively under this anaesthetic technique. Wake-up testing was performed in 23 patients. Average wake-up time was 10 minutes (SD 3.7 min). Evoked responses suitable for spinal monitoring could be obtained in 60 of 61 patients.

INTRODUCTION

Major spinal surgery is associated with the risk of neurological damage [1]. The consequences of spinal trauma can be kept to a minimum if functional damage is detected during surgery. Cases have been described in which corrective surgical measures were taken in response to a positive spinal monitoring test resulting in complete recovery of the patient without neurological deficit [2], [3]. Two monitoring methods are currently in general clinical use for intraoperative detection of spinal cord damage. The first method is known as the wake-up test. It was first described by Vauzelle in 1973 [4]. This test employs voluntary movement of the patient to command. The second method uses the technique of somatosensory evoked potentials to monitor viability of spinal cord function [5]. A pure motor function test using magnetic transcranial stimulation of the motor cortex has been described [6]. With peripheral EMG recording this form of stimulation might in future prove to be a better solution for the spinal monitoring problem, but at present this method cannot be considered for a routine monitoring.

In a recent review of spinal cord monitoring Nash and Brown suggested the need to include the stimulus site, recording site and evoked potential in the nomenclature [5].

In accord with their suggestion the method of evoked potential recording used in this study has been abbreviated as SCEP (SomatoSensory Cortical Evoked Potentials).

Alfentanil is a potent short-acting opioid with considerable hypnotic activity. It has been shown to have a short elimination half life without postoperative respiratory depression even after prolonged periods of continuous infusion [7], [8]. Stable adequate surgical analgesia can be obtained in most patients using a bolus injection followed by a continuous infusion in combination with nitrous oxide [9]. This technique gives a level of anaesthesia that can be changed rapidly as is required for wake-up testing. One case of successfull wake-up testing under continuous alfentanil anaesthesia has been published [10]. Opioids especially when given by infusion have less influence on cortical activity when compared with inhalational agents, thereby allowing cortical SCEP to be recorded during opioid anaesthesia [11],

[12]. Nitrous oxide tends to reduce SCEP amplitude but the response remains measurable [13].
The aim of the present study was to assess if both methods of monitoring intact spinal cord function can be applied during an anaesthetic technique with a continuous infusion of alfentanil and ventilation with a nitrous oxide/oxygen mixture.

METHODS

Table 5.1
Patient data. Values are given as Mean (Min/Max.SD).

Number	Age (yr)	Duration of surgery (min)	Total alfentanil (mg)
68	29.5 (5/60,13)	226 (101/390,87)	24.5 (12.9/45,8.7)

68 patients were included in the study for which local ethical committee approval had been obtained. All patients were to undergo thoracic or lumbo-thoracic spinal fusion for scoliosis or trauma (2 patients). Relevant patient data are given in Table 5.1. In 7 patients spinal monitoring consisted of wake-up testing alone, in 16 patients both tests were used and in 45 patients SCEP alone. The choice of monitoring type was made after consultation with the surgeon and was based on the preoperative severity of the deformity.
Preoperatively, patients were fully informed of the monitoring method to be used and gave their verbal consent.

Anaesthetic technique

Premedication consisted of 10 mg diazepam given orally 1 hour before induction. Alfentanil 50 $\mu g \cdot kg^{-1}$ was given iv for induction, followed by thiopentone 2 $mg \cdot kg^{-1}$ and vecuronium 100 $\mu g \cdot kg^{-1}$. Anaesthesia was maintained using a continuous infusion of alfentanil 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. A bolus injection of 50 $\mu g \cdot kg^{-1}$ iv was given 1 minute before incision, thus

bringing the total loading dose of alfentanil up to 100 μg·kg^{-1}. A continuous infusion of vecuronium was started. The patients were ventilated with nitrous oxide/oxygen 70/30% to an end-tidal PCO_2 between 4.0-5.0 KPa. When there was a response to surgical stimulation, indicated by a rise in blood pressure and/or pulse rate of more than 20% above steady state level, a 1 mg bolus of alfentanil was given.

Monitoring

Monitoring consisted of ECG, intra-arterial blood pressure through a 20 gauge needle inserted in the radial artery, skin and core temperatures, FIO_2 and $ETCO_2$ measurement. Train of four stimulation of the ulnar nerve was used to monitor neuromuscular transmission. Resulting twitches of the adductor pollicis muscle were palpated and the administration of neuromuscular blocker was adjusted so that only two twitches were palpable.

SomatoSensory SCEPs were recorded using a Nicolet Pathfinder II system. Stimulation was provided by a constant current applied through skin electrodes to the popliteal nerve at the back of the knee or the posterior tibial nerve at the ankle of the left and right legs. Only one leg was stimulated at a time. For preoperative SCEP a current of 2 times sensory threshold with a pulse duration of 200 microseconds and a repetition rate of 2.7 sec^{-1} was used. Intraoperatively stimulus current was increased to 30 mA. Ten millimeter tinned disk electrodes were used in a Cz'-Fpz montage according to the international 10-20 system. Electrode impedance was kept below 4000 Ohm. A large surface electrode on the upper leg was used as ground. Sensitivity of the amplifier was set at 100 μV full scale. High and low pass filters were set at 5 and 1500 Hz respectively. The timebase was 200 msec (512 data points). The number of sweeps averaged was 300.

Each patient was used as his own control. A SCEP shortly after induction of anaesthesia, before the start of surgery after the second loading dose of 50 μg·kg^{-1} alfentanil served as control. Specific complex amplitudes and latencies were compared to evaluate sensory pathway conduction. We defined the specific complex as the first positive peak in

the 25-45 msec window (P35) followed by a negative peak (N45). A reduction in peak-peak amplitude of more than 50% or an increase of latency by more than 10% was taken as an indication of potential neurological damage.

To perform a wake-up test the infusions of alfentanil and vecuronium were discontinued. In one case reversal of neuromuscular block with edrophonium was necessary. After 8 minutes with 4 twitches palpable nitrous oxide was discontinued and the patient ventilated with 100% oxygen. The patients name was then repeated once every 30 seconds followed by a request to move a hand until a first response was noted. Subsequently the patient was asked to move both legs and the response was checked. The anaesthetic was continued with nitrous oxide/oxygen 70/30%, a bolus dose of alfentanil 1 mg and vecuronium 2 mg and reinstitution of the continuous infusions of alfentanil and vecuronium. The time from discontinuation of the infusions till the first motor response of the hand was recorded as wake-up time. Blood pressure and pulse rate were recorded at the time of interruption of the infusion and at the time of response to command. Change in pulse rate and blood pressure is calculated as a percentage of the last value before discontinuation of the infusions.

All patients were checked for signs of neurological damage 24 hours after the operation. The patients were also asked on this occasion if they remembered anything of the wake-up test.

RESULTS

It was possible to obtain intraoperative SCEP recordings suitable for spinal monitoring in 60 out of 61 patients. In one patient for reasons that could not be explained no reproducible SCEP recordings could be obtained pre- as well as peroperatively although the patient had no preoperative neurological symptoms. In this case only wake-up testing was used for spinal cord monitoring.

The mean peak-peak amplitude of P35-N45 was 0.73 μV (sd 0.53) for the first SCEP after induction of anaesthesia. A satisfactory response was obtained in all cases where wake-up testing was performed. During

Table 5.2
Results of the Wake-up test. Results are given as Mean (Min/Max.SD).

Number	Time till w-up (min)	%Change HR	%Change Syst. bp.
23	10.4 (6/25,3.7)	27 (0/99,23)	16 (4/30,9)

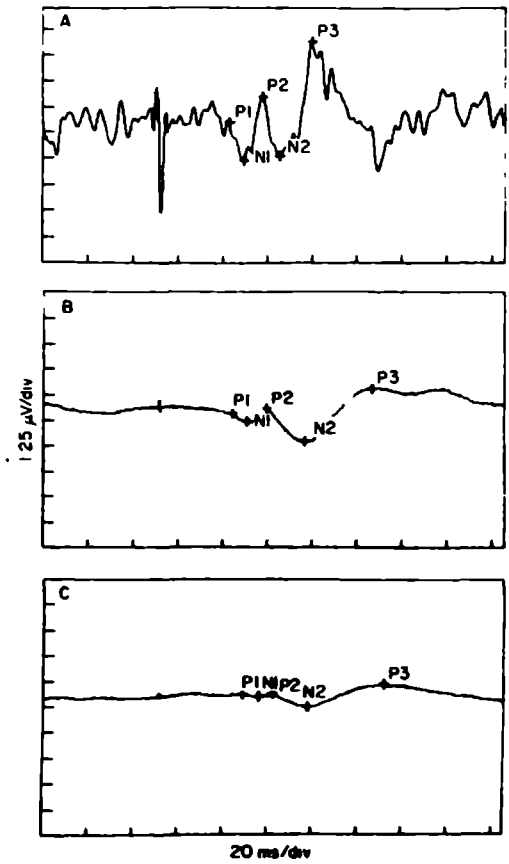
the wake-up test the average increase in systolic blood pressure was 16% and in heartrate was 27% (Table 5.2). The rate pressure product even during the awake episode remained less than 12.000 because the steady state pulse rate with alfentanil infusion is low. The average time till first response was 10.4 minutes (minimum 6 minutes, maximum 25 minutes). In 6 cases spontaneous movement started before discontinuation of nitrous oxide (Table 5.2).

In one case a change in SCEP shape intraoperatively was detected from the right leg with a significant reduction in P35-N45 peak to peak amplitude and an increase in the latencies, while the response from the other leg remained normal and the wake-up test was normal (Fig 5.1). Because of normal movement during wake-up testing no surgical measures were taken. This patient showed dysaesthesia in the right leg postoperatively. Neurological examination suggested damage to the dorsal root of L5. Neurological symptoms gradually disappeared over the course of three months. One patient showed no movement of the left leg during the wake-up test while SCEP remained normal. Postoperatively there were no signs of neurological damage. Changes in SCEP fulfilling the criteria of potential neurological damage were seen in no other patient. No other postoperative neurological sequelae were seen in the first 24 hours postoperatively.

Three out of 23 patients in the wake-up test group had some vague memory of the awake episode. One patient had more explicit memory of occurrences during the wake-up test. No experience of pain or anxiety was expressed by any of the patients.

Fig 5.1
SCEP results from the patient with neurological sequelae.

A. Pre induction SCEP right leg. P1N1 amplitude 1.64 μV, P1 latency 30.8 msec.
B. After surgical manipulation left leg. P1N1 amplitude 0.44 μV, P1 latency 32.4 msec.
C. After surgical manipulation right leg. P1N1 amplitude 0.24 μV, P1 latency 36.8 msec.



DISCUSSION

Several cases have been reported in the literature in which evoked potential monitoring failed to detect motor loss during surgery. This might partly be due to dificulty in interpreting the evoked potential signal especially when amplitudes have been reduced by anaesthesia and temperature loss. It is therefore recommended that wake-up testing should still be available even when SCEP monitoring is performed [5], [14]. According to Nash and Brown the wake-up test should still be considered as gold standard in spinal monitoring [5]. Any anaesthetic technique for vertebral column surgery should therefore allow intraoperative evaluation of spinal cord function with both methods.

We chose to study spinal monitoring under alfentanil continuous infusion because in previous work it had been shown that with this technique a stable level of anaesthetic depth and of analgesia can be obtained in most cases with a fast and smooth recovery without prolonged respiratory depression [9]. We expected therefore to perform the wake-up test with only small changes in cardiovascular stability and to perform SCEP monitoring with predictable and acceptable changes caused by the anaesthetic.

An alternative technique would employ an inhalation agent as anaesthetic during maintenance. With inhalation anaesthesia an additional difficulty would be introduced as the inhalation agent would cause a variable increase in latency of SCEP components [15] which does not occur in our technique. In the group of patients described by Jones et al [3] a hypotensive technique with high concentrations of halothane was used (personal communication). This might explain why the authors after three trial cases of cortical recording abandoned this technique in favor of epidural recording. We could obtain reproducible SCEP's in 60 of 61 patients even after procedures of long duration - in one case as long as 7 hours using alfentanil. We saw a reduction in amplitude caused by alfentanil and particularly nitrous oxide [13]. This was partially counteracted by increasing the stimulus current in our patients. Because of this and of intraindividual variability in latency and amplitude of the SCEP we chose to use each patient as own control

comparing each SCEP to one recorded soon after the second loading dose of 50 $\mu g \cdot kg^{-1}$ alfentanil before the start of surgery.

Our experience shows that at any time during alfentanil nitrous oxide anaesthesia a wake-up test can be initiated. It will take on average 10 minutes before a patient may be successfully prompted to move. In dogs spinal cord compression was compatible with complete recovery if compression was relieved after 30 minutes [16]. It may therefore be expected that the delay in waking up with our technique would not endanger the chances of complete recovery when corrective measures are taken in response to a negative wake-up test.

An interesting observation was that, when interviewed 24 hours after the procedure, only 4 out of 23 patients reported conscious recollection of the wake-up episode without memory of anxiety or pain. A wake up test could be seen as an acceptable episode of awareness, the awareness being positively confirmed by the patients correct response to verbal command. Our experience therefore supports the view, expressed for quite some time, that awareness can exist during anaesthesia without conscious recollection [17]. During the anaesthesia described in this paper awareness during wake-up testing did not cause memorable anxiety or pain in contrast with unintentional awareness. We presume that anxiety was reduced because:

1. Adequate analgesia was provided by the alfentanil infusion.
2. Patients could communicate by movement because of reduction of neuromuscular blockade.
3. During the preoperative visit patients had been informed.

CONCLUSION

An anaesthetic technique with alfentanil infusion may be a good choice as an anaesthetic technique when spinal monitoring by recording of SCEPs and/or by wake-up testing is indicated. It is a safe technique both peroperatively and postoperatively. It does not prohibit clinically useful SCEP recording and it enables a smooth wake-up test without signs of pain.

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CHAPTER 6

DEPTH OF ANESTHESIA DURING ALFENTANIL INFUSION WITH NITROUS OXIDE

Clinical assessment, alfentanil plasma concentration and somatosensory cortical evoked potentials.

H. van Beem

Department of Anesthesiology, University of Nijmegen, the Netherlands.

SUMMARY

SomatoSensory Cortical Evoked Potentials were measured in 15 ASA I patients undergoing lower spinal surgery. The influence of the anesthetic technique -alfentanil fixed rate infusion and nitrous oxide oxygen controlled ventilation- on the Evoked Potentials was studied. After induction amplitudes fell by 50%. There was little change in latencies. Responses during anesthesia were variable without good correlation with clinical signs or alfentanil plasma concentration thus prohibiting the use of this monitoring technique as a measure of anesthetic depth.

INTRODUCTION

In a number of studies it has been shown that continuous infusion of alfentanil can be used as part of an intravenous anesthestic technique [1], [2]. During this type of anesthesia depth of anesthesia is not easily determined by clinical observation alone. Both insufficient depth opening the possibility of awareness and an unnecessary deep level leading to prolonged recovery are potential hazards. Therefore the need

exists to find an indicator of depth of anesthesia not dependent on clinical signs like blood pressure and pulse rate. Neurophysiological monitoring in particular evoked potential recording has been shown to offer potential in this area [3]. In a review of spinal cord monitoring Nash and Brown suggested to include stimulus site + recording site + evoked potential in the nomenclature [4]. Following their suggestion the method of evoked potential recording used in this study has been named Tibialis SomatoSensory Cortical Evoked Potential (TSCEP).

From work by other authors and from our own experience we know that the primary complex of TSCEP remains measurable during intravenous anesthesia with alfentanil. Small shifts in latency and a reduction of the amplitude of the primary complex have been reported [5], [6]. The influence of nitrous oxide is also mentioned in the literature [7], [8]. Here the main effect is a reduction in amplitude. The aim of the study presented here was to analyze the possibility of defining these changes of the TSCEP signal in terms of anesthetic depth.

METHODS

Anesthetic technique

Premedication consisted of 10 mg of diazepam by mouth 1 to 1½ hours before operation.

Patients were induced with 50 $\mu g \cdot kg^{-1}$ alfentanil, 100 $\mu g \cdot kg^{-1}$ vecuronium and 2 $mg \cdot kg^{-1}$ thiopental. Just before incision a second bolus of 50 $\mu g \cdot kg^{-1}$ alfentanil was given, bringing the total loading dose of alfentanil up to 100 $\mu g \cdot kg^{-1}$. Patients were intubated and artificially ventilated with oxygen in nitrous oxide 40/60 %. Ventilation was adjusted to keep end-tidal Pco_2 between 4.5 and 5.5 kPa. An infusion of alfentanil 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was used to maintain analgesia. Muscle relaxation was maintained by an infusion of vecuronium 0.8 $\mu g \cdot .kg^{-1} \cdot min^{-1}$. A rise in blood pressure and/or pulse rate of 20% or more from the level at steady state was taken as a sign of insufficient analgesia. In that case a bolus of 1.0 mg alfentanil was given. Patients were kept warm with a warming blanket.

Monitoring

The following parameters were monitored throughout the procedure.

- ECG/heart rate.
- Blood pressure via 20G cannula in the radial artery.
- End-tidal CO_2.
- Neuromuscular relaxation by train of four stimulation of the ulnar nerve and manual assessment of adductor pollicis muscle contraction.
- Oesophageal temperature.

The patients were watched at regular intervals for sweating and tear formation. Observation was made of any sign of frowning or other movement in response to surgical stimulus. These observations together with blood pressure/pulse rate data were used to give a clinical assessment of depth of anesthesia. Absence of signs of autonomic stimulation was scored as "adequate". The same situation in the first 10 minutes after a bolus dose of alfentanil was scored as "deep". When a response to surgical stimulation was observed or when after termination of alfentanil infusion blood pessure was back to normal or above depth was scored as "light".

10 ml blood samples were taken from the catheter in the radial artery at predetermined intervals and at moments of clinically significant changes in anesthetic depth for determination of alfentanil plasma concentration. The blood was centrifuged and the supernatant plasma was stored at minus 20 degrees centigrade until further assayed. Alfentanil plasma concentration was measured using a Radio Immuno Assay [9].

Evoked Potential Recording

TSCEP recordings were made on a Nicolet Pathfinder II system equipped with a dual constant current stimulus unit. The posterior tibial nerve of the right ankle was stimulated transdermally with silver silver chloride pregelled baby ECG electrodes. The nerve was identified by motor response. Stimulus current was adjusted to twice the sensory threshold. Stimulus pulse duration was 200 microseconds, repetition rate 2.3 per second. The response was recorded from the scalp using

tinned silver cup electrodes filled with chloride electrode gel held in place with collodion. Impedance was kept below 4000 ohms. Locations Fpz and Cz' (two centimeters behind Cz), according to the International 10-20 system, were used as positive and negative input to the amplifier respectively. A scalp electrode equidistant to Fpz and Cz' was used as ground. 300 sweeps were averaged with 512 datapoints per sweep over 200 milliseconds. Whenever the patient gave his consent TSCEP was recorded in the awake, premedicated patient.

Interpretation of TSCEP curves

Individual TSCEP curves were measured with the Pathfinder II cursor according to the system described by Spehlmann [10] (Fig.2.5). Latencies of identifiable peaks and interpeak latencies were calculated for each averaged response obtained.

Each time a TSCEP recording was made, anesthetic depth was scored as light, adequate or deep.

RESULTS

Fifteen ASA class I or II patients without any known neurological symptoms were studied. Patient characteristics are given in table 6.1. Patients were fully informed of the monitoring technique to be used. They gave their verbal consent to take part in the study. All patients were scheduled for lumbar or lumbo-sacral spondylodesis.

The pattern of alfentanil bolus doses was the same as we saw in an earlier study (Chapter 3) [11]. In the present group no cases of persistently unstable anesthesia were seen.

Results of plasma concentration measurement, TSCEP parameters and clinical assessment are summarized in table 6.2. Statistical significance is only reached by the difference in amplitudes pre and post induction, not between depth levels during anesthesia.

Only for the score "light" was there a significantly lower plasma concentration. Between "deep" and "adequate" there was no statistical difference in alfentanil plasma concentration.

Table 6.1
Patient data.

Patient number	Sex	Age (yr)	Weight (kg)
1	M	61	61
2	F	38	60
3	M	31	90
4	F	17	36
5	M	31	48
6	F	42	52
7	F	33	57
8	F	14	42
9	F	36	64
10	F	47	64
11	F	77	68
12	F	34	64
13	M	43	70
14	M	33	73
15	F	64	125
Mean		40	65
SD		17	21
Range		17-77	36-125

DISCUSSION

Studies in conscious volunteers have indicated that Cortical Evoked Potentials can be used as a correlate of pain response [12]. However the late peaks in the TSCEP signal correlating with this type of response are in a majority of cases no longer recognizable in the signal after induction of anesthesia.

The nervous sytem pathway the impulse travels by is assumed to consist of Aδ fibers, but not C fibers, the substantia gelatinosa and the associated spinal tracts, the thalamus and its cortical projections. It is the electrical activity of this cortical projection that is registered by the scalp electrodes of the CSEP monitoring system. The pathways involved in the conduction of the TCSEP include central nervous structures

Table 6.2
The only difference which is statistically significant is pre- post induction amplitude

Depth of anesthesia	Awake	Light	Adequate	Deep
[C] Alfentanil ($ng \cdot ml^{-1}$)	0	166.3 (57.4)	291.1 (80.5)	299.3 (44.8)
Latency N_1	38.3 (2.0)	37.6 (5.1)	38.9 (4.8)	42.4 (0.7)
Latency P_1	45.8 (4.1)	46.8 (4.4)	49.6 (4.8)	50.9 (2.3)
Latency N_2	56.0 (5.6)	60.3 (8.5)	64.9 (9.6)	70.8 (3.2)
Latency P_2	69.1 (9.1)	77.7 (13.6)	83.3 (16.5)	
Amplitude P_1-N_1	1.87 (1.02)	0.44 (0.36)	0.52 (0.36)	0.58 (0.37)
Amplitude P_1-N_2	1.49 (0.97)	0.71 (0.70)	0.80 (0.58)	1.30 (0.58)
Amplitude P_2-N_2	1.98 (0.97)	0.68 (0.84)	1.00 (0.74)	

containing a large number of mu opiate receptors [13]. Therefore we expected to see effects of opiates on the TCSEP.

It has been suggested that somatosensory evoked potentials show changes during anesthesia that are related to the response to surgical stimulation. Sebel showed in 8 patients that latency and amplitude of the median nerve evoked potential complex change with increasing dosage of anesthetic and with response to surgical noxious stimulation [14]. We found no correlation between TSCEP changes and clinically scored depth of anesthesia so, we could not confirm this for TSCEP.

The inhalation of nitrous oxide does influence cortical evoked potentials [7],[8]. In the literature an average reduction in amplitude of the SCEP of 50% is quoted. The reduction found in this study is somewhat larger. This might reflect an additional effect of alfentanil. A minor part of the pre-post induction difference in amplitude and latency must be attributed to cooling because oesophageal temperature fell but never more than 1.5 degrees centigrade. The biggest problem however in our study was the variability in amplitude and latency during anesthesia as can be seen from the standard deviation figures. This variability prohibits statistical evaluation of small changes in amplitude that might be contributed by alfentanil. The same problem was noticed by

Kalkman et al with reference to the use of TSCEP for spinal monitoring [15]. Two explanations may be given for this observation.

- The much smaller amplitude of the evoked potential will make that interference plays a relatively large role in changes in amplitude and latency. Furthermore the visual evaluation of peaks and valleys becomes less accurate.
- Nitrous oxide may through its differential influence on different parts of the central nervous system have a destabilizing effect on the functional status of the brain.

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CHAPTER 7

ASSESSMENT OF ANESTHETIC DEPTH DURING INTRAVENOUS ANESTHESIA WITH PROPOFOL INFUSION

H.van Beem, J.van Egmond, E.Kapteyns.

H. van Beem, Consultant anesthetist.
J. van Egmond Ph D, Physicist.
E. Kapteyns, Research fellow.
Department of Anesthesiology, Nijmegen University Hospital

SUMMARY

During epidural analgesia six patients were anesthetized with a continuous infusion of propofol 12 $mg \cdot kg^{-1} \cdot hr^{-1}$ for 30 minutes. To determine the usefulness of EEG monitoring for the estimation of depth of anesthesia the Fourier transform of a four lead EEG was recorded together with blood pressure, pulse rate and propofol plasma concentration. Mean frequency correlated well with plasma concentration. Systolic blood pressure was also a good indicator of anesthetic depth. An indication of the instant of loss and regaining of consciousness can be found in the EEG but the transition is not precisely defined. EEG Fourier analysis can assist in the determination of depth of anesthesia but it can not be used as the sole monitored variable.

INTRODUCTION

A good estimation of depth of anaesthesia is needed during intravenous anaesthesia. This is particularly true when a continuous infusion of a

short acting hypnotic is used, because here anaesthetic depth can change rapidly. Classical clinical signs such as changes in blood pressure or pulse rate are often not linearly related to depth of anaesthesia and are therefore unreliable [1]. Both overdosage and underdosage could result. Overdosage may lead to unnecessary prolongation of effect or to unacceptable side-effects. Underdosage may lead to awareness with or without conscious recollection. Any measurement of depth of anaesthesia should therefore not only show deepening of the anaesthetic level, but should ideally also allow the detection of awareness.

The use of Propofol as an intravenous anaesthetic during surgery under loco-regional analgesia with and without intubation has been documented. A two stage infusion of 6 $mg \cdot kg^{-1} \cdot hr^{-1}$ followed by 4 $mg \cdot kg^{-1} \cdot hr^{-1}$ provided light sedation during spinal anaesthesia in unintubated patients. An induction bolus of 2.5 $mg \cdot kg^{-1}$ plus an infusion of 12 $mg \cdot kg^{-1} \cdot hr^{-1}$ was, however, not satisfactory for anaesthesia with intubation in patients with various types of regional block [2],[3].

Schüttler and Schwilden have described the change in median frequency of the EEG frequency spectrum with a steady state propofol infusion [4]. After induction they used a computer feedback control system to monitor and maintain the level of anesthesia. Their paper focused on maintenance of steady state. Not much attention was given to induction and wake-up stages. The aim of the study presented here was to evaluate the usefulness of EEG analysis for estimation of depth of anesthesia throughout a full range of anesthetic depths during a continuous fixed rate infusion of propofol.

METHODS

Six patients gave their informed consent to take part in the study. All patients were ASA class 1. Patient data are given in Table 7.1. The study was performed during orthopedic surgery of the hip or femur. Premedication consisted of Diazepam 10mg by mouth 1-2hr before

Table 7.1
Patient data.

Patient number	Sex	Age (yr)	Weight (kg)
1	F	66	67
2	M	68	93
3	F	20	60
4	M	58	85
5	M	34	82
6	F	77	77

operation. An 18G lumbar epidural catheter was inserted at the L3-4 level. Epidural block was induced with Mepivacaine 2% plus adrenaline 1:200.000 18-20 ml. Thirty minutes after epidural injection of the local anaesthetic the adequacy of the regional block was tested. Subsequently an infusion of propofol $12mg \cdot kg^{-1} \cdot hr^{-1}$ was started and maintained at that rate for 30 minutes. The infusion was stopped and the patient was allowed to wake up. The loss of the eyelash reflex was taken as induction time and first spontaneous opening of the eyes as wake up time.

Respiration was monitored by observation of the patient and counting respiratory rate at regular intervals.

Arterial blood samples for estimation of plasma concentration of propofol were taken at 1, 3, 5, 10, 30 minutes from the start of infusion. Further samples were taken at 1, 3, 5, 10, 15, 30, 45, 60, 120, 210 minutes after cessation of infusion. The blood was centrifuged and plasma stored at -20 degrees centigrade until assayed by High Pressure Liquid Chromatography [5].

Four channels of EEG were recorded using F1-C1, C1-O1, F2-C2, C2-O2 montage according to the international 10-20 system. The EEG was recorded and on-line analysed for 12 second epochs using a Nicolet Pathfinder II system with the Nicolet Frequency Analysis Program (FAP) (Nicolet Biomedical Instruments, Madison Wisconsin USA). Amplification was adjusted to set the highest voltage just below full

range of the AD converter. High and low bandpass filters were set at 1 Hz and 120 Hz respectively. The FAP allows simultaneous on line Fourier analysis of EEG on four channels. The power spectrum can be split into four bands and for each band mean frequency and total power are calculated. The four frequency ranges used as bands in this study were:

A: 2.00-5.00 Hz
B: 5.25-8.00 Hz
C: 8.25-24.00 Hz
D: 2.00-24.00 Hz

In addition the FAP allows for the calculation of eight derived parameters for each epoch using any of the available band frequency and power parameters. We used this facility to calculate the power ratio of a high frequency band (C) against low frequency (A). All data are made available as an ASCII string for a serially connected printer. To facilitate further analysis of the on-line data we connected the serial port of the Pathfinder to the RS432 port of an Acorn BBC B microcomputer. A program written in BBC Basic mixed with assembly language was used to capture and store on disc the data from the Pathfinder.

Blood pressure was monitored continuously with a calibrated transducer (Hewlett Packard) connected to an intra arterial cannula in the radial artery. Every 12 seconds systolic pressure and pulse rate were read by the Analog to Digital converter of the BBC computer and stored on disk together with the EEG data.

All descriptions of EEG changes in this paper are from a unilateral central-occipital montage. In patients operated in the lateral position we chose the EEG recording from the upper side. In the other cases we chose the side with the least artefact.

From the available spectral data single indices for description of EEG changes were derived. Indices tested were:

- Total power of the EEG signal.
- Mean global frequency.
- Power in band A divided by power in band C

Correlation with the time course of plasma concentration and with the timing of clinical events was made graphically. Statistical evaluation was made for timepoints; loss of eyelash reflex, 15 minutes, 30 minutes (end of infusion), spontaneous eye opening.
Where changes are compared statistically a test for repeated measurements is used. A value of $p<0.05$ is taken as significant.

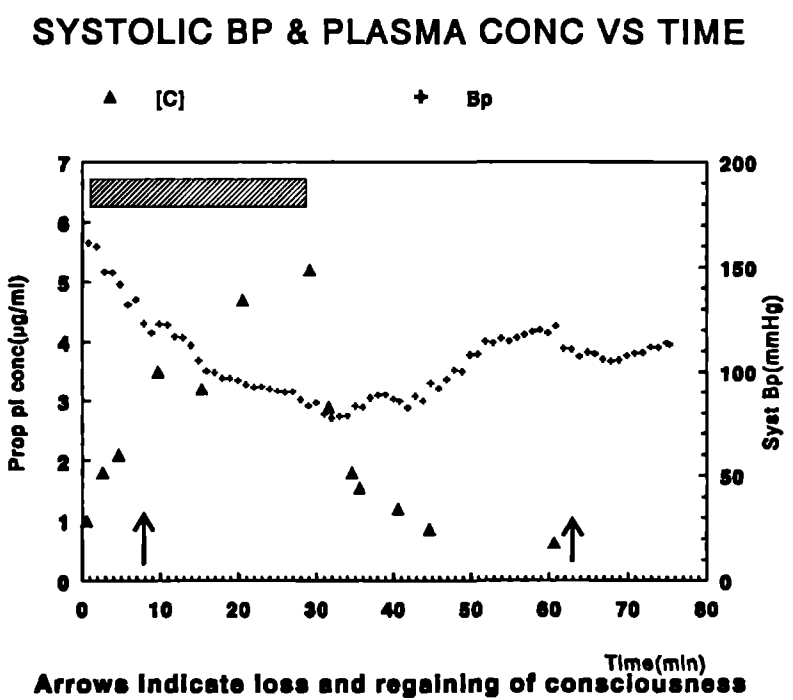
RESULTS

Timing
At induction average time until the loss of eyelash reflex was 6 (SD 3) min. Average time from cessation of infusion until first spontaneous eye opening was 31 (SD 7) min.

Blood pressure
All blood pressure changes were related to a control value taken from the average of five readings from the arterial line the minute before induction. In all cases the blood pressure steadily dropped from the start until the end of infusion. A typical case of the course of blood pressure against time is illustrated by Fig. 7.1. Blood pressure drop was statistically significant at 15 minutes and at 30 minutes. From the cessation of infusion at 30 minutes the blood pressure started rising again. At the time of spontaneous opening of the eyes blood pressure in all cases was still below starting level.

Respiration
In the course of the infusion breathing became shallower but not insufficient. There was no significant change in respiratory rate.

EEG
Mean frequency of the 0-24 Hz spectrum showed a reduction with the same time course as plasma concentration in all cases. A typical example is given in Fig 7.2. Mean power and the high/low frequency


SYSTOLIC BP & PLASMA CONC VS TIME
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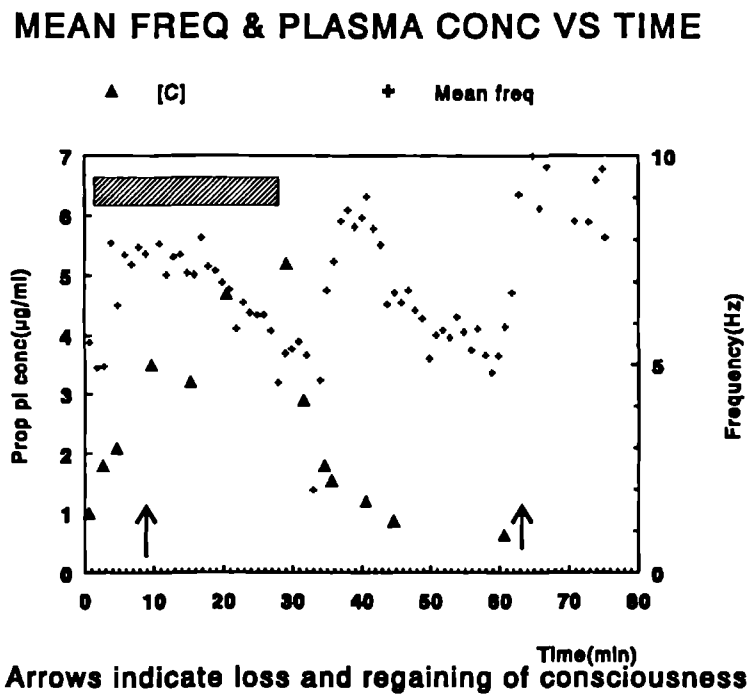
Arrows indicate loss and regaining of consciousness

Fig. 7.1



Arrows indicate loss and regaining of consciousness

Fig. 7.2

ratio showed no useable correlation with the time course of plasma concentration and clinical events.

DISCUSSION

A single parameter derived from the EEG frequency spectrum -Median Frequency- has been shown to predict steady state anesthesia during propofol infusion. It was even used in a feedback loop [6]. The authors payed less attention to the assessment of induction and emergence of anesthesia. The aim of the present study was to evaluate EEG changes throughout a full range of depth of anesthesia.

Clinical effects.

Hypnotic effect.

At 12 $mg.kg^{-1}.hr^{-1}$ in the unintubated patient propofol provides adequate anesthesia in combination with epidural block.

Effect of propofol on blood pressure.

All blood pressure changes were related to a control value taken from the average of five readings the minute before induction. This means that most of the drop in blood pressure caused by the epidural block had already taken place. In the setting of this study propofol significantly depresses systolic blood pressure. Thus the findings of this study prove that in the presence of an epidural block to Th10-Th8 propofol produces a dose dependent drop in blood pressure.

EEG

The visual analysis of a raw EEG signal is time consuming and takes substantial expertise. Therefore techniques have been developed to extract information from the EEG allowing ready interpretation of data by less experienced personnel. Such a technique is the Fourier analysis of the EEG. The frequency spectrum obtained by Fourier analysis can be presented in various forms as a simple display conveying simplified information about the EEG signal which becomes available in seconds [7].

Attempts have been made to extract from the Fourier spectrum an univariate descriptor to be used as indicator of anesthetic depth. The aim of the present study was to test the usefulness of various calculated parameters from the EEG Fourier spectral analysis as an estimate of depth of anaesthesia through the widest acceptable range of stages of anaesthestetic depth for propofol including induction and emergence. The papers describing EEG registration during propofol infusion all use a different electrode montage. Apparently the changes produced by propofol are global throughout both hemispheres.

The Fourier analysis used in this study is based on the assumption that the EEG signal is a constant process during a 12 second sampling period. Thus it cannot be concluded whether burst suppression was present at the deepest levels of anaesthesia.

On the other side of the spectrum of anaesthetic level the transition from awake pattern to a pattern with characteristic changes in the EEG power spectrum and from anaesthetised pattern to awake pattern are not synchronous with clinical observation. There remains a time lag in the EEG power spectrum versus clinical observation. We conclude therefore that EEG Fourier analysis can be used for measuring anaesthetic depth during the sleep stage of propofol infusion. It is however not a reliable indicator of awareness during propofol anaesthesia.

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GENERAL DISCUSSION

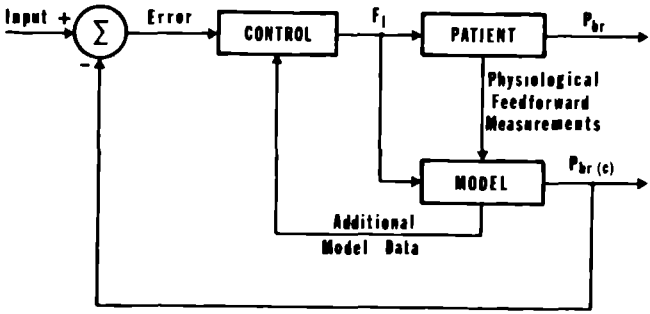
INTRODUCTION

Rationale

The aims of this thesis share one general purpose. The results should improve the management of intravenous general anesthesia. During the administration of an anesthetic the anesthesiologist can be compared with the feed-back, feed-forward controller in a closed loop (Fig.8.1)

Fig 8.1

Schematical diagram of the feedforward concept. From Anesthesiology, Feedback and Feedforward, 1988 Institute for Anesthesiology, Nijmegen. Reproduced with permission. Model predictions preset the controller. Model parameters are dynamically updated by results from physiological measurements.



[1]. The function of the controller in this context is to maintain

optimum depth of anesthesia. This function is performed by manipulating dosage of drugs [2]. For successful feed-forward control a model of the controlled object is needed. Part of such a model is formed by pharmacokinetic and pharmacodynamic parameters. Thus to assume the role of such a controller the anesthesiologist needs access to variables indicating depth of anesthesia as well as a model of the pharmocokinetics of the drugs used. Therefore this thesis contains both the study of drug kinetics and the search for indicators of drug effect (anesthetic depth).

Depth of Anesthesia

The main object of general anesthesia is to produce a state of unconsciousness throughout a surgical procedure without awareness and without (memory) storage or conscious recall [3]. Research into an indicator of depth of anesthesia will only make sense given an accurate definition. Unfortunately despite numerous publications no clear definition of depth of anesthesia has emerged. Every attempt at defining the concept of depth of anesthesia ends with a description of adequate depth in terms of absence of responses -autonomic or (sub)conscious- to surgical stimuli together with complete lack of awareness [4]. Thus depth of anesthesia is defined in terms of an alteration in the functional status of the central nervous system. Monitoring of autonomous responses represented by changes in blood pressure and pulse rate, sweating and lacrimation has until today formed the backbone of anesthetic efforts to estimate depth of anesthesia. However the application of recently introduced powerful intravenous drugs means that awareness with or without recall can exist in absence of significant autonomous response. The isolated forearm technique has shed doubt on the adequacy of anesthetic depth during various anesthetic techniques. In this technique one forearm is excluded from the circulation to prevent paralysis by muscle relaxants. When the patient is verbally prompted to move his hand, purposeful movement can be observed while all other clinical signs would indicate adequate anesthetic depth [5]. In chapter 4 of this thesis a similar observation is made during wake-up testing. Patients gave proof of

being aware by obeying verbal commands, yet changes in blood pressure and pulse rate were moderate to absent. Also postoperative recall was absent in most cases. This emphasises the need for better methods of monitoring anesthetic depth.

Clinical signs

The studies with the alfentanil infusion technique involved a continuous infusion of vecuronium at such a rate that a train of four stimulation elicited at least two palpable twitches. Attempts of a patient to move spontaneously would have resulted in identifiable muscle activity. During our techniques of intravenous anesthesia, depth of anesthesia must have varied considerably as judged from plasma concentration and blood pressure/pulse rate data. Only at the instant of awakening was spontaneous movement observed. From this we conclude that spontaneous movement was not a consistent sign of depth of anesthesia. This contrasts with the isolated forearm technique of measurement of anesthetic depth. An explanation for this apparent contradiction might be that our patients had analgesia provided at all times. Had we been able to record muscle activity at an Electromyographic level we might have seen changes over the course of an anesthetic.

Neurophysiological monitoring

Adequate anesthesia by definition is associated with an absence of efferent response to surgical stimuli. The usual response to surgical stimuli during anesthesia involves processing of sensory input through structures in the brain. The centres involved -thalamus, limbic system, reticular formation- all have close interconnections with the cerebral cortex. Therefore monitoring cortical function, spontaneous- and evoked- should yield direct information about anesthetic depth. The research described in this thesis tries to define the contribution to measurement of anesthetic depth by well known neurophysiologic techniques: ElectroEncephaloGraphy and SomatoSensory Cortical Evoked Potentials. Right from the start it was clear that until now no

single monitoring technique exists that can fulfil all criteria of the 'ideal' indicator of anesthetic depth as quoted from Sebel in Chapter 2 [6].

EEG

The EEG is formed by the changes in electrical potential recorded between two electrodes placed on the scalp. Potential changes from individual cells form random patterns that tend to cancel out on scalp electrodes. The tracing we can see forming the EEG must be caused by more global synchronised potential changes in cells within the cerebral cortex. The changes in potential responsible for the signal that can be recorded from the scalp can not be action potentials. Action potentials last for about 1 msecond. Postsynaptic excitation and inhibition lead to depolarisation and hyperpolarisation respectively of several mvolts lasting for up to 100 msecond. Most likely the generators of the EEG are the pyramidal cells in the cortex. They are oriented vertically within the cortex. Their dendrites penetrate almost to the surface of the cortex. Currents flowing along these cells can therefore penetrate to the scalp. Rhythmicity appears to be dependent on interactions between the cortex and thalamus and the interconnections between the cortical cells. Activation of reticular formation leads to loss of rhythmicity, whereas depression of reticular formation leads to slow rhythmic waves in the EEG. Thus it is in theory understandable that the typical changes in functional state of the brain caused by anesthetics produces patterned changes in frequency and power of the EEG [7].

SomatoSensory Cortical Evoked Potentials

The generation of somatosensory evoked potentials is not fully understood. The stimulus intensity used for SEP's excites only the largest myelinated fibers in the peripheral nerve (cutaneous and subcutaneous somaesthetic and proprioceptive fibers and alpha motor axons). Literature suggests that transcutaneous stimulation to stimulate pain C-fibers may not even be possible without damage to the skin [8]. Cell bodies of the large fiber dorsal column sensory system lie in the dorsal root ganglia; their central processes travel rostrally in

ipsilateral posterior columns of the spinal cord and synapse in the dorsal column nuclei at the cervicomedullary junction. Second order fibers cross to the opposite side shortly after origination and travel to the primary receiving nucleus of the thalamus -the ventroposterolateral nucleus- via the medial lemniscus. Third order fibers continue from thalamus to frontoparietal sensorimotor cortex. The generator of evoked potential signal measured from the scalp lies in the cerebral cortex [9],[10]. This anatomical line of propagation explains how SEP waveforms can be recorded from the scalp even with the highest dosages of opioids. On the other hand the influence of the opioid on anatomical structures in the brain propagating SEP makes it theoretically probable that depth of anesthesia during continuous infusion with an opioid would be reflected by changes in CSEP. Changes in latency and amplitude must therefore be a result of effects of the opioid on the brain.

RESULTS

Alfentanil

Clinical effects

In chapters 2 and 3 we could confirm that a fixed rate infusion of alfentanil in combination with nitrous oxide can produce steady state intravenous anesthesia. A plasma concentration of 200-300 $ng \cdot ml^{-1}$ is in most cases sufficient for stable analgesia with the type of surgery used in our patients. In chapter 2 we describe a stable cardiovascular state in 27 of 29 patients. The remaining two patients showed increases in blood pressure most likely due to insufficient analgesia. On average recovery was complete 16 minutes after the end of the alfentanil infusion. The kinetic parameters we found in our study described in chapter 3 support the view of alfentanil as a rapid acting drug. After cessation of a continuous infusion this concentration decreases initially with a half life of approximately 12 minutes. Given in a dose of 100 $\mu g \cdot kg^{-1}$ alfentanil does not only have a strong analgesic effect but

also acts as a sedative making the patients virtually unresponsive to verbal command within 1-2 minutes [11] This might mean that alfentanil, although considered as mainly a μ receptor agonist [12] produces strong κ receptor effects in the dose range mentioned. This capability of producing unresponsiveness makes alfentanil a suitable agent to be used in an intravenous anesthetic technique.

Comparison with criteria for the "ideal" narcotic

In the Introductory chapter 2 Moldenhauer and Hug were quoted with their criteria for the ideal narcotic Chapters 2 and 3 describe features of continuous alfentanil infusion In a number of aspects alfentanil meets the points raised by Moldenhauer and Hug for the ideal narcotic

Specificity and efficacy

In our experiments with continuous infusion of alfentanil we have shown that it is an efficient analgesic. In most of the patients described response to major orthopedic surgical stimulation was completely suppressed In animal experiments alfentanil had been described as a specific μ receptor agonist. From pharmacological studies we know that μ receptor effect is mainly analgesia and sedation is produced by κ receptor stimulation Our patients became unresponsive after the initial bolus dose of 50 μg kg^{-1} This indicates that alfentanil is not specific for the μ receptor but also binds with the κ receptor.

Without respiratory depression

Alfentanil has a definite respiratory depressant side effect Within one minute after the initial bolus of 50 μg kg^{-1} all respiratory activity ceased. In the recovery phase however we saw no significant respiratory depression as shown by normal blood gases one hour after cessation of the continuous infusion

Without nausea

In our experience alfentanil nitrous oxide anesthesia was accompanied by a high percentage postoperative nausea and vomiting However no antiemetic drugs were used either in the premedication or peroperatively

Without intestinal cramping
The studies in this thesis all involved spinal surgery. No observations about intestinal effects can be made.
Fast onset and short duration
Both our clinical study (chap 3) and our kinetic study (chap 4) support the view that alfentanil is a drug with a very fast onset and short duration of action without accumulation. In chapter 3 is described how onset of effect is a matter of seconds. The experiments of chapter 4 show that even after infusion of several hours duration the terminal half life of alfentanil is very short compared to other opiates. Steady state plasma concentration results from a balance between elimination and infusion rate. We showed that elimination half life is age dependent. Therefore the shortest duration of effect will be guaranteed if age is taken into account when calculating steady state infusion rate.
Non-addictive.
The duration of administration of alfentanil in our experiments is too short to be able to judge the addictive potency of alfentanil.
Lack of tolerance
Over the time course of our experiments with a maximum duration of infusion of 7 hours we never needed to increase dosage for adequate analgesia. Also in other studies using alfentanil for intravenous anesthesia we found no mention of acute tolerance [13].

SomatoSensory Evoked Potentials and alfentanil / nitrous oxide
Recent literature shows that opiates administered directly intrathecally do not change SomatoSensory evoked Potentials in awake humans [14]. In dogs it was shown by Swenzen and coworkers that sympathetic output in response to noxious stimulation of C-fibers is suppressed by much lower dosages of alfentanil than is needed to suppress response to A-delta fibers [15]. It is this A-delta fiber stimulation that is thought to be responsible for the SomatoSensory evoked potential as we described earlier in this chapter. Therefore it might be expected that evoked potentials can be elicited under alfentanil infusion as we have seen in chapter 5 of this thesis. So it seems reasonable to expect changes in the SCEP to reflect the cerebral

system effects of alfentanil, not the spinal effects. In some studies alfentanil did produce measurable changes in amplitude and to a lesser extent in latency. In our study of chapter 6 general anesthesia was produced by alfentanil in combination with ventilation with an oxygen/nitrous oxide mixture. Amplitude changes and to a lesser extent latency changes ocurred. However variance was too large for these changes to be of use for the quantification of anesthetic depth.
The location of depression of SomatoSensory Evoked Potentials by nitrous oxide has recently been studied in cats. The results suggest that thalamo-cortical relay of sensory information is suppressed. At the same time reticular formation activity is enhanced [16]. This finding offers some explanation why nitrous oxide acts as a weak anesthetic but strongly suppresses cortical SomatoSensory Evoked Potentials. In our study the effects of nitrous oxide on the brain obscured changes produced by alfentanil. Recent literature suggests that substituting a propofol infusion for nitrous oxide inhalation and ventilating the patient with an oxygen/air mixture produces a SCEP that is much less variable [17].

Propofol

Clinical effects
In chapter 2 we mentioned some properties an intravenous hypnotic should have.

- Smooth induction
- Fast recovery
- No active metabolites
- Specificity without side effects

We compare these with our findings of chapter 7 using propofol in combination with regional anesthesia.
Smooth induction.
Propofol given at a rate of 12 $mg \cdot kg^{-1}$ in combination with epidural block gives good anesthesia with a smooth induction.It might be argued

that our dosage of propofol 12 $mg \cdot kg^{-1} \cdot hr^{-1}$ is rather high. De Grood and co-workers however have shown that to enable smooth intubation and ventilation without coughing 9 $mg \cdot kg^{-1} \cdot hr^{-1}$ can be too low [18]. This illustrates that the dosage we used is within the clinically acceptable range.

Fast recovery.

The relatively high dosage used in our study explains why recovery was not as fast as described by other authors.

No active metabolites.

The literature mentiones as an advantage of propofol with respect to recovery that once the patient is awake recovery is more complete in comparison with other anesthetics [19]. This aspect was not subject of our study of chapter 7.

Side effects.

We also describe in chapter 7 a significant drop in blood pressure correlating with plasma concentration. In this respect propofol thus is not an ideal intravenous hypnotic.

Given at the correct dosage propofol is an effective hypnotic. Clinically depth of anesthesia is difficult to predict between the stage of unresponsiveness and the instant of spontaneous response again. As we have shown in chapter 7 propofol effect on EEG can be used to monitor depth of anesthesia during steady state infusion.

Neurophysiologic monitoring during propofol infusion

The study reported in chapter 6 of this thesis shows that a steady state anesthesia by infusion of propofol is reflected by specific changes in the EEG power spectrum. The exact moments of loss and regaining of consciousness are not well predicted by EEG power spectrum analysis. Here EEG changes seem to lag behind clinical signs. Several causes may be postulated to explain this lack of sensitivity of EEG.

- The Fourier spectrum and any derived parameters are calculated over epochs of EEG signal of a certain length (from one to several seconds). Thus changes cannot become visible until after at least one epoch.

- The EEG only represents activity of certain classes of cortical cells. Global changes will be reflected in the EEG, but a local process like memory storage or thought processes may go unnoticed.

PROBLEMS REMAINING

The elimination of noise

Especially in the operating theatre electrical interference is responsible for a high noise level in neurophysiological signals. This noise is only partly eliminated by the analog filtering techniques mostly employed. Other methods will have to be developed for prevention of noise and improvement of filtering of neurophysiological signals. Improvement can sometimes be achieved by stopping data collection during periods of diathermia interference [20].

Problems in evaluating Evoked Potentials

Up to date most investigators use no other method of evaluation of the information contained in evoked potentials than the peak latency method. Especially in a noisy signal simple visual inspection of a curve can be inaccurate and ambiguous for the detection of a peak. Computer techniques for peak detection might improve this situation. The complex evoked potential signal contains more information with relevance to the effects of anesthetics than what is extracted by the peak latency method. Improvements are to be expected from novel techniques for computer analysis of the evoked potential signal [21]. These will include a posteriori artifact elimination and automatic peak detection.

Time lag

The introduction of fast computing power has made considerable improvement in the time needed to obtain a Fourier spectrum or an averaged evoked potential. Nevertheless detection of changes in cerebral

function lags behind real time. Novel techniques of data collection and processing will be needed to help solve this problem [21].

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CHAPTER 9

CONCLUSIONS

One single parameter representing "Depth of anesthesia" is not available. The concept of depth of anesthesia is based on the functional status of the central nervous system characterized by the abscence of awareness and the abscence of efferent response to surgical -nociceptive- stimulation. Any conclusion about the functional status of the central nervous system can only be drawn from a combination of observations and measurements of physiological parameters. Anesthesiologists are taught to draw such conclusions through a mixture of logical combination and intuition. For a more scientific approach of depth of anesthesia computer technology will provide a strong aid. Before computers can however start to support decision making in the clinical setting software has to be developed. Techniques like neural networking might in the future form a basis for the process of infering conclusions from large numbers of data collected from the patient.

Plasma concentration and depth of anaesthesia are not the same. Even a good model incorporating the relationship between plasma concentration and concentration at the target organ -the receptor compartment- will not be adequate for predicting anesthetic depth. The concentration needed at the receptor for a stable anesthesia is not a constant, but depends on circumstances such as nociceptive input, presence of other anesthetics and other factors.

The studies in this thesis employing neurophysiological monitoring show, that especially around the moment of spontaneous recovery of consciousness neurophysiological monitoring fails to indicate depth of anesthesia. Furthermore, from the literature it can be shown that

parameters derived from neurophysiological monitoring give different responses with different anesthetic techniques and drugs.

The Potentials in propofol / alfentanil infusion technique have a higher amplitude after induction than before. In our study using nitrous oxide / alfentanil we saw the opposite. Questions like these concerning basic neurophysiology will have to be solved before SomatoSensory Evoked Potentials can be considered an indicator of depth of anesthesia. Other Evoked Potentials -for instance Auditory Evoked Potentials- might provide more information. Other techniques of analysing the information content of the signal might also contribute towards employment as measurement of anesthetic depth.
EEG frequency analysis shows a better potential for measuring the graded functional status of the central nervous system than SSCEP. It did, however, not allow precise determination of the time of spontaneous awakening. This is a crucial point in monitoring depth of anesthesia. Our patients should be guarded against awareness by all available means.

The anesthesiologist has to manage his patient by a continuous process of decision making about which drugs and gases to administer and in what dosages. These decisions are based on a concept of depth of anesthesia. In order to rationalise his actions the anesthesiologist needs a better definition of this depth of anesthesia and better tools to measure it.

Chapter 1 describes the reasoning leading up to the aims of the study:

1. Exploration of two intravenous anesthetic drugs. By testing a pure analgesic and a pure hypnotic in separate experiments, we try to show the clinical usefulness of both drugs in future intravenous techniques. This part of the work will give some answers to the question how well these drugs fulfil the criteria of steady state intravenous anesthesia.

2. Testing the possibilities of using Neurophysiological monitoring for the assessment of anesthetic depth during these two types of intravenous anesthesia.

3. Efforts to correlate three elements in the determination of anesthetic depth during intravenous infusion of these drugs: clinical signs, neurophysiological changes and plasma concentration.

Chapter 2 gives an overview of the literature. A historical summary is given of the concept of depth of anesthesia.

The development of intravenous techniques of anesthesia is followed from literature. The objectives of anesthesia are summarized as:

- Analgesia
- Unconsciousness
- Muscle relaxation
- Autonomic reflex suppression

Although no final definition of anesthetic depth can be found in the literature a working definition is given for the purpose of this thesis:

> *Anesthetic depth is the degree of suppression of consciousness and responsiveness of the central nervous system to noxious stimulation.*

Existing methods of assessing anesthetic depth are discussed. Both observation and measurement of clinical signs and neurophysiological monitoring have been mentioned in the literature. Various techniques are described to extract a "depth of anesthesia" parameter from EEG and Evoked Potential monitoring.
Finally a summary is given of the literature describing the influence of various anesthetics on EEG and Evoked Potentials.

Chapter 3 describes a clinical assessment of the use of loading dose followed by a fixed rate continuous infusion of a short acting opioid -alfentanil- in combination with Nitrous Oxide / Oxygen ventilation and vecuronium muscle relaxation. In 25 of 27 patients a satisfactory stable anesthesia was obtained. The remaining two patients needed multiple additional bolus doses.

Chapter 4 describes a study of the pharmacokinetics of alfentanil in the same regime as in chapter 3. Two methods of calculating half life and clearance are compared: a traditional curve fitting method and a model independent approach. Both methods performed equally well. Regression analysis showed no statistical relationship between T½ß, Cl or Vd and the duration of the infusion, total dose, or body weight. We found no significant correlation between age and T½ß of alfentanil for patients younger than 40 yr. For patients older than 40 yr, T½ß increased linearly with age.

Chapter 5 describes the use of Tibial SomatoSensory Cortical Evoked Potentials and wake-up testing during continuous alfentanil anesthesia. It is shown that these two forms of spinal monitoring can

be employed effectively under this anesthetic technique. Wake-up testing was performed in 23 patients. Average wake-up time was 10 minutes (sd 3.7 min). Evoked responses suitable for spinal monitoring could be obtained in 60 of 61 patients.

Chapter 6 describes a study to correlate clinical indicators of depth of anesthesia with alfentanil plasma concentration and Tibial SomatoSensory Cortical Evoked Potentials. After induction amplitudes fell by 50%. There was little change in latencies. Responses during anesthesia were variable without good correlation with clinical signs or alfentanil plasma concentration thus prohibiting the use of this monitoring technique as a measure of anesthetic depth.

Chapter 7 describes a study to test the use of EEG monitoring for the assessment of depth of anesthesia with the hypnotic drug propofol. Propofol is given as a fixed rate infusion of 12 $mg \cdot kg^{-1} \cdot hr^{-1}$. Patients are made analgesic by a lumbar epidural block for lower limb surgery. Mean EEG frequency correlated well with plasma concentration. Systolic blood pressure was also a good indicator of anesthetic depth. An indication of the instant of loss and regaining of consciousness can be found in the EEG but the transition is not precisely defined.

Chapter 8 discusses the results of the studies against the background of the literature referenced in chapter 2.

In chapter 9 some conclusions are drawn. Estimation of plasma concentration is helpful in establishing a model aiding the anesthesiologist in his decisions about depth of anesthesia. So is neurophysiological monitoring. However no single descriptor of depth of anesthesia can be found.

SAMENVATTING

In hoofdstuk 1 wordt de gedachtengang weergegeven, die tot het idee voor dit proefschrift heeft geleid. Een anesthesist moet tijdens zijn werk de dosis van de geneesmiddelen bepalen. Hiervoor dient hij een beeld te hebben van de bereikte effecten van alle toegediende middelen tezamen. De laatste jaren zijn in de anesthesiologie intraveneuze middelen geïntroduceerd met een hoge specificiteit. Hiermee is het mogelijk het ideaal te benaderen om de verschillende elementen van een algehele anesthesie afzonderlijk te verzorgen. We onderzoeken in dit proefschrift twee van deze middelen, een pijnstiller en een slaapmiddel.
De doelen van het in dit proefschrift beschreven onderzoek zijn als volgt gedefinieerd:

1. De bruikbaarheid onderzoeken van de pijnstiller en het slaapmiddel in intraveneuze anesthesie technieken.
2. De mogelijkheden onderzoeken van neurofysiologische technieken om anesthesie diepte te meten tijdens toepassing van deze twee middelen.
3. Pogen een synthese te maken van drie elementen bij de bepaling van anesthesie diepte: Klinische waarneming, neurofysiologische meting en plasma concentratiebepaling.

Hoofdstuk 2 bevat een overzicht en samenvatting van relevante literatuur. Een historisch overzicht van de ontwikkeling van intraveneuze anesthesie technieken. Een historisch overzicht van de ontwikkeling van het begrip anesthesie diepte. Er wordt ingegaan op de gewenste eigenschappen van een pijnstiller en een slaapmiddel voor anesthesie. Er wordt een afweging gegeven van intraveneuze tegenover inhalatie anesthesie. Er wordt ingegaan op de observaties, die de anesthesist leiden bij het vaststellen van de anesthesie diepte.
Neurofysiologische technieken worden besproken.

De volgende definitie wordt gesteld voor gebruik bij het onderzoek in dit proefschrift:
Anesthesie diepte is de mate van onderdrukking van het bewustzijn en van de reactie van het centraal zenuwstelsel op inwerking van beschadigende prikkels.

Hoofdstuk 3 is een publikatie die de klinische aspecten beschrijft van een anesthesie techniek met continue infuus van de kort werkende pijnstiller alfentanil in combinatie met spierverslapping en beademing met een zuurstof / lachgas mengsel. Conclusie is dat in 23 van 25 patiënten de techniek goed werkt en een stabiele anesthesie oplevert. In 2 gevallen moet met korte intervallen alfentanil extra worden toegediend.

Hoofdstuk 4 is een publikatie over de berekening van de opname, verdeling en uitscheiding van alfentanil over het lichaam aan de hand van de bepaling van de concentratie in plasma monsters. De anesthesie techniek is dezelfde als in hoofdstuk 3. Er worden twee berekeningstechnieken vergeleken. Geconcludeerd wordt, dat een stabiele plasmaconcentratie wordt verkregen met de toegepaste infuus techniek (dezelfde als in hoofdstuk 3). De twee berekeningstechnieken geven statistisch niet van elkaar verschillende resultaten. Op valt, dat de terminale halfwaardetijd bij patiënten boven de 40 jaar een lineair verband heeft met de leeftijd.

Hoofdstuk 5 is een publikatie over de toepassing van dezelfde anesthesie techniek uit de hoofdstuk 3 bij wervelkolom chirurgie. Het blijkt, dat de gebruikelijke methoden om beschadiging van het ruggemerg op te sporen, SomatoSensore Evoked Potentials en ontwaaktest goed zijn toe te passen. Hiermee is aangetoond, dat SomatoSensore Evoked Potentials zijn te registreren tijdens alfentanil infuus met lachgas beademing. Op valt, dat met de ontwaaktest wordt bewezen, dat een patiënt gericht op vragen kan reageren tijdens anesthesie en dit na de operatie niet meer weten.

Hoofdstuk 6 beschrijft een studie naar de relatie tussen veranderingen in het SomatoSensore Evoked Potential signaal, de plasma concentratie van alfentanil en de anesthesie diepte. Zodra de patiënt onder anesthesie is gebracht neemt de hoogte van het Evoked Potential signaal af met ongeveer 50%. Variaties in grootte en tijdsrelaties in het signaal doen zich daarna wel voor. Er is echter geen duidelijk verband met plasma concentratie en geschatte anesthesie diepte te vinden.

Hoofdstuk 7 is een studie met een continu infuus van het slaapmiddel propofol voor anesthesie bij patiënten, die eerst complete pijnstilling hebben gekregen met epidurale verdoving. Bloeddruk en polsfrequentie werden gemeten en vastgelegd via een computer. Tevens werd tijdens anesthesie continu het Electro Encephalo Gram (EEG) geregistreerd en met een computerprogramma bewerkt. Op het EEG signaal is Fourier transformatie toegepast, waarna een aantal waarden uit het frequentiespectrum werden vastgelegd. Op gezette tijden werd de plasmaconcentratie van propofol bepaald. Er werd getracht uit de resultaten een patroon te vinden in verandering van EEG frequentie inhoud dat correleert met de verandering in anesthesie diepte en plasma concentratie. De gemiddelde frequentie uit het spectrum uitgezet tegen de tijd tezamen met plasma concentratie laat zien ,dat bij de aanvang van de anesthesie en in de diepe fase een verlaging van de frequentie optreedt, die een verloop heeft overeenkomstig de andere gemeten grootheden. De stap naar een hogere frequentie inhoud, die past bij ontwaken, wordt bereikt, nadat de patiënt klinisch tekenen van ontwaken heeft vertoont.

Hoofdstuk 8 bespreekt de bevindingen uit de studies van hoofdstukken 3 tot en met 7 tegen de achtergrond van de literatuur uit hoofdstuk 2.

Hoofdstuk 9 trekt conclusies. Geen enkele van de toegepaste technieken van monitoring is geschikt gebleken om op zich zelf de anesthesie diepte mee te meten. Een bepaling van anesthesie diepte zal moeten volgen uit het combineren van klinische waarneming en een aantal fysiologische metingen. De getallen, die hieruit komen dient de

anesthesist te combineren met gebruikmaking van zijn ervaring. Uit dit proces volgt dan, ten dele intuïtief, een inschatting van anesthesie diepte.

CURRICULUM VITAE

Herman Bernard Hendrik van Beem werd geboren op 5 november 1943 te 's-Gravenhage.
In 1962 behaalde hij het eindexamen gymnasium beta aan het Willem de Zwijgerlyceum te Bussum.
In 1972 legde hij het artsexamen af aan de Universiteit van Amsterdam.
Van 1-7-1972 tot 1-1-1976 volgde hij de opleiding tot anesthesioloog aan de afdeling anesthesiologie van het Academisch Ziekenhuis bij de Universiteit van Amsterdam. Opleider:
Prof D.M.E. Vermeulen-Cranch CBE FFARCS.
Van 1-1-1976 tot 1-1-1977 was hij Senior Registrar in het Royal Victoria Infirmary, het Academisch Ziekenhuis bij de Universiteit van Newcastle upon Tyne, Engeland.
Daarna was hij tot 1-8-1982 als Chef de Clinique en voorzitter van de Opleidingscommissie verbonden aan de afdeling Anesthesiologie van het Academisch Ziekenhuis bij de Universiteit van Amsterdam, het Wilhelmina Gasthuis. Vanaf 1981 gevestigd in het Academisch Medisch Centrum.
Van 1979 tot 1986 was hij voorzitter van het Concilium Anesthesiologicum en uit dien hoofde lid van het bestuur van de Nederlandse Vereniging voor Anesthesiologie.
Sinds augustus 1982 is hij als staflid van het Instituut voor Anesthesiologie in de rang van wetenschappelijk hoofdmedewerker werkzaam in het Academisch Ziekenhuis Nijmegen, St. Radboud-ziekenhuis.
Hij is lid van de Anaesthetic Research Society van Engeland sinds 1977.

STELLINGEN

behorende bij het proefschrift
Depth of Intravenous Anesthesia
H.B.H. van Beem

1. De infusiesnelheid tijdens een steady state infuus met alfentanil dient aangepast te zijn aan de leeftijd bij patiënten boven 40 jaar. (Dit Proefschrift)

2. Wanneer bewaking van de ruggemergsfunctie tijdens wervelkolom-chirurgie wordt toegepast, verdient een totaal intraveneuze anesthesietechniek de voorkeur. (Dit proefschrift)

3. De toestand "onder anesthesie" is een vloeiende, constant veranderende beïnvloeding van de functionele toestand van het centraal zenuwstelsel, geen on-off fenomeen. (Bonke B. ed. Memory and awareness in anaesthesia. Swets & Zeitlinger bv, Amsterdam 1990:73)

4. Voor bepaling van de anesthesiediepte dient een combinatie van een aantal waarnemingen en metingen aan de patiënt te worden verwerkt met de ervaring van de anesthesioloog.

5. Dat artsen vaak onbekend zijn met het bestaan van niet opiaat-gevoelige pijn is de oorzaak van veel onnodig lijden bij kankerpatiënten.

6. Regelgeving is nodig om wildgroei te voorkomen bij facilitaire ondersteuning thuis voor patiënten die behandeld worden met continue spinale infusie.

7. In principe verdient biologische reconstructie van beschadigd gewrichtskraakbeen de voorkeur boven herstel met een prothese.

8. Gecontroleerde hypotensie tijdens het inbrengen van een gecementeerde heupprothese kan de penetratie van het methyl-metacrylaat in trabeculair bot bevorderen.

9. Surgery begets surgery.

10. Sommige regels in het Wegen Verkeers Reglement dienen niet zozeer de verkeersveiligheid als wel de belangen van handelaren in tweewielers.

ISBN 90-9005774-9