WHEN THE PATIENT IS ASLEEP…

Intraoperative awareness and depth of anesthesia in children

Terwijl de patiënt onder zeil is…

Wakker worden tijdens de operatie en diepte van anesthesie bij kinderen

The work presented in this thesis was performed at the Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands.

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1 General introduction

INTRODUCTION

Advances in technology, pharmacology and anesthetic technique during the last four decades have attributed to a substantial decrease in morbidity and mortality related to anesthesia in the adult and pediatric surgical populations. Nevertheless, the current anesthesia-related morbidity is still reason for concern. Children are even at higher risk than adults because of larger anesthetic requirements and the associated increased incidence of cardiovascular instability.[1] Furthermore, children appear to show a more pronounced patient-to-patient variability in drug metabolic capacity than adults, and many organ systems are still immature.[2] They therefore have greater likelihood of clinically important variations in pharmacokinetic (PK) and pharmacodynamic (PD) responses. Finally, because of incomplete, or absent drug evaluation and inadequate drug labeling, children are most at risk for developing side effects of drugs.[3] Therefore, the act of balancing between deep and light levels of anesthesia is one of the major challenges in pediatric anesthesiology. Both too deep and too light levels of anesthesia might have unwanted consequences. Overdosing results in a deep hypnotic state which may lead to hypotension, longer wake-up times, and longer stay in the recovery room. Recent studies in animals suggest that particularly neonates and the very young may be susceptible to potentially toxic effects of anesthetic agents on the brain.[4-6] These may even bring longer-lasting behavioral changes.[7] Although it is not clear whether these finding might be applicable to humans and the anesthetic practice as well,[8,9] they have raised concerns for the pediatric anesthesiologist.

Next to alarming reports of neurodegenerative effects of anesthetics, epileptiform activity in the EEG was detected in children receiving high concentrations of sevoflurane anesthesia.[10] For instance, during inhalation induction of anesthesia with sevoflurane and nitrous oxide, up to 88% of young patients develop epileptiform EEG changes.[11] So there is every reason to prevent anesthetic overdoses.

On the other hand, underdosing of anesthetics and analgesics in infants and children may have harmful effects as well, and result in poor outcome.[12] Furthermore, underdosing of anesthetics may cause intraoperative awareness, defined as explicit recall of events during a procedure performed under general anesthesia.[13]

By now, anesthesiologists have come to realize that individualized dosing of anesthetics in children is essential to maintain optimal levels of anesthesia and thus avoid potential problems from under- and overdosing. The investigations in this thesis focus on intraoperative awareness, monitoring of depth of anesthesia, and PK/PD modeling of different anesthetics in children.

Intraoperative awareness

The problem of intraoperative awareness is as old as anesthesiology itself. A first case of awareness was described as early as 1846, when William Morton demonstrated a procedure using ether as anesthetic agent and the patient later reported that he had been awake during the procedure. Since then, incidences of awareness have continued to be documented even after the introduction of modern anesthesia techniques. At present, incidence, causes and consequences of awareness have mainly been studied in adults. Incidences from 0.1 - 0.2% have been reported in non-high risk surgery.[14,15] Adult patients who experience recall may subsequently exhibit post-traumatic stress and psychological symptoms.[16,17] Subsequent to the recent studies on intraoperative awareness, the Joint Commission on Accreditation of Healthcare Organizations has classified intraoperative awareness as a Sentinel Event.[18]

Considerably less is known about intraoperative awareness in children. In the 1970s and 80s, the so-called 'Liverpool technique' (i.e. nitrous oxide, muscle relaxants, and no volatile or IV anesthetic) was used in children to avoid cardiodepressant effects of anesthetics. It is not surprising therefore that the first study on awareness in children in 1973 reported an incidence as high as 5%.[19] The 'Liverpool technique' having being abandoned since, the attention to intraoperative awareness in pediatric patients waned until the beginning of this century. Two recent studies have demonstrated that awareness occurs in pediatric anesthesia even using modern techniques.[20,21] Nevertheless, there is still little knowledge about the incidence, causes and consequences of awareness in children.

Monitoring depth of anesthesia

Anesthesia is based on different components: hypnosis, analgesia, amnesia, immobility and reduction in reflex autonomic responses (such as hypertension and tachycardia) associated with nociceptive stimuli. Like in all published studies so far dealing with depth of anesthesia, in this thesis, the term "monitoring depth of anesthesia" exclusively refers to monitoring the hypnotic component of anesthesia.

Reliable monitoring of the hypnotic component of anesthesia could help anesthesiologists to maintain optimum levels of anesthesia and avoid problems caused by underdosing and overdosing. At present, many anesthesiologists rely on somatic signs (motor responses, changes in respiratory pattern) and autonomic signs (tachycardia, hypertension, lacrimation, sweating) to guide the dosage of anesthetic agents. These clinical signs do not always correlate with depth of anesthesia, however, and are often masked by the use of neuromuscular blockers and other drugs, such as beta-blockers or calcium channel blockers.

Various methods for objective measurement of depth of anesthesia have been developed. Basically these can be classified into those that analyze the spontaneous electro-

encephalogram (EEG) and those that measure EEG responses triggered by acoustic stimuli; or auditory evoked potentials (AEPs) (see Table 1). The Bispectral Index (BIS), derived from the EEG, is the most widely studied monitor for evaluating depth of anesthesia. Potential benefits of BIS guided anesthesia in adults include improved hypnotic drug titration[18,32-34] and faster recovery times.[32,34] Controversy exists, however, regarding the usefulness of BIS to prevent intraoperative awareness in adults.[35,36] The newer AEP/2 monitor has been shown to decrease anesthetic delivery, and may lead to faster postoperative recovery in adult patients.[32,34,37]

Before routine monitoring can be advocated in pediatric anesthesia, both monitors need to be validated against a gold standard. Regrettably, anesthesia depth is a poorly defined and abstract concept. There is no gold standard measure of anesthetic depth with which to compare indices derived from depth of anesthesia monitors. Consequently, we must resort to indirect measures such as anesthetic drug concentration and sedation scales.

Pharmacokinetic and pharmacodynamic variability of anesthetics

Dose requirements of anesthetics vary with age, sex, physiologic condition, and a range of pathophysiologic factors. Children will undergo a series of physiological changes and their different organs will mature at different ages. Thus, there is significant variability in pharmacokinetics and pharmacodynamics between and within individual children, which may give rise to suboptimal concentrations of anesthetics. Furthermore, appropriate dosing regimens for different age categories are lacking. For propofol, a widely used anesthetic, covariates such as weight, age, sex, and cardiac output have been shown to influence the pharmacokinetics.[38,39] In general, larger doses of propofol in children are required and it has been suggested that this is due to differences in pharmacokinetics[40] and/or sensitivity.[41] Nevertheless, the large observed inter-individual variability in the effect of anesthetics remains unexplained so far. Furthermore, real time monitoring of propofol concentrations is not possible. Consequently, adequate propofol dosing is often uncertain, leading to possible over or under-dosage potentially responsible for prolonging delay of recovery or intraoperative awareness. There is a need for dosing schemes with accurate endpoints to prevent too deep and too light levels of anesthesia. An important tool to this aim is pharmacokinetic and pharmacodynamic modeling, in particular Nonlinear Mixed Effect Modeling (NONMEM), as it describes and explores factors (covariates) influencing intra- and interpatient variability.

Table 1 Available depth of anesthesia monitors

Monitor	Index	EEG parameters used	Publications in pediatric anesthesia	References to describe function
BIS	Bispectral index	Power-frequency ratio, bispectral index, burst suppression	+++++	22, 23
M-Entropy	State entropy and response entropy	Degree of disorder in the EEG	+++	24, 25
Narcotrend	Narcotrend index	Pattern recognition in the EEG	+++	26
AEP/2	composite AAI	Mid-latency auditory evoked potential and passive EEG	++	27
Cerebral State monitor	Cerebral state index	Spectral analysis using fuzzy logic	+	28
PSA4000 or SED line	Patient state index	Power, frequency, phase coherence between different regions	-	29
SNAP II	Snap II index	Both low and very high EEG frequencies	-	30
IoC - View	Index of Consciousness	Chaos mathematical analysis	-	31

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OUTLINE OF THE THESIS

The studies in this thesis aim to improve the knowledge on intraoperative awareness and monitoring on depth of anesthesia in children. Furthermore, pharmacokinetics and pharmacodynamics of different anesthetics were studied. This thesis therefore is defined in three parts:

Intraoperative awareness

In **chapter 2**, two cases of intraoperative awareness in our institution are described, which triggered a systematic evaluation of the incidence of awareness in our hospital. In **chapter 3**, the incidence of awareness in children during general anesthesia in our hospital is studied.

Monitoring depth of anesthesia

In **chapters 4, 5, and 6** different anesthesia monitors (Bispectral Index Monitor and the AEP/2 monitor) are evaluated and compared for their value to objectively assess different hypnotic levels during different types of anesthesia, using the University of Michigan Sedation Scale (UMSS)[42] as gold standard. Furthermore, in **chapter 4**, postoperative explicit recall is evaluated after a period of planned intraoperative wakefulness during scoliosis surgery, the so-called wake-up test.

Pharmacokinetics and pharmacodynamics of anesthetics

In **chapters 6 and 7** the pharmacokinetic and dynamic profiles of isoflurane and propofol are described, using BIS and cAAI as pharmacodynamic endpoints.

Chapter 8 provides a general discussion and directives for future research.

Chapter 9 summarizes the results.

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2

Awareness in children: another two cases

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ABSTRACT

Intraoperative awareness is an anesthesia complication and occurs when a patient becomes conscious during a procedure performed under general anesthesia and subsequently has recall of these events. Awareness is well described phenomenon in adults, with an incidence of 0.1 - 0.2% for low-risk surgical procedures. Recent studies have shown that awareness in children is more common than in adults. However, causes and the long-term psychological impact of awareness in children are unknown. We report on two cases of intraoperative awareness in children in an attempt to throw further light on this complex problem.

INTRODUCTION

Intraoperative awareness is an unwanted complication and occurs when a patient has explicit recall of events during a procedure performed under general anesthesia. Awareness is well described in adults, for whom incidences for low-risk surgical procedures in the order of 0.1 - 0.2% have been reported.[1] Until recently awareness in children had not been studied extensively. The exact aetiology is unknown and the true incidence of awareness in children is still to be defined for all age groups.

Two studies on awareness recently reported significantly higher incidences in children than in adults.[2,3] It appeared that awareness was less likely to be reported in the immediate postoperative period and that the yield was greater at interviews up to a month later. In practice the anesthesiologist is less likely to be in contact with the child at these times. The true incidence may therefore be even greater than reported.

Awareness may have devastating psychological effects on the individual and lead to a post-traumatic stress disorder. The long-term psychological impact of awareness in children is unknown. Our impression from previous studies[2,3] is that the psychological impact is less traumatic in children. We here describe two cases of intraoperative awareness in children in an attempt to throw further light on this complex problem. Both children reported recall in the recovery room immediately following surgery and both have been followed for at least a year since the event.

Case 1

A 12-year-old boy, weighing 49 kg, ASA status II, diagnosed with a leptomeningeal disseminated ependymoma, presented for removal of a ventriculo-peritoneal drain. He had no history of psychiatric disease, was not on medication, and was attending public school in an appropriate grade. Previous anesthetics had been uneventful. He received no premedication. In the induction room a pulse oximeter was applied and IV access was secured. Anesthesia was induced with 150 mcg fentanyl (3 µg/kg) and 300 mg thiopentone (5 mg/kg). Endotracheal intubation was facilitated with 30 mg rocuronium (0.6 mg/kg). Anesthesia was maintained with isoflurane at approximately 1 MAC i.e. 1.5% endtidal in oxygen/air. The lungs were mechanically ventilated to normocapnia (endtidal carbon dioxide 35 - 40 mmHg). After surgical incision the hemodynamic parameters started to rise with blood pressure peaking at 115/73 mmHg (baseline 105/55 mmHg) and pulse rate 115 (baseline 90). There were no other signs indicative of light anesthesia. An additional bolus of 50 mcg fentanyl (1 µg/kg) was administered and anesthesia was temporarily deepened. No cerebral function monitor was available. The only other drug administered was cefazolin for antibacterial prophylaxis.

Surgery lasted 1 h, during which blood pressure and heart rate remained stable. The blood loss was insignificant. At the end of surgery, isoflurane was discontinued and the patient was extubated without incident when spontaneous breathing had returned and he responded to verbal commands. No emergence delirium was reported.

In the recovery room, however, the boy started to cry and was upset. He told the recovery staff that he had been awake during incision. The anesthetic staff were alerted and they visited the child in the pediatric ward later the same day and asked about his experience during surgery. Open-ended questions were used in an attempt not to influence his response. Specific questions were used when it became clear that he had explicit recall of events, so as to obtain more detailed information. The interview was repeated on the 4th postoperative day and again at 3 weeks postoperatively according to the Brice methodology.[4] We report on some extracts of these interviews.

> "I woke up and heard the surgeon talking [….] I could recognize his voice [….] Then I felt the incision behind my ear […..] I heard the surgeon saying that the incision should be larger […..] then I felt that the incision was opened with a sort of clamp […..] I tried to move and warn the doctor that I was awake, but I couldn't move […] I was panicking and I felt a tube in my throat [….] I thought I was going to suffocate and tried to swallow, but that was not possible […..] Then I felt that I didn't have to breathe because something else was doing that for me […..] I was not in pain, but the feeling was not very nice" [Note: MPEG1 digital video file displaying the postoperative interview 16 months after the operation is provided.]

During the interviews the boy volunteered that he did not want to tell anyone about his experience. His major concern was that no one would believe him. Still he was relieved that his story was taken seriously. On direct questioning he denied that he had been in pain.

The boy continues to do well and at follow-up by the anesthesia staff over the past 16 months he has had no further complaints. He is attending school and has had no sleep disturbance or other psychological problems related to this incident.

Case 2

An 8-year-old boy, weight 35 kg, ASA status II, with a left parietal tumour presented for an elective open biopsy. The patient had a history of epilepsy that was controlled with 100 mg carbamazepine twice daily. He had no previous history of psychiatric disease, and was attending public school. He had had no previous anesthetics. He was given no premedication besides EMLA cream applied to the dorsum of both hands. Anesthesia was induced with 125 mg thiopentone (3.6 mg/kg), 100 mcg fentanyl (3 µg/kg) and 20 mg rocuronium (0.6 mg/kg) to facilitate intubation. During intubation an increase in pulse rate was noted and a further bolus of 35 mg thiopentone (1 mg/kg), 50 mcg fentanyl (1.5 µg/kg) and 10 mg rocuronium

was administered. There were no other signs of awakening or light anesthesia. Anesthesia was maintained with 1 MAC isoflurane i.e. in the range of 1.5% end-tidal in oxygen/air. Ventilation was controlled with an end-tidal carbon dioxide maintained between 3.8 and 4.6 mmHg. No cerebral function monitor was available. Cefazolin was the only other drug given for antibacterial prophylaxis.
Surgery lasted 1 h, during which time blood pressure and pulse remained stable. The blood loss was insignificant. At the end of surgery, isoflurane was discontinued and when awake the patient was extubated without any problem.

In the recovery room he told recovery staff that he had been awake during intubation. This was occasion for us to question him about his experience according to the Brice methodology.[4]
Pertinent extracts of his interview are as follows.

> "I felt my mouth was opened with a plate and subsequently a 'pipe' was put in my mouth [……] I panicked and tried to move and warn them that I was awake, but I couldn't move [….] I was not in pain, but could exactly feel what was going on [….] I was thinking that this was a strange situation, on the (preoperative) video they didn't mention that I could be awake [……]"

On direct questioning he also denied experiencing any pain. He also has had no sleep disturbance or other psychological sequelae since. The parents have refused to give consent for a follow-up video interview.

DISCUSSION

Intraoperative awareness is not often reported in children. Classically defined as the explicit recall of events during a procedure performed under general anesthesia, this definition is not applicable to all age groups.[5] Children require explicit memory to have explicit recall and explicit memory develops not until the age of 3 years.[5] Hence an important group of children are excluded by this 'adult' definition.

Awareness in children may also have been ignored previously for a variety of reasons. In the past children were not considered good witnesses and their testimonies were considered to be unreliable. Attitudes have changed and this phenomenon has been increasingly recognized. Nevertheless**,** no more than two large studies performed at different institutions have addressed this problem so far.[2,3]
There are indications that awareness may have a different etiology in children as compared with adults. The use of induction rooms may have played a role in a study by Davidson *et al*.[2,3] Davis in an editorial suggested that these patients may have become 'light' during

transfer from the induction room to the operating room.[6] Interestingly, the incidence of awareness in the study by Davidson *et al.* did not exceed that in the study by Lopez *et al.* in which induction rooms were not used. Lopez *et al.*[3] identified multiple manoeuvres to secure airways as a risk factor for intraoperative awareness in children. The use of muscle relaxants was not considered a risk factor in either of these studies.

An induction room was used for both our patients, but transit time to the operating room was short. In addition, the incision described by the boy in case 1 did not occur immediately after transfer**.** Although one child gave graphic descriptions related to the laryngoscope or endotracheal tube, this procedure was considered an easy intubation.

Two factors that perhaps make our patients atypical are that both received thiopentone and fentanyl at induction and both received rocuronium. Modern ultra-short acting anesthetic agents have also been implicated as a possible risk factor for awareness in children.[2,3] Although relatively short acting, thiopentone has amnesic properties and is often used in the belief that it will prevent recall. Fentanyl has also been used to blunt intubation response both in adults and children. Despite a seemingly adequate dose, these children nonetheless had explicit recall of being intubated or of early events during the surgical procedure. Muscle relaxants, a major risk factor in adults, have not been implicated in children. Both our patients received rocuronium to facilitate intubation. As per our usual practice, the patients were switched to 100% oxygen at this time. It seemed unlikely that anesthesia may have lightened as both intubations were achieved without undue delay relative to what would be considered normal.

Pain does not seem to be a feature of awareness in children.[2,3] Indeed, neither of our patients complained of pain despite their explicit recall of painful events such as skin incision, skin stretched by a retractor, laryngoscopy and endotracheal intubation. It is not clear why this should be so, and this experience may simply indicate a lesser stage of awareness based on the stages of awareness in adults.[7] These stages have not been validated in children.

Awareness may have significant psychological impact on adults.[8] Children seem less affected by this experience in the short term.[2,3] However, the long-term psychological consequences of awareness have not yet been reported. Neither of our patients seemed traumatised by the event despite detailed recall up to 16 months after the event. Neither developed the classic signs of post-traumatic stress disorder, such as nightmares, flashbacks or intrusive thoughts related to the surgery. Signs of depression such as anorexia and weight loss were present but were considered to be consequence of chemotherapy. The parents of the second child refused further follow-up after one year, as they were concerned it would trouble him. Up to then he had not shown any negative impact from his experience.

Monitoring depth of anesthesia using clinical signs of an autonomic response such as hypertension, tachycardia, dilated pupils, sweating and lacrimation is unreliable. Although both our patients' rises in blood pressure and pulse were sufficient to consider increasing the depth of anesthesia, the possibility of awareness was not entertained. Evidence of intraoperative wakefulness was not considered a risk factor in the Lopez study.[3] Cerebral function monitoring has been suggested as a means to prevent or reduce the incidence of awareness. Neither of our patients had cerebral function monitoring as this modality was not yet available at our institution at the time. Studies in adults at high risk for awareness have demonstrated that Bispectral Index (BIS) monitoring of anesthesia reduces the incidence of awareness.[9,10] The value of BIS monitoring in children is controversial[11,12] since a variety of factors can influence BIS.[11] BIS measures cortical function. Different drugs affect the cortex differently and a variety of drugs including muscle relaxants may affect the interpretation of BIS values. Its value as a tool for prevention of awareness in children is still to be determined.

Finally, the incidence of awareness at our institution is unknown. Approximately 7000 children are anesthetized in our hospital per annum. These two events described here have had great impact on our anesthetic practice. Firstly, it has highlighted that awareness is a very real problem in pediatric anesthesia. Secondly, it has prompted a large prospective study in our hospital to determine both the incidence of awareness and the risk factors involved.

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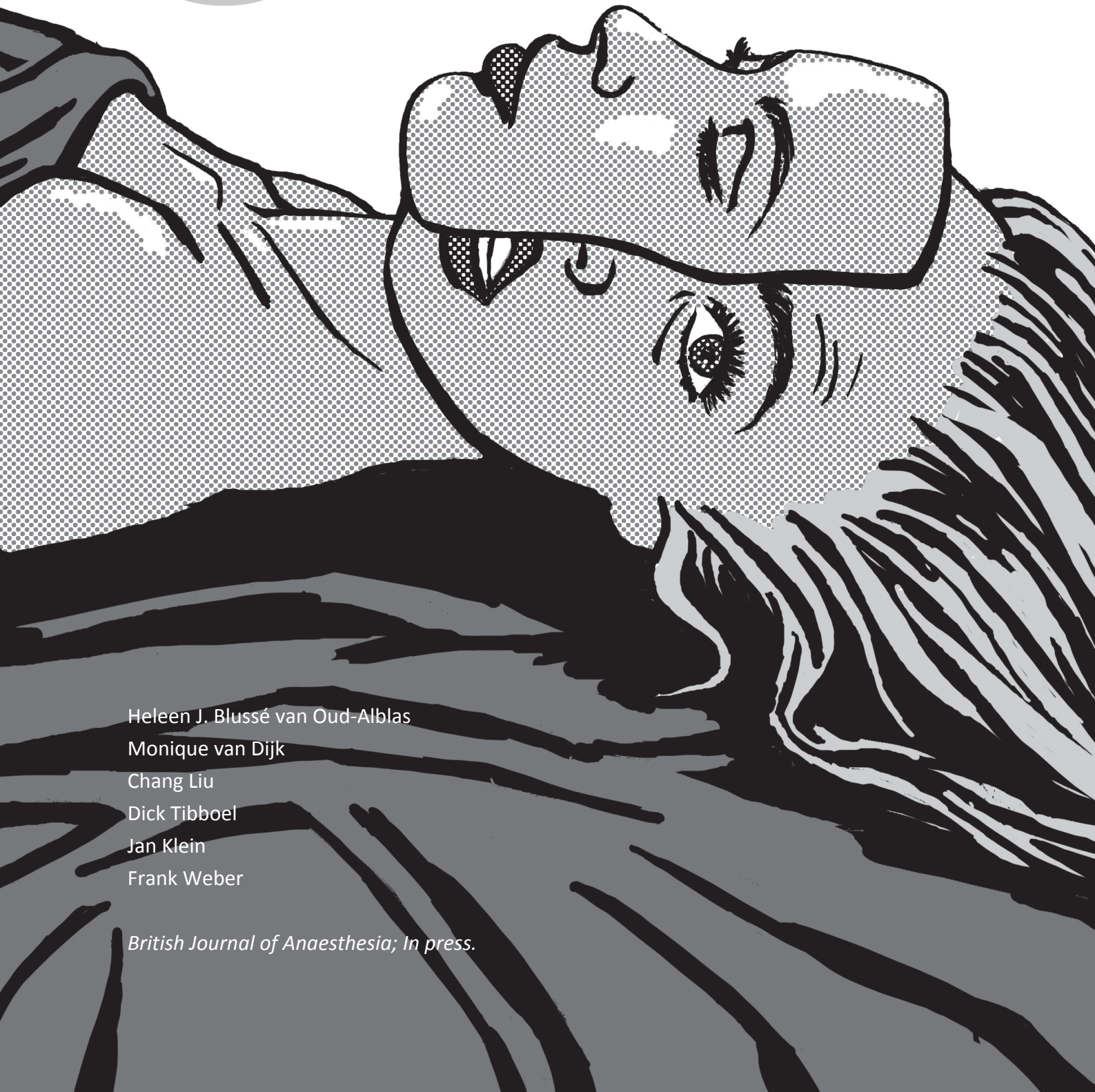
3

Intraoperative awareness during pediatric anesthesia



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ABSTRACT

Background

Previous studies indicate a higher incidence of awareness during anesthesia in children than in adults, i.e. around 1% versus 0.2%. In this prospective cohort study we determined the incidence of intraoperative awareness in children undergoing elective or emergency surgery at a university children's hospital.

Methods

Data from 928 consecutive pediatric patients, aged 5 - 18 yr, were collected prospectively over a 12-month period. Interviews using a structured questionnaire were scheduled at three time points: within 24 hours after the operation, and 3 - 7 and 30 days postoperatively. Reports of suspected awareness were sent to four independent adjudicators. If they all agreed, the case was classified as a true awareness case.

Results

The interviews generated twenty-six cases of suspected awareness. Six cases were judged to be true awareness, equalling a 0.6% incidence (95% confidence interval 0.03% - 1.40%). Auditory and sensory perceptions were the sensations most reported by these 6 children. Pain, anxiety and paralysis were less often mentioned. The children in general did not report awareness as stressful.

Conclusions

The incidence of awareness in this study, in children undergoing general anesthesia, is comparable to recent reports from other countries, and appears to be higher than that reported in adults.

INTRODUCTION

Intraoperative awareness refers to a patient's explicit recall of events during a procedure performed under general anesthesia. Awareness is well described in adults, with an incidence in the order of 0.1 - 0.2% for low-risk surgical procedures.[1,2] Being conscious during surgery is a traumatic event that may result in developing chronic posttraumatic stress disorder.[3] Until recently the incidence and aetiology of awareness in children had not been studied extensively. Two cohort studies in Australia and Switzerland in 864 and 410 children, respectively, both reported an incidence of awareness of around 1%, which is considerably higher than in adults.[4,5] Two recent cases of awareness in our institution[6] triggered a systematic approach to evaluate whether awareness is a problem in pediatric anesthesia. As incidences of awareness may depend on an institution's anesthetic practice and patient population, the aim of this prospective study was to investigate the incidence of intraoperative awareness in children in our hospital and to determine possible causes. Our hypothesis was that the incidence of awareness in our hospital would be similar to those reported in recent studies on awareness in children.

PATIENTS AND METHODS

After approval from the institutional review board (Erasmus University Medical Centre, Rotterdam, the Netherlands), and written informed parental consent, children were enrolled in the study between May 2006 and May 2007. Inclusion criteria were age 5 - 18 years, and receiving general anesthesia for elective or emergency procedures. Exclusion criteria were visual or hearing impairments, not being able to communicate in Dutch, cognitive impairment, expected ventilation postoperatively, out-of-hours emergency procedure, or additional neurophysiologic monitoring of depth of anesthesia. Children were secondarily excluded it they were too sleepy or too nauseous to be interviewed. Inclusion was not until after the operation so as to prevent the influence of knowing one is participating in a study on awareness. Furthermore, preanesthetic patient inclusion could have an impact on anesthesia management, seeing that the anesthesiologist might tend to prevent episodes of intraoperative awareness as best of possible. The anesthesia department nevertheless had been formally informed of the study. The anesthesia technique during the study was entirely at the discretion of the attending anesthesiologist. For all patients, anesthesia was induced in an induction room, after which they were transferred to the operation room.

Children were interviewed by purpose-trained interviewers, using an adapted interview from Brice *et al*. (See Appendix 1).[7] Children in day care were interviewed before discharge, hospitalised children were interviewed within the first 24 hours after operation. Parents were present during the interview, but were asked not to influence the child's response. Follow-up interviews were held by phone 3 to 7 days later and at 30 days after the

operation. On these interviews, we first asked the parents whether they had seen any changes in the child's general behaviour.

Awareness was defined as the ability of patients to recall events happening between the induction of anesthesia and return of consciousness. When awareness was suspected from the first interview, the principal investigator (HB) talked with the child to obtain more details. If the first evidence of potential awareness emerged during the second or third interview, the principal investigator next interviewed the child by phone.

Interview

The questionnaire consisted of hierarchically organized questions. The first questions were open-ended, non-leading questions about events in the induction room and last memories before falling asleep. If a child could not respond to an open question, it was asked a concrete question. For example: "Who was with you before you fell asleep?", "Did the doctor put something on your arm or face to put you to sleep?", and "What did the doctor put on your arm or face?". The next questions were on first memories after surgery. Again, concrete questions were asked if the child could not respond to an open question. For example: "Where did you wake up after surgery?", and "Were you alone or was someone with you when you woke up", and "Who was with you when you woke up?". Finally, direct questions were asked on recall of events during the operation.

If the child replied 'yes' to "Did you feel anything during the operation", or "Did you hear anything during the operation", (s)he was first asked to describe memories of the events in more detail. The principal investigator asked the child the awareness-specific questions originally described by Moerman *et al*. (See Appendix 1).[8] These specific questions were not administered to children who had replied 'no' to the two questions on recall. At the end of the first interview, all children were asked whether they had recalled events during previous operations.

Every child with suspected awareness was offered referral for counselling or psychological support.

For every case of suspected awareness a report was made with the child's age and sex, details of the operation, and memories described in the child's own words. After the end of the study, all reports were sent to four experienced pediatric anesthesiologists in different university hospitals in the Netherlands. These adjudicators independently rated the cases as 'awareness', 'possible awareness', or 'no awareness'. If all four adjudicators rated a case as 'awareness', then it was defined as a 'true awareness' case. If at least one adjudicator classified the case as awareness, the case was defined as a 'possible awareness' case.

Data collection included basic demographic data (age, sex, ASA physical status, type of surgery and admission), details of induction and maintenance of anesthesia, use of sedative premedication, use of tracheal intubation or laryngeal mask; use of neuromuscular blocker, caudal or epidural block, locoregional techniques, and length of anesthesia.

Data are presented in descriptive form. The small number of true awareness cases precluded comparative analysis with the non-awareness group.

RESULTS

One thousand and fifteen children were approached for participation in the study, of whom 36 (3.5%) refused informed consent. Fifty-one children (5%) were too sleepy or nauseous to be interviewed and were secondarily excluded from the study. The remaining 928 children all were interviewed following the operation. Seven hundred thirty-five (80%) children were interviewed at 3 - 7 days and 733 (79%) at 30 days after surgery. The dropout was caused by failure to reach the children and/or parents, or by refusal to be interviewed again. Types of surgical procedures are shown in Table 1.

Table 1 Details of procedures performed under general anesthesia

Type of procedure	Number of children
General surgery and urology	229
Ear, nose and throat surgery	172
Orthopedic surgery	142
Plastic surgery	100
Lumbar puncture or bone marrow aspirate	60
Gastroscopy or colonoscopy	59
Dental surgery	48
Cardiac catherization	30
Ophthalmology	29
Radiology procedures	24
Neurosurgery	10
Bronchoscopy	9
Other	15

Experiences of twenty-six children (11 boys, 15 girls) were identified as 'suspected awareness'. The four adjudicators rated six of these cases as 'true awareness' (Table 2, cases 1 - 6), resulting in an incidence of true awareness of 0.6% (95% confidence interval 0.03% - 1.40%). Eight cases (0.8%) were classified as 'possible awareness' (Table 2, cases 7 - 14). The overall incidence of true and possible awareness combined was 1.5% (95% confidence interval 0.90% - 2.50%). The patients' experiences of true and possible awareness are listed in Table 2. The 12 cases classified as 'no awareness' concerned children with auditory memories of events that could have occurred in the induction room before anesthesia was fully induced, or in the recovery room.

Five of the six true awareness cases were identified at the first interview, one at the second interview. In one true awareness case (Case 2) the child panicked and spontaneously reported his awareness experience to the medical staff. One child with possible awareness (Case 11) first reported awareness to her mother.

Most awareness experiences were tactile or auditory (see Table 3). Two children with true awareness reported mild and severe pain during surgery, respectively. The demographic characteristics of patients with true and possible awareness and details of the anesthesia are listed in Table 4.

Patient characteristics and anesthetic details of the six true awareness cases are compared with those of the non-awareness population in Table 5. Relatively more children in the first group received neuromuscular blockers: 67% versus 44% in the non-awareness group. As indicated in the Methods section, the small number of true awareness cases does not allow for statistical comparisons. Thirty-three per cent of children in the true awareness group reported dreaming during anesthesia versus 9% of the children with no awareness.

Three hundred sixty-seven children from the non-awareness group had previously undergone general anesthesia. Ten of these (2.7%), seven boys and six girls, reported they had experienced awareness at the time. One thirteen-year-old girl reported awareness and a near-death experience five years earlier during two different operations.

As reported by his mother, one boy (Case 3) in the true awareness group had sleeping problems and nightmares for two weeks, which had resolved at the time of the final interview. None of the families requested psychological referral.

Table 2 Experiences of children with true and possible awareness

Patient no.	Experience
1	"Felt they were removing hair from my head." "Felt operating at my ribs." "It was not painful." "Heard the surgeon talking during the operation." The child dreamt of her grandfather, her niece and God.
2	"Heard voices and recognized the voice from the doctor." "Felt pain in my back." "Wanted to warn, but it was not possible to move my feet."
3	"Was in a tube and was tied at my belly." "I enjoyed it in the beginning, but I was later also afraid."
4	The child heard people talking during the catherization. "Adult's talk." Did not feel anything.
5	"Heard doctors talk about holding a rib during the operation." "It hurt a little." On request she gave a pain score of 7. "Felt something in my throat." "Later felt tickling went they closed the skin." The child dreamt of a girlfriend.
6	"Noticed two injections in my back." "Felt something in my throat." "Heard people talk and sounds of a machine." "It was interesting."
7	"Heard rrrrrrrrrrrrrrrrrrrr." The child imitates the sound of the MRI. The child dreamt of Bob the Builder toys.
8	"Felt the tubes going into my ears." "It did not hurt but was a strange feeling." The child dreamt about her doll.
9	"Heard beeping sounds during the operation." "Thought I was dreaming but that was not the case." Did not feel anything and did not try to warn.
10	"Heard beeping during the operation." "Knew I was not dreaming, had no pain and felt it was normal."
11	"The surgeons were busy in my belly."
12	"Heard doctors talking." The child did not know hat they were talking about. "Did not feel anything." The child dreamt of her mom and dad, and the dog.
13	"Heard voices during surgery, did not recognize the voices, did not know what it was about." "Felt slimy stuff in my throat." The child dreamt of a horse and a tiger.
14	"Heard voices during the operation, I did not know what was said, and how long it took."

Patients 1 - 6 were classified as true awareness, with all four adjudicators in agreement. For the other patients, at least one adjudicator, but not all, classified the case as awareness.

Table 3 Details of awareness in true and possible awareness cases

Case No.	Awareness	No. adjudicators classifying case as awareness	Dream as well as awareness	Time of recall			Sensation	Pain	Comment
				first day	1 week	1 month			
1	True	4	Yes	Yes	Yes	Yes	Tactile and auditory	None	
2	True	4	No	Yes	Yes	Yes	Tactile and auditory	Moderate	Told recovery personnel
3	True	4	No	No	Yes	Yes	Tactile	None	
4	True	4	Yes	Yes	Yes	Yes	Auditory	None	
5	True	4	No	Yes	Yes	Yes	Tactile and auditory	Severe	
6	True	4	No	Yes	Yes	Yes	Tactile and auditory	None	
7	Possible	3	Yes	Yes	No	No	Auditory	None	
8	Possible	2	Yes	No	Yes	Yes	Tactile	None	
9	Possible	2	No	Yes	Yes	Yes	Auditory	None	
10	Possible	2	No	Yes	Yes	Yes	Auditory	None	
11	Possible	2	No	Yes	No	No	Tactile	None	Told her mother
12	Possible	1	Yes	No	Yes	Yes	Auditory	None	
13	Possible	1	Yes	Yes	Yes	Yes	Tactile and auditory	None	
14	Possible	1	No	No	No	Yes	Auditory	None	

Table 4 Details of demographics and anesthesia in true and possible awareness cases

Case No.	Awareness	Sex	Age	ASA Status	Procedure	Sedative Premedication	Induction	Maintenance	Neuromuscular blocker	Local anesthesia	Other drugs
1	True	F	16	I	Ear reconstruction	No	Propofol	Isoflurane	Esmeron	No	No
2	True	M	7	II	Bone marrow punction	No	Propofol	Isoflurane	No	No	No
3	True	M	6	I	MRI	No	Propofol	Propofol	No	No	No
4	True	F	8	II	Cardiac catheterisation	No	Propofol	Isoflurane	Esmeron	No	No
5	True	F	9	I	Ear reconstruction	No	Propofol	Isoflurane	Esmeron	No	No
6	True	F	13	I	Excision biopt sacrum	No	Propofol	Isoflurane	Mivacron	No	No
7	Possible	M	6	I	MRI	No	Propofol	Propofol	No	No	No
8	Possible	F	7	I	Adenotomy and ear tubes	No	Propofol	Sevoflurane	Mivacron	No	No
9	Possible	F	13	I	Orthopedic surgery	No	Propofol	Isoflurane	No	Yes	Morphine
10	Possible	F	6	I	Eye surgery	No	Propofol	Sevoflurane	No	No	No
11	Possible	F	6	I	Abdominal surgery	No	Propofol	Isoflurane	No	Yes	No
12	Possible	M	6	I	Gastroscopy	No	Sevoflurane	Sevoflurane	Mivacron	No	No
13	Possible	M	6	I	Abdominal surgery	No	Propofol	Isoflurane	No	Yes	No
14	Possible	F	13	I	Eye surgery	No	Propofol	Isoflurane	Mivacron	No	No

Table 5 Comparative demographics of true awareness and non-awareness groups

Variable	Aware (n = 6)		Non-aware * (n = 922)	
Sex				
Male	2	(33%)	505	(55%)
Female	4	(67%)	417	(45%)
Age (yr)	9.8	(3.9)	11	(3.5)
ASA				
I	4	(67%)	834	(90%)
II	2	(33%)	81	(9%)
III	0		7	(1%)
Elective surgery	6	(100%)	919	(99%)
Emergency surgery	0		3	(1%)
Sedative premedication	0		0	
Intravenous induction	6	(100%)	849	(91%)
propofol	6	(100%)	835	(90%)
pentothal	0		70	(0.8%)
Etomidate	0		7	(0.8%)
Inhaled induction	0		71	(7.7%)
*Neuromuscular blocker **	4	(67%)	401	(44%)
Esmeron	3	(50%)	164	(17.7%)
Nimbex	0		11	(1.2%)
Norcuron	0		3	(0.3%)
Mivacron	1	(17%)	217	(23.4%)
Tracrium	0		7	(0.8%)
Suxamethonium	0		2	(0.2%)
Airway management				
Endotracheal intubation	4	(67%)	455	(49%)
Laryngeal mask airway	2	(33%)	389	(42%)
Facial mask	0		66	(7%)
Maintenance of anesthesia				
Total IV anesthesia	1	(17%)	97	(11%)
Isoflurane	5	(83%)	514	(55.4%)
Sevoflurane	0		280	(30.2%)
Midazolam	0		11	(1.2%)
Analgesia				
Caudal block	0		95	(10.2%)
Epidural	0		15	(1.6%)
Local anesthetic	1		232	(25%)
Morphine	1		171	(18.4%)
Ketamine	0		37	(4%)
Duration of anesthesia	70	(52)	65	(50)
Admission				
Ambulatory ward	3	(50%)	566	(61%)
In-patients	3	(50%)	362	(39%)
Dreaming	2	(33%)	87	(9%)

*Patients were classified as aware when all four adjudicators agreed on this. Data are presented as number (%) or mean (SD). ASA = American Society of Anesthesiologists. * Anesthetic data for 8 patients in the non-aware group are missing. ** Patients only received a single dose neuromuscular blockers.*

DISCUSSION

Demonstrating a 0.6% incidence of intraoperative awareness in children in our hospital, our study confirms recent reported incidences from other countries. [4,5] The incidence in children appears to be higher than that reported in adults (0.1 - 0.2%).[1,2] There are several similarities between our data and recent pediatric studies.[4,5] First, the incidences of awareness are comparable. Second, auditory and tactile sensations were most frequently recalled, more than pain, anxiety and paralysis. Third, in general awareness was not experienced as stressful. The results from our study therefore add to the validity of the previously reported findings. Intraoperative awareness during pediatric anesthesia appears to be a complication that occurs at an estimated incidence of around 1%, irrespective of geographic location, institution or anesthetic practices.

The estimate of the incidence of awareness in our hospital is relatively conservative, based on cases of 'true' awareness only. Including the cases of possible awareness would have raised the incidence to 1.5% (14 out of 928 children). Alternatively, applying the criteria applied by Lopez *et al*. (unanimous coding of 'awareness' or two adjudicators coding 'awareness' and the third 'possible awareness'), would have resulted in a 1.2% incidence (11 out of 928 children).[5]

The pediatric studies which have assessed awareness vary in number of patients, number and type of interviews, and the definition of awareness (see Table 6). Davidson *et al*. administered a structured postoperative interview to 864 children aged 5 - 12 yr within 24 hours, and at 3 days and 30 days after surgery. Cases were classified as awareness when all four adjudicators agreed on this. Thus, seven cases were classified as awareness, giving an incidence of 0.8%.[4] Lopez *et al*. administered two interviews adapted to children's cognitive abilities in 410 patients aged 6 - 16 yr, respectively within 24 hours and at 1 month after surgery. Awareness was defined as the coding of 'awareness' by three adjudicators or when two adjudicators coded them as 'awareness' and the third adjudicator as 'possible awareness'. This resulted in an incidence of awareness of 1.2%.[5] Older studies have reported incidences between 0 and 5%.[9-11] Comparison with these studies is rather futile, however, as anesthesia was by the now abandoned so-called Liverpool technique (nitrous oxide, a neuromuscular blocker, and no volatile or continuous IV anesthetic). Furthermore, samples in these studies were small, and the children were interviewed only once.[10, 11]To facilitate comparisons between previous studies and to permit replication of the results we basically applied the same study design as Davidson *et al*.[4] We deviated from this design in that we administered the follow-ups interviews ourselves, whereas in the study by Davidson *et al*. parents conducted these follow-up interviews.

Table 6 Previous awareness studies using postoperative interviews

Authors, year	Patients	Interview	Awareness incidence	Risk factors	Comments
McKie *et al*. 1973[9]	7 - 14 yr. n = 202	2 hr; 30 d	5%		2nd interview by parents
Hobbs *et al*. 1988[10]	6 - 12 yr n = 120	same day	0%		
O'Sullivan *et al*. 1988[11]	n = 144		0%		
Davidson *et al*. 2005[4]	5 - 12 yr n = 864	1 d; 3 d; 30 d	0.8% according to 4 adjudicators	Induction room	2nd and 3rd interview by parents
Lopez *et al*. 2007[5]	6 - 16 yr. n = 410	36 hr; 30 d	1.2% according to 2 out of 3 adjudicators	Multiple airway manoeuvres	Interview by psychologist Adapted interview to cognitive abilities

Our results indicate that children may not report awareness experiences spontaneously, as only one out of 6 children later identified as having experienced true awareness reported this to the medical staff upon recovery. A postanesthetic visit could therefore be helpful. As children often fail to distinguish between the different perioperative periods, the use of a semi-structured interview such as in our study is recommended (See Appendix 1).

Several possible risk factors for awareness have been suggested. Studies in adults pointed at muscle relaxants as a risk factor.[1] In the present study, four of the six children who experienced true awareness received muscle relaxants, versus 401 of the 922. Noteworthily, these four children did not report paralysis. A larger multi centre study is needed to explore whether neuromuscular blocking agents are indeed a risk factor for awareness in children. All in all, we failed to identify specific risk factors for the occurrence of awareness in our study population.

In an editorial Davis suggested that the use of induction rooms may increase the incidence of awareness in children because administration of anesthetics is discontinued during transfer to the operation room.[12] Interestingly, the incidence reported by Lopez *et al*.,[5] who did not use induction rooms, is higher than that found in our study and that reported by Davidson *et al*.,[4] both using induction rooms. In adult studies, too, the use of induction rooms does not seem to influence the incidence of awareness.[2,13]

Although no formal post hospitalisation behaviour follow-up was applied and the number of awareness cases was small, the children who reported awareness in our study did in general not seem to be traumatized by this experience. Likewise, Davidson *et al*. and Lopez *et al*. both reported that the children in their studies did not seem to be upset about their experiences.[4,5] One prospective follow up study in children found no evidence for posttraumatic stress disorder one year after the event.[13] Nevertheless, some children may be at risk for developing posttraumatic stress disorder, as a case series of adults with post traumatic stress disorder included patients who had experienced awareness as a child when the occurred.[3] Although the children in our study seemed in general not to be distressed, some observations are worth mentioning. One child (Case 7) reported nightmares, which however resolved after 30 days. Another patient (Case 2) was in great distress after his awareness experience, and in all three interviews reported memories. Interestingly, three months later, undergoing another procedure under general anesthesia, he did not remember his previous awareness. Ten of 367 children (2.7%) reported a previous episode of awareness during general anesthesia. Remarkably, none of these children was afraid to undergo anesthesia again. A planned follow-up study in our institution will explore the long-term consequences of awareness.

The diagnosis of awareness relies on the patient's postoperative self-report, which especially in children may be subjective and unreliable. The present guidelines on detecting and verifying awareness do not always lead to identification of true awareness. Two studies used the isolated forearm technique to detect wakefulness during anesthesia in children.[14,15] Byers *et al*. found that eight of 41 children aged 5 - 16 years responded to a command during surgery using the isolated forearm technique without explicit recall.[15] Recently, Andrade *et al.* replicated this study in 184 children aged 5 - 18 yr. Two children made verified responses to command on the isolated forearm technique, resulting in an incidence of intraoperative wakefulness of 1.1%. Still, explicit memory formation was not demonstrated.[14] These findings seem to indicate that there is no association between intraoperative wakefulness and postoperative awareness in children.

The children in our study were mostly ASA I or II patients undergoing elective surgery. As previous research in adults has demonstrated an increased risk of awareness in severely ill patients (ASA physical status III - V) undergoing major surgery,[2] this may have led to underestimation of the incidence. Furthermore, we may have missed potential cases of awareness in patients who could not complete the three interviews and the 36 children (3.5%) who refused to participate in the study. Theoretically, any or all of these children could have had awareness, so there may be a detection bias.

In summary, 6 out of 928 children (0.6%) undergoing general anesthesia in our hospital had postoperative recall of intraoperative events. A relatively high proportion of these six children received neuromuscular blocking agents. Children with awareness did not seem to be traumatized by the experience on the short term. A two-year follow-up study will explore possible effects on the longer term. The large number of pediatric patients given general anesthesia may generate many cases of awareness in the years to come. There is every reason to direct efforts at identifying risk factors for awareness in children as well as its possible long-term consequences.

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APPENDIX

Structured Awareness interview

Interview on Day 1

1. Were you upset, worried, or frightened about your operation?
2. How upset, worried or frightened were you?
3. What was the last thing you remember before the operation?
4. How did the doctor make you go to sleep?
5. What is the first thing you remember after your operation?
6. After you fell asleep, do you remember anything that happened during the operation?
7. Did you have any dreams during the operation?
8. Did you feel anything during the operation?
9. Did you hear anything during the operation?
10. Did you have pain after the operation?
11. Did you have an operation before?
12. Did you hear or feel anything during previous operations?

Interview on Day 3 - 7 and Day 30

1. What was the last thing you remember before the operation?
2. How did the doctor make you go to sleep?
3. What is the next thing you remember after your operation?
4. Did you have any dreams during the operation?
5. Did you feel anything during the operation?
6. Did you hear anything during the operation?

Additional questions for suspected awareness cases

1. Did you notice sounds?
2. Did you notice tactile sensations?
3. Did you have visual perceptions?
4. Did you feel pain?
5. Were you paralyzed?
6. Did you feel something in your mouth or throat?
7. What went through your mind?
8. Did you believe you were dreaming?
9. How long did it last?
10. Did you try to alert anyone?
11. Did you inform your parents or the doctor?

4

Comparison of composite auditory evoked potential index and bispectral index during propofol - remifentanil anesthesia for adolescent scoliosis surgery with intraoperative wake-up test

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ABSTRACT

Background

The EEG-derived Bispectral Index (BIS), and the composite A-line ARX index (cAAI), derived from the EEG and auditory evoked potentials, have been promoted as anesthesia depth monitors. The performance of both indices in distinguishing different hypnotic states, as evaluated by the University of Michigan Sedation Scale, was compared in children and adolescents during propofol-remifentanil anesthesia for scoliosis surgery with an intraoperative wake-up test. Furthermore, postoperative explicit recall was evaluated.

Methods

20 patients (aged 10 - 20 years) were enrolled. Prediction probabilities were calculated for induction, wake-up test, and emergence. Furthermore, BIS and cAAI were compared at the start of the wake-up test, at purposeful movement to command, and after the patient was reanesthetized. During the wake-up test patients were instructed to remember a color. Patients were interviewed for explicit recall.

Results

Prediction probabilities of BIS and cAAI for induction were 0.82 and 0.63 ($p < 0.001$); for the wake-up test 0.78 and 0.79 ($p < 0.001$), and 0.74 and 0.78 for emergence ($p < 0.001$). During the wake-up test a significant increase in mean BIS and cAAI ($p < 0.05$) was demonstrated at purposeful movement, followed by a significant decline after reintroduction of anesthesia.

Conclusions

During induction BIS performed better than cAAI. Although cAAI was statistically a better discriminator for the level of consciousness during the wake-up test and emergence, these differences to not appear to be clinically meaningful. Both indices increased during the wake-up test, indicating a higher level of consciousness. No explicit recall was demonstrated.

INTRODUCTION

Both the Bispectral Index (BIS), derived from the EEG, and the composite A-Line ARX Index (cAAI), derived from auditory evoked potentials and the EEG, continue to be evaluated as tools to measure depth of anesthesia and to detect intraoperative awareness. Recent studies in adults comparing the usefulness of BIS and cAAI demonstrated that both monitors were comparable indicators of depth of hypnosis.[1,2] Whereas BIS has been studied extensively in pediatric patients, there are only 2 published studies investigating the cAAI in children.[3,4] Weber *et al*. demonstrated in an outcome study in children undergoing strabismus repair that cAAI guided anesthesia resulted in lower propofol consumption and shorter recovery times.[4] Furthermore, a study from Ironfield *et al*. suggested that in children under sevoflurane-based anesthesia, the cAAI is a poor predictor of depth of anesthesia compared to BIS.[3] Until now there are to our best knowledge no published pediatric data comparing both indices under the condition of total intravenous anesthesia with short acting drugs such as propofol and remifentanil. Spinal cord fusion for idiopathic scoliosis, usually performed in adolescents, appears to be an almost perfect setting for comparing the performance of depth of anesthesia monitors. Besides general anesthesia, a period of planned intraoperative wakefulness, the so called "wake-up test", is a standard feature of this surgical procedure.

The main purpose of this study was to compare the performance of BIS and cAAI in children and adolescents with respect to their ability to distinguish between different hypnotic states, as evaluated by the responsiveness scores to the University of Michigan Sedation Scale (UMSS).[5] This was specifically performed during the intraoperative wake-up test, which can be regarded as an intentional episode of intraoperative awareness. We hypothesized that both monitors performed equally, which was tested by calculating prediction probabilities as the primary outcome parameter. Secondly, the incidence of explicit recall was evaluated.

METHODS

Institutional Review Board approval and written informed consent of parents and patients was obtained. Twenty patients, ASA status I or II, undergoing correction of idiopathic scoliosis were enrolled in the study. Exclusion criteria were hypacusis or deafness, any neurological disease, medication affecting the central nervous system, or any contraindication to the protocol.

Patients were instructed during the preoperative visit about the wake-up test and told that during the wake-up test the anesthesiologist would first ask them to squeeze his hand with their fingers, then to wiggle their toes, and finally to remember a given color.

The principal investigator supervised recording of all data and was blinded to BIS and cAAI values. Values were recorded with a BIS monitor A-2000, software version 3.2; (Aspect Medical Systems, Newton, M.A.) and an AEP monitor/2 software version 1.6 (Danmeter A/S, Odense, Denmark). A BIS pediatric four sensor probe (BIS Pediatric Sensor, Aspect Medical Systems International BV, De Meern, The Netherlands) was placed on the patient's forehead according to the manufacturer's instructions. For the AEP monitor/2, headphones for auditory stimuli and three sensors (Danmeter A/S, Odense, Denmark) were positioned at the mid-forehead (+), right forehead (reference), and right mastoid (-). BIS and cAAI measurements started before induction to obtain pre-anesthetic awake values and continued until return of consciousness (ROC) after finishing anesthesia, defined as eye opening of the patient.

Patients received a standardized anesthetic regimen without premedication. Anesthesia was induced with remifentanil 1 μg/kg/min, infused over one minute. Thereafter propofol (4 mg/kg), and a single dose of rocuronium (0.6 mg/kg) were administered to facilitate endotracheal intubation. Patients were mechanically ventilated to normocapnia (end-tidal CO_2 35 - 40 mmHg). An arterial line and a central venous catheter were inserted for invasive continuous measurement of arterial blood pressure and central venous pressure and a urinary catheter was placed. Thereafter, patients were moved to prone position.

Anesthesia was maintained with propofol by continuous infusion (2 - 10 mg/kg/h) and remifentanil (0.2 - 1 μg/kg/min) at the discretion of the anesthesiologist. During the procedure no additional muscle relaxants were given. Intraoperatively intrathecal morphine (5 μg/kg) was administered for both intra- and postoperative pain treatment by the orthopedic surgeon.

For the wake-up test, propofol and remifentanil infusions were stopped. Patients were asked repeatedly to move their hands until they responded, and thereafter to wiggle their feet. Thereafter, patients were verbally instructed to remember a color. After finishing the wake-up test, patients were reanesthetized and maintenance of anesthesia was continued as previously described.

Thirty minutes before the estimated end of surgery, 100 μg/kg morphine was administered intravenously. At the end of surgery, propofol and remifentanil infusions were discontinued, and patients were extubated when sufficient spontaneous breathing had returned and they responded to verbal commands. Thereafter, patients were transferred to the Pediatric Surgical Intensive Care.

The attending anesthesiologist was blinded to BIS and cAAI values throughout the study and estimated the level of consciousness using the UMSS (table 1). UMSS level assessment started before induction until administration of rocuronium during induction, and was furthermore performed during the wake-up test and emergence every 2 minutes.

Table 1 The University of Michigan Sedation Scale for Children (UMSS)

Score	Responsiveness
0	Awake and alert
1	Minimally sedated; tired/sleepy, appropriate response to verbal conversation or sound
2	Moderately sedated; somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated; deep sleep, arousable only with significant physical stimulation
4	Unarousable

The following events were specifically registered for further closed examination:

1. loss of consciousness (case milestone LOC),
2. start of the intraoperative wake-up test at stopping propofol and remifentanil (case milestone START),
3. purposeful patient movement to a verbal command during the wake-up test (case milestone MOVE),
4. patient re-anesthetized after the wake-up test (case milestone REANES),
5. return of consciousness during emergence (case milestone ROC).

Furthermore possible episodes of patient movement in response to intubation, or surgical stimuli, indicating a low level of anesthesia were specifically noted and linked to their corresponding BIS and cAAI values.

In addition to continuous BIS and cAAI monitoring, ECG, heart rate, noninvasive and invasive arterial blood pressure, central venous pressure, end tidal CO_2, oxygen saturation via pulse oximetry, and rectal temperature were continuously monitored, collected at 5-sec. intervals using Rugloop (Demed, Temse, Belgium), and synchronized with Labgrab software (Demed).

Patients were interviewed by the principal investigator using a standard questionnaire based on the Brice-interview[6] on three different occasions: on the first postoperative day, one week, and one month postoperatively. They were asked whether they remembered intraoperative events, the wake-up test, had any dreams and specifically whether they remembered pain or the color specified at the time of the wake-up test.

Statistics

All continuous data were tested for normality using the Kolgomorov-Smirnov method. For data sets that followed a normal distribution, parametric tests were used. For all other data sets the appropriate non-parametric tests were applied. Data were analyzed using SPSS V12.0.1 (SPSS Inc., Chicago, IL) and MedCalc® V9.3.1 (MedCalc Software, Mariakerke, Belgium). A *p* value smaller than 0.05 was considered statistically significant.

The ability of different indicators to describe the anesthetic drug effect was evaluated using prediction probability (P_K), which compares the performance of indicators having different units of measurements or different data types (i.e. continuous versus ordinal or categorical data). P_K was calculated using a custom spreadsheet macro P_K MACRO (written in Microsoft Excel; Microsoft Corp., Redmond), described and provided by Smith *et al*.[7] A P_K value of 1 means that the values of the predicting variable (e.g. BIS or cAAI) always correctly predicts the variable to be predicted (e.g. the UMSS). Alternatively, a P_K value of 0.5 means that the prediction is not better than chance alone; a P_K value below 0.5 indicates an inverse relationship. P_K values of paired measurements were calculated for all patients.

To assess the relation between BIS and cAAI versus UMSS, P_K data were analyzed for 3 study periods: (A) induction: the period from just before induction of anesthesia until administration of rocuronium; (B) the wake-up test: from the start of the wake-up test to reestablishment of anesthesia after finishing the wake-up test, and (C) emergence: from termination of surgery to final ROC. A Mann-Whitney test was used to evaluate whether P_K for BIS differed from cAAI. Repeated measure ANOVA was used to compare BIS, cAAI, mean arterial blood pressure and heart rate at case milestones START, MOVE and REANES.

We further investigated the performance of BIS and cAAI for discrimination between consciousness versus unconsciousness by computing values of cumulative occurrence.

According to recent recommendations by the manufacturer of the AEP monitor/2, and a study by Vereecke *et al.*, we decided to analyze our cAAI data on a scale of 0 - 60 (all values above 60 are set to 60).[2]

RESULTS

Twenty patients were included in the study (male: female ratio = 3:17). The mean age was 15.6 ± 2.4 yr, and mean weight was 58.5 ± 12.8 kg.

The ability of BIS and cAAI to predict the UMSS score, as presented by the P_K values, is shown in table 2. 325 paired data were available for analysis at the different clinical states; cAAI was responsible for missing 26 data points, whereas 87 BIS points were missing. During induction P_k values for BIS were significantly higher than for cAAI ($p < 0.001$), whereas during the wake-up test and emergence P_k values for cAAI were higher than for BIS. Awake BIS values varied between 32 and 98 (median 95), awake cAAI values were between 14 and 60 (median 49). With increasing sedation (increase in UMSS score from level 0 to level 4), median BIS decreased significantly from 94 to 50 ($p < 0.001$), and median cAAI decreased

significantly from 50 to 15 ($p < 0.001$) (Figure 1). The transition from wakefulness to loss of consciousness occurred at a median BIS value of 46, and at a median value of 38 for cAAI.

Table 2 Prediction Probabilities for the University of Michigan Sedation Scale

	UMSS		
	BIS	**cAAI**	
Induction	0.83 ± 0.09	0.64 ± 0.1	$p < 0.001$
Wake-up test	0.78 ± 0.06	0.79 ± 0.05	$p < 0.001$
Emergence	0.74 ± 0.03	0.78 ± 0.03	$p < 0.001$

Data are presented as mean +/- SE. p-values (BIS vs. cAAI, Mann-Whitney-U-test); BIS = Bispectral Index; cAAI = composite A-line ARX Index; UMSS = University of Michigan Sedation Scale

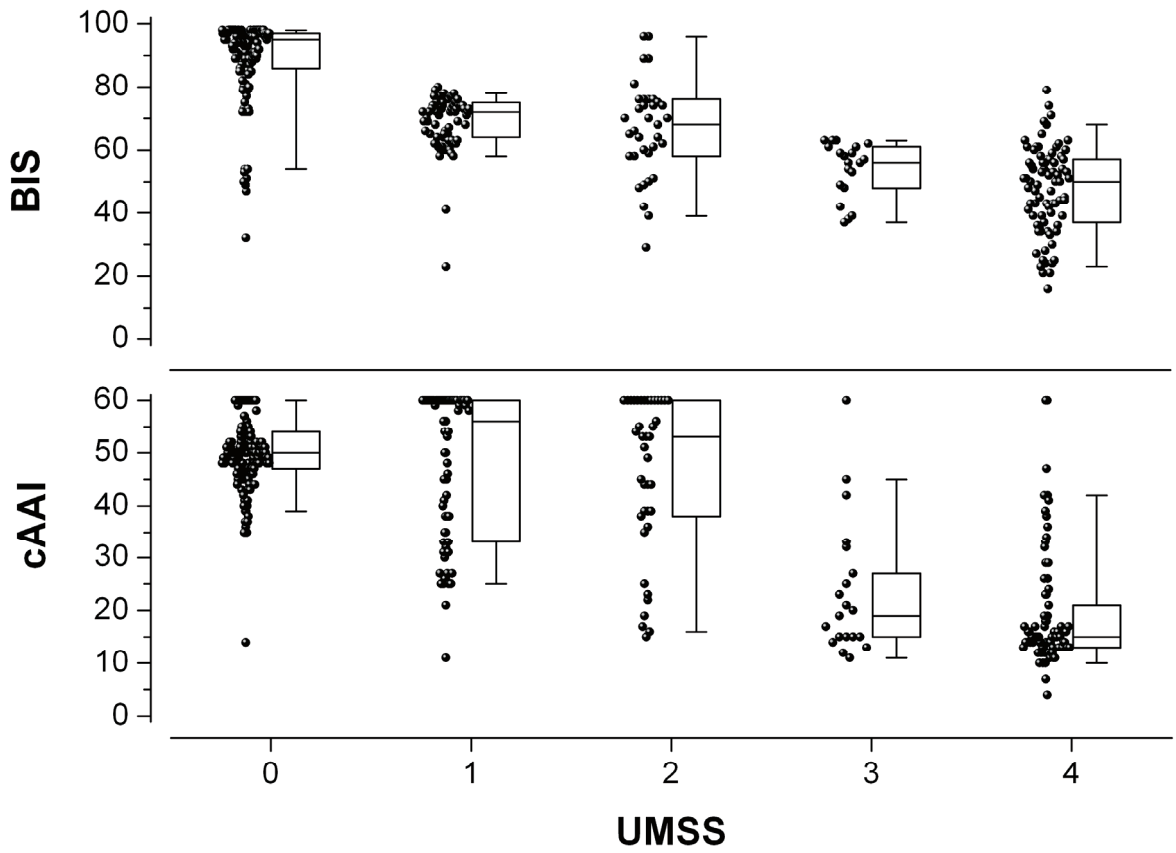

Figure 1 *Boxplot graphics (median and 25th and 75 percentiles [box top and bottom] and 5th and 95th percentiles [Whiskers]) and real data for (A) Bispectral Index (BIS), and (B) composite A-line ARX Index (cAAI), at different levels of the University of Michigan Sedation Scale (UMSS).*

Anesthetic data are shown in Table 3, and BIS, cAAI, MAP and HR during the wake-up test are displayed in Table 4. The cumulative occurrence curves for consciousness and unconsciousness are shown in figure 2 A for BIS and figure 2 B for cAAI.

During the three postoperative interviews no explicit recall or intraoperative pain was reported. Even after having been given associations of the color, no patient could remember what color had been presented during the wake-up test. Although there was no attempt to test for implicit recall in this study, one patient who was instructed to remember the color yellow, dreamed of yellow bananas, smileys and toys. Patients were unable to recall any other intraoperative events before or after the wake-up test.

Table 3 Anesthetic data and recall following the wake-up test

Anesthesia duration before wake-up test (min)	325 ± 49
Duration of operation (min)	417 ± 58
Duration of propofol infusion (min)	389 ± 53
Duration of anesthesia until ROC (min)	417 ± 58
Onset time of wake-up test (min)	23 ± 10
Duration of consciousness during wake-up test (sec)	45 ± 38
Recall of intraoperative events before and after wake-up test (n)	0
Recall of wake-up test (n)	0
Pain during wake-up test (n)	0

Data are presented as mean ± SD. ROC = Return of consciousness

Table 4 Changes in mean Bispectral Index, composite A-line ARX Index, Mean Arterial Blood Pressure, and Heart Rate during the Wake-Up Test

	Before wake-up test (START)	**Wake-up (MOVE)**	**After wake-up test (REANES)**
BIS	41 ± 11	70 ± 7 *	40 ± 18 ***
cAAI	14 ± 2	48 ± 1 *	36 ± 13 **, ***
MAP	62 ± 8	89 ± 15 *	73 ± 18 **, ***
HR	73 ± 10	89 ± 18 *	87 ± 16 **

Data are presented as mean ± SD.
**p < 0.05 MOVE versus START, ** p < 0.05 REANES versus START, *** p < 0.05 REANES versus MOVE. BIS = Bispectral Index, cAAI = composite A-line ARX Index, MAP = Mean Arterial Blood Pressure, and HR = Heart Rate*

DISCUSSION

This study was conducted to compare the performance of BIS and cAAI in distinguishing different hypnotic states and to evaluate the incidence of explicit recall in children and adolescents as a consequence of the mandatory intraoperative wake-up test during scoliosis surgery.

During induction we found BIS to perform better than cAAI, as indicated by P_k values. During the wake-up test and emergence P_k values for cAAI were statistically higher. In terms of clinical relevance however, these differences do not appear to be meaningful. Both monitors were not found to be ideal, as considerable overlap in both BIS and cAAI values was present when compared with each level of the UMSS. Furthermore, the cumulative occurrence data in Figure 2 A-B showed a remarkable overlap between "conscious" and "not conscious" data. That means, BIS and cAAI data within the commonly accepted target ranges for general anesthesia do not always indicate an unconscious patient. This also applies for the conscious patient, who may present with index values usually associated with deep levels of anesthesia. Our results correspond with findings previously reported in adults, indicating some overlap of both monitors during propofol anesthesia.[8]

Ironfield *et al.* compared BIS and cAAI during sevoflurane anesthesia in children aged 0 - 12 years undergoing cardiac catherization.[3] In their study BIS appeared to be a better predictor of sevoflurane steady-state concentrations compared to cAAI. In the 2 - 12 years group, the P_K for BIS (0.89) was significantly higher than the P_K for cAAI (0.53). When comparing our results with the data published by Ironfield, P_K for BIS in both studies were comparable. However, P_k values for cAAI in our study are higher compared to the results of Ironfield.

In our study patients were capable of cognitive action during the wake-up test with mean BIS values of 70 ± 7 and mean cAAI values of 48 ± 15. Thus our patients were fully awake with low mean BIS values, whereas mean cAAI values were within a typical range of wakefulness. Interestingly, no patient recalled the wake-up test or any other intraoperative event. A possible reason that explicit recall was absent in our study may be that the use of propofol has led to memory impairment, as previously described in adults.[9,10] In contrast to our results, Nordstrom and Sandin showed that 35% of their adult study patients undergoing incontinence surgery under propofol anesthesia with an intraoperative wake-up test recalled awareness.[11] Unfortunately no data on depth of anesthesia are being provided. Therefore, we found it inappropriate to compare both studies. Glass *et al.*[12] reported absence of recall at BIS values of 70 ± 18 whereas Liu *et al.*[13] demonstrated that only 8% of shown pictures were recalled at BIS levels below 80. Our findings are consistent with the aforementioned studies with respect to the relationship between the BIS and the rate of explicit recall.

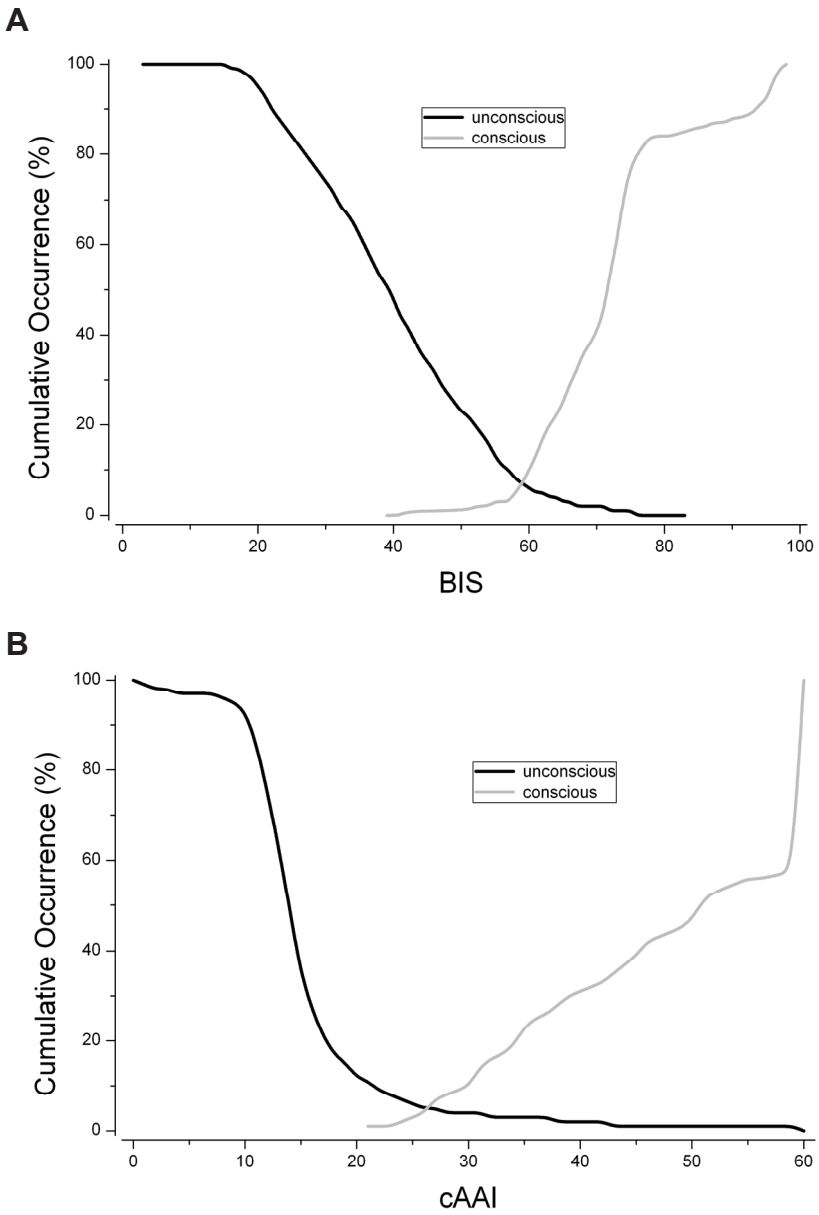

Figure 2 *Cumulative occurrence for consciousness and unconsciousness as a function of the University of Michigan Sedation Scale for the (A) Bispectral Index (BIS), and the (B) composite A-line ARX Index (cAAI)*

Another possible reason is that our patients underwent a rapid recovery during the wake-up test, rather than a long period of arousal. In addition, patients were in a deep anesthesia before and after the wake-up test. Finally, it is well known that negative stimuli are commonly better remembered than pleasant ones. (Intraoperative) pain, for example, secondary to hormonal responses affecting the amygdala, enhances the ability to remember events.[14] Nociceptive stimuli during the procedure were depressed by intrathecal morphine, which made patients wake up comfortably without pain. As no patient reported any intraoperative pain, this may, in parts, explain the absence of recall in our study.

Despite the absence of explicit recall in our study, the occurrence of unconscious implicit memory cannot be entirely precluded. Although there was no attempt to test for implicit recall in this study, one patient who was instructed to remember the color yellow, dreamed of yellow bananas, smiley's and toys. BIS, cAAI and hemodynamic data of this patient did not differ from other patients. The importance and possible psychological consequences of this kind of implicit memory process during general anesthesia are, however, not known.

The absence of recall in our study contradicts to recent studies by McCann *et al*.[15] and Ting *et al.*,[16] who both evaluated BIS and explicit recall for an intraoperative wake-up test. McCann *et al.* demonstrated explicit auditory recall in 18% of their patients. Ting *et al.* showed that desflurane anesthesia was not associated with recall, whereas anesthesia with fentanyl and nitrous oxide, led to 25% rate of explicit auditory recall of the wake-up test. Interestingly, BIS levels at which patients responded during the wake-up test in our study (70 ± 7) were significantly lower than the corresponding mean BIS levels reported by McCann *et al.* (BIS > 88) and Ting *et al.* (BIS > 90). This may possibly be a consequence of the different anesthesia regimen in the studies.

The performance of wake-up tests requires an anesthetic regimen that provides fast recovery and fast return of cognition to allow immediate neurological evaluation. Therefore, total intravenous anesthesia (TIVA) with propofol and remifentanil is chosen as the standard anesthetic regimen in our institution to perform intraoperative wake-up tests during scoliosis surgery. It might be criticized that we used conventional infusion pump technology for administration of both propofol and remifentanil, though target controlled infusion systems are more and more becoming a standard. As surgical procedures such as scoliosis repair are commonly associated with significant blood loss and substantial changes in circulating volume, TCI might not be a meaningful choice.

The wake-up onset time is in our study is much longer than 9.4 ± 2.4 minutes reported by Grottke and colleagues in their propofol-remifentanil maintenance groups.[17] The differences between our findings and these observations may be due to intrathecal administration of morphine.

A shortcoming of our study is the lack of the ideal tool to assess our patients' hypnotic state. We selected the UMSS because it provides good correlation with clinical reflection of the hypnotic component of anesthesia and has been validated in children.[5] However, subjective clinical scoring systems such as the UMSS are only indicative for a specific moment, and by their nature introduce potential error via individual implementation and interpretation. Furthermore, depending on the intensity of potentially distressing painful physical stimulation they are not necessarily only a measure of cortical activity, but also of spinal reflexes. Therefore we cannot expect total agreement between the UMSS and BIS and cAAI scores.

In conclusion, when comparing BIS and cAAI with the level of consciousness as defined by the UMSS, we found BIS to perform significantly better than cAAI during induction, whereas during the wake-up test and emergence both indices performed equally. BIS and cAAI values increased significantly during the wake-up test, indicating a higher level of consciousness, however, no explicit recall was demonstrated. Care has to be taken not to extrapolate our results, which are probably specific for propofol - remifentanil anesthesia in adolescents, to other anesthesia regimens or younger children.

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5

Comparison of bispectral index and composite auditory evoked potential index for monitoring depth of hypnosis in children

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ABSTRACT

Background

In pediatric patients, the Bispectral Index (BIS), derived from the electroencephalogram, and the composite A-Line autoregressive index (cAAI), derived from auditory evoked potentials and the electroencephalogram, have been used as measurements of depth of hypnosis during anesthesia. The performance and reliability of BIS and cAAI in distinguishing different hypnotic states in children, as evaluated with the University of Michigan Sedation Scale, were compared.

Methods

Thirty-nine children (aged 2 - 16 yr) scheduled to undergo elective inguinal hernia surgery were studied. For all patients, standardized anesthesia was used. Prediction probabilities of BIS and cAAI *versus* the University of Michigan Sedation Scale and sensitivity/specificity were calculated.

Results

Prediction probabilities for BIS and cAAI during induction were 0.84 for both and during emergence were 0.75 and 0.74, respectively. At loss of consciousness, the median BIS remained unaltered (94 to 90; not significant), whereas cAAI values decreased (60 to 43; $p < 0.001$). During emergence, median BIS and cAAI increased from 51 to 74 ($p < 0.003$) and from 46 to 58 ($p < 0.001$), respectively. With respect to indicate consciousness or unconsciousness, 100% sensitivity was reached at cutoff values of 17 for BIS and 12 for cAAI. One hundred percent specificity was associated with a BIS of 71 and a cAAI of 60. To ascertain consciousness, BIS values greater than 78 and cAAI values above 52 were required.

Conclusions

BIS and cAAI were comparable indicators of depth of hypnosis in children. Both indices, however, showed considerable overlap for different clinical conditions.

INTRODUCTION

Electroencephalography-derived variables, such as the Bispectral Index (BIS; Aspect Medical Systems Inc., Newton, MA) and midlatency auditory evoked potentials (MLAEPs), have been proposed as measures of the hypnotic state during anesthesia. The BIS is an empirically derived multifactorial electroencephalographic parameter that relies on the correlation of the phases between frequency components of the electroencephalogram.[1] In adult patients, several studies have demonstrated that the use of BIS during anesthesia can decrease drug requirements,[2-5] decrease the incidence of intraoperative awareness,[6,7] and lead to a faster recovery.[3,5] Despite the much smaller number of pediatric outcome studies using BIS, there is evidence that these positive effects of BIS-guided anesthesia can also be found in children.[8-10]

Midlatency auditory evoked potentials, extracted from the electroencephalogram 10 - 100 ms after an auditory signal, represent the earliest cortical response to an acoustic stimulus. Amplitudes and latencies of the MLAEPs are influenced by anesthetics and surgical stimuli and are therefore believed to be useful in measuring the level of hypnosis during anesthesia.[11] The AEP Monitor/2 (Danmeter A/S, Odense, Denmark), a recently commercialized system for monitoring hypnosis levels of anesthesia, extracts MLAEPs from the electroencephalographic signal using an autoregressive model with an exogenous input adaptive method (ARX).[12] A monitoring variable indicating the patient's hypnotic state, the composite A-Line ARX Index (cAAI), is then calculated from the MLAEP and the electroencephalogram.[13] Specifically, the cAAI is preferably derived from the MLAEP, but in case of low MLAEP signal quality, it is entirely based on the spontaneous electroencephalogram. The majority of previous studies in adults investigated the A-Line Monitor (Danmeter A/S), which is a former version of the AEP Monitor/2 and is entirely based on MLAEP information. These studies suggest that the AAI might be helpful in distinguishing between the awake and unconscious state and in the detection of intraoperative awareness with recall.[14-16] In addition, the use of the A-Line monitor has been shown to decrease anesthetic delivery and may lead to faster postoperative recovery in adult patients.[3,5,17]

More recent studies in adults comparing the usefulness of BIS and cAAI demonstrated that both monitors were comparable indicators of depth of hypnosis.[13,18] Whereas BIS has been studied extensively in pediatric patients, there are only two published studies investigating the cAAI in children.[19,20] Weber *et al.*[20] demonstrated in an outcome study in children undergoing strabismus repair that cAAI-guided anesthesia resulted in lower propofol consumption and shorter recovery times. Furthermore, a study from Ironfield *et al.*[19] suggested that in children during sevoflurane-based anesthesia, the cAAI is a poor predictor of depth of anesthesia compared with the BIS. Whether this applies to other volatile anesthetics remains unknown. The main purpose of the current study was to compare the

performance of the BIS and the cAAI with respect to their ability to distinguish between different hypnotic states, as evaluated by the responsiveness scores to the University of Michigan Sedation Scale (UMSS).[21] We hypothesized that prediction probabilities, which were calculated as the primary outcome parameter, were equal for both monitors.[22,23] Second, we investigated sensitivity and specificity characteristics for both the BIS and the cAAI in children.

MATERIALS AND METHODS

Study population

After approval from the institutional ethics committee (Erasmus Medical Center, Rotterdam, The Netherlands) and written informed parental consent, 47 children scheduled to undergo elective inguinal hernia repair were enrolled in the study. Children were considered eligible for enrollment if they had an American Society of Anesthesiologists physical status classification of I or II, were older than 2 yr, and were scheduled to undergo elective inguinal hernia repair. Children were excluded from the study if they had hypacusis or deafness, significant cardiovascular, respiratory, or neurologic disease, or if they were taking medication affecting the central nervous system.

Study Protocol

All patients received a standardized anesthetic regimen. No premedication was administered before induction. In accordance with hospital standards, EMLA cream (Eutectic Mixture of Local Anesthetics; AstraZeneca BV, Zoetermeer, The Netherlands) was applied locally to the skin at least 30 min before induction of general anesthesia to facilitate placement of an intravenous catheter. In the induction room, a pulse oximetry sensor was applied and intravenous access was secured. Anesthesia was induced with fentanyl (2 μg/kg) and a bolus of propofol (3 - 5 mg/kg). After loss of consciousness (LOC), defined as loss of eyelash reflex, manual ventilation via a facemask was established, and a laryngeal mask airway (LMA Unique™; The Laryngeal Mask Company Limited, Oxon, United Kingdom) was inserted. Patients ventilated spontaneously. Anesthesia was maintained with isoflurane with 30% oxygen in air. After induction, patients received a caudal block using 0.2% plain ropivacaine, and rectal acetaminophen and diclofenac were administered for both intraoperative and postoperative pain treatment. Thereafter, patients were transferred to the operating room. Anesthesia was maintained with isoflurane, adjusted to the age-corrected 1 minimal alveolar concentration.[24] In addition, 1 μg/kg fentanyl was administered as needed. In cases of hypoventilation, controlled ventilation was begun to maintain an end-tidal carbon dioxide tension of 35 - 45 mmHg. During maintenance of anesthesia, all patients were assessed for signs of inadequate anesthesia, defined as sudden increases in either systolic blood pressure by more than 15%, or heart rate by more than 15% in the absence of hypovolemia, or other

autonomic signs such as sweating or flushing, and somatic responses such as movement or swallowing. At the end of surgery, isoflurane was discontinued, and the laryngeal mask was removed. Patients awoke in the recovery room and were discharged when they were pain free and fully awake.

In addition to BIS and cAAI, electrocardiogram, heart rate, noninvasive blood pressure, end-tidal carbon dioxide, oxygen saturation *via* pulse oximetry, end-tidal concentration of isoflurane, and rectal temperature were monitored continuously during anesthesia. All data were collected in 5-s intervals (Rugloop; Demed, Temse, Belgium) and synchronized (Labgrab; Demed) on a laptop computer.

Measurements

The attending anesthesiologist, blinded to BIS and cAAI monitoring, assessed the patient's level of consciousness using the UMSS (table 1). The study period started just before induction of anesthesia and was continued until the return of consciousness (ROC). ROC was defined as eye opening, purposeful movement, or age-appropriate phonation. The following specific case milestones for UMSS assessment were defined *a priori*: awake, LMA insertion, at caudal block placement, and at surgical incision. During surgery, the UMSS was assessed every 5 min. During the emergence phase, the UMSS was assessed every 2 min. During emergence from inhalation anesthesia, the transition from unconscious to conscious is frequently accompanied by excitation phenomena, and additional external stimuli could significantly increase the risk of developing laryngospasm. Therefore, if patients were in the excitation phase, UMSS assessment was not performed. In addition, the following events were specially registered:

1. loss of consciousness (case milestone LOC),
2. return of consciousness (case milestone ROC), and
3. patient movement in response to LMA, caudal block placement, or surgical stimuli, indicating a low level of anesthesia.

Table 1 The University of Michigan Sedation Scale for Children (UMSS)

Score	Responsiveness
0	Awake and alert
1	Minimally sedated; tired/sleepy, appropriate response to verbal conversation or sound
2	Moderately sedated; somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated; deep sleep, arousable only with significant physical stimulation
4	Unarousable

Electroencephalographic and Auditory Evoked Potential Recording

The principal investigator supervised recording of all data and was blinded to BIS and cAAI values. Values were recorded with a BIS® monitor (A-2000, version 3.2; Aspect Medical Systems, Newton, MA) and an AEP Monitor/2 (Danmeter A/S; software version 1.6). Before induction of anesthesia, a pediatric four-sensor BIS® probe (BIS® Pediatric Sensor; Aspect Medical Systems International BV, De Meern, The Netherlands) was attached to the left side of the patient's forehead for BIS registration. For the AEP Monitor/2, a headphone for auditory stimuli and three disposable electrodes (A-Line AEP electrodes; Danmeter A/S) were positioned at the midforehead (+), right forehead (reference), and right mastoid (-). The sensors and headphone were removed after patients regained consciousness.

According to recent recommendations by the manufacturer of the AEP Monitor/2 and based on the results of a study by Vereecke *et al.*,[13] we decided to analyze our cAAI data on a scale of 0 - 60 (all values above 60 are set to 60). cAAI levels higher than 45 indicate wakefulness, whereas levels between 15 and 25 are considered to reflect surgical anesthesia. The BIS ranges from 0 to 99. According to the manufacturer, values above 90 indicate wakefulness, and the target range for a patient during general anesthesia is 40 to 60.

For both BIS and cAAI, electrode impedances were considered acceptable if they were below 10 kΩ. The principal investigator checked impedances at the beginning and end of the recording period. When unreliable registration of the electroencephalographic parameters was suspected, corrective actions were performed. The smoothening time of the BIS® monitor was set at 15 s. The MLAEPs were elicited with a binaural click stimulus of 2 ms in duration, with a repetition rate of 9 Hz. The MLAEP analysis window was 20 - 80 ms. Detailed information on cAAI signal processing has been shown by Vereecke *et al.*[13] Just before induction of anesthesia, BIS and cAAI measurements were started to obtain awake baseline values. Measurements continued until the patient was awake in the recovery room.

Statistical Analysis

All continuous data were tested for normality using the Kolmogorov-Smirnov method. For data sets that followed a normal distribution, parametric tests were used. For all other data sets, the appropriate nonparametric tests were applied. For multiple comparisons of interindividual data, Friedman repeated-measures analysis of variance on ranks with subsequent all pairwise multiple comparison procedures (Tukey test) was applied. Data were analyzed using SPSS version 12.0.1 (SPSS Inc., Chicago, IL) and MedCalc® version 9.3.1 (MedCalc Software, Mariakerke, Belgium). A p value smaller than 0.05 was considered statistically significant.

Ordinal values as provided by the UMSS may not demonstrate a perfect linear relation between the observed sedation level of the patient and BIS and cAAI. To account for this, the

prediction probability (P_K), which compares the performance of indicators having different units of measurements or different data types (*i.e.*, continuous *vs.* ordinal or categorical data), provides a better alternative to investigate the overall relative performance of the different indicators in describing a sedation level. P_K was calculated using a custom spreadsheet macro, P_K MACRO (written in Microsoft Excel; Microsoft Corp., Redmond, CA), described and provided by Smith *et al.*[22,23] A P_K value of 1 means that the value of the predicting variable (*e.g.*, depth of hypnosis indicator such as BIS or cAAI) always correctly predicts the variable to be predicted (*e.g.*, the hypnotic state). Alternatively, a P_K value of 0.5 means that the predictive indicator is not better than chance alone; a P_K value below 0.5 indicates an inverse relation. To assess the relation between BIS and cAAI *versus* UMSS, P_K data were analyzed for the periods of

1. preanesthetic wakefulness to postoperative ROC (overall period),
2. the induction phase (the period from induction of anesthesia until placement of LMA), and
3. the emergence phase (from the termination of surgery to ROC). P_K values of paired BIS and cAAI data were calculated for every individual patient.

Then a Mann–Whitney U test was used to evaluate whether the individual P_K for BIS differed from that of cAAI. A Friedman test was used to calculate whether individual P_K for BIS and cAAI were different for the aforementioned study periods.

It is known that there is a time delay in signal processing for both BIS and cAAI. To deal with this problem, comparison of BIS and cAAI values at LOC and ROC were performed. For LOC, awake values *versus* values at LOC and 30 s thereafter (LOC_{30}) were used. For ROC, we used values 5 min before ROC *versus* ROC and 30 s thereafter (ROC_{30}).

We further investigated the performance of BIS and cAAI for determining consciousness-unconsciousness. Values of cumulative occurrence, sensitivity and specificity, and positive and negative predictive values were calculated. For these calculations, we used independent data for consciousness and unconsciousness (*i.e.*, a single median BIS and cAAI value for each patient). *Positive* denotes a test result that suggests consciousness, whereas *negative* denotes a test result that suggests unconsciousness. We computed the cumulative occurrence of consciousness (*i.e.*, the number of BIS and cAAI data points below a previously chosen cutoff value) as the percentage of such occurrences with index values below the cutoff (threshold) value for BIS and cAAI. Similarly, we computed the cumulative occurrence of unconsciousness as the percentage of such occurrences with index values above the cutoff values for BIS and cAAI. Sensitivity was computed as the proportion of conscious patients with positive results (index value higher than various cutoff values for BIS and cAAI); specificity is the proportion of unconscious patients with negative test results (index value lower than the cutoff values for BIS and cAAI). Positive predictive values were computed as the proportion of patients with positive test results that were correctly diagnosed as

conscious. Negative predictive values were defined as the proportion of patients with negative test results that were correctly diagnosed as unconscious. This approach has previously been described by Struys *et al.*[16]

RESULTS

Forty-five patients were recruited for the study; 6 patients were excluded from the study because of violation of the anesthesia protocol (*e.g.*, use of muscle relaxants). Therefore, data of 39 patients were analyzed. The demographics (mean ± SD) are as follows: age, 6.2 yr (SD, 3.3 yr); weight, 20 kg (SD, 10.4 kg); and female:male ratio, 15:24.

In 21 patients, BIS and AEP sensors were applied before induction to obtain awake BIS and cAAI values; in 18 children, either the parents did not allow the sensors to be applied before induction of anesthesia or the children were afraid and agitated. Because of excessive artifact contamination, awake BIS values were obtained in 10 children, and awake cAAI values were obtained in 20 children.

Before induction of anesthesia (case milestone Awake), all children were fully awake and therefore assigned to level 0 of the UMSS. After induction of anesthesia, LMA insertion led to clinically visible reactions and heart rate alterations in four patients; therefore, these patients were assigned to UMSS level 3. Patients without clinically visible reactions or heart rate alterations were assigned to UMSS level 4.

The ability of BIS and cAAI monitoring to predict the UMSS score, as presented by the P_K values, is shown in table 2. The performance of BIS did not differ from that of the cAAI ($p = 0.244$). However, overall P_K values for both BIS and cAAI were higher than P_K values for the induction and emergence phases separately (BIS $p < 0.001$, cAAI $p = 0.007$). In addition, for both BIS and cAAI, P_K values for the induction phase were higher than for the emergence phase ($p < 0.001$).

Table 2 Prediction Probabilities for the University of Michigan Sedation Scale

	UMSS		
	cAAI	**BIS**	***p* value**
Overall	0.9 ± 0.08	0.91 ± 0.1	NS
Induction phase	0.84 ± 0.08	0.84 ± 0.04	NS
Emergence phase	0.74 ± 0.02	0.75 ± 0.02	NS

Data are presented as mean ± SE. p-values: Bispectral Index (BIS) vs. composite A-Line ARX (cAAI), Mann-Whitney-U-test. NS = not significant; UMSS = University of Michigan Sedation Scale.

With increasing sedation (increase in UMSS score from level 0 to level 4), the median BIS decreased significantly from 79 to 40 ($p < 0.001$), and the median cAAI decreased from 60 to 19 ($p < 0.001$; figure 1). During induction (case milestone Awake to LOC), we observed a significant decrease in median cAAI values (60 to 43; $p < 0.001$), whereas median BIS values remained unaltered (94 to 90; not significant). Median BIS and cAAI values for case milestone LOC were also computed with a time delay of 30 s (case milestone LOC_{30}). Significant changes in median BIS (94 to 36; $p = 0.008$) and cAAI (60 to 35; $p < 0.001$) were found when comparing awake values and values at LOC_{30}. During the emergence phase, median BIS and cAAI increased from 51 to 74 ($p < 0.001$) and from 46 to 58 ($p = 0.03$), respectively, when comparing the values taken at 5 min before ROC with values 30 s after ROC.

The cumulative occurrence curves are shown in figure 2 for BIS and in figure 3 for cAAI. Sensitivity and the corresponding specificity, and positive and negative predictive values for both the BIS and the cAAI at different cutoff values are displayed in tables 3 and 4.

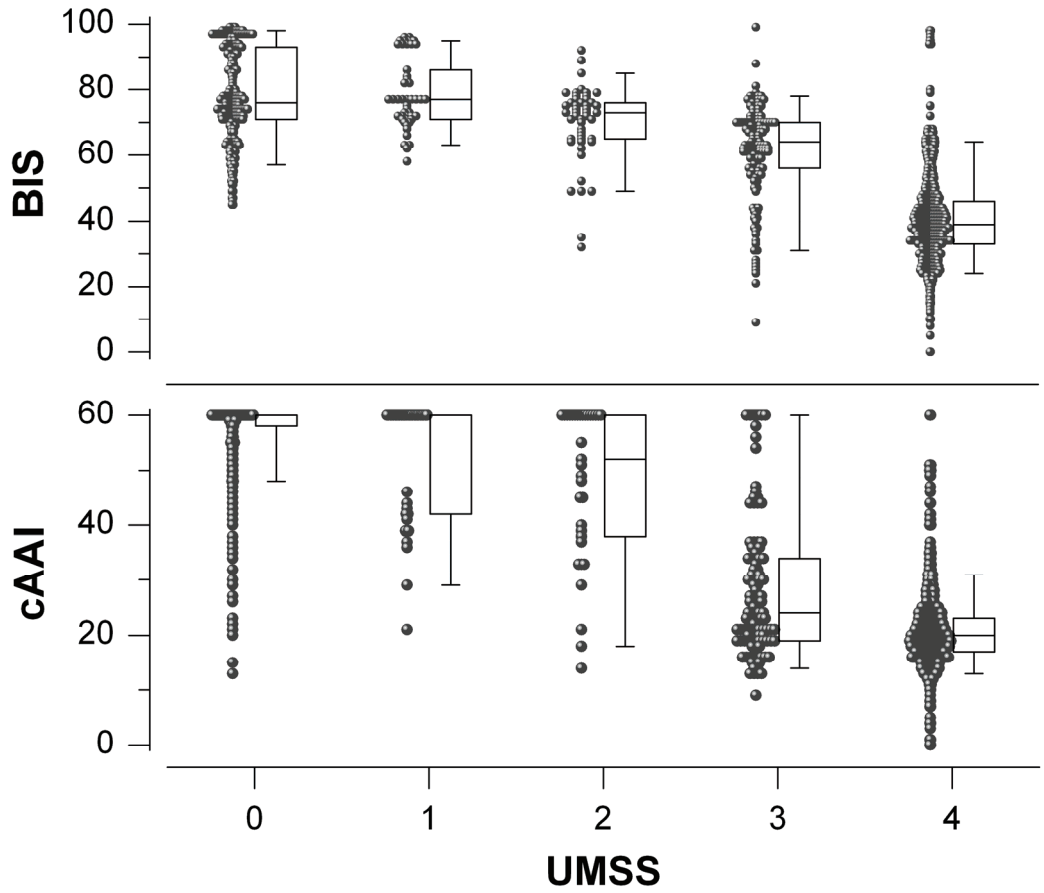

Figure 1 *Boxplot graphics (median and 25th and 75th percentiles [box top and bottom] and 5th and 95th percentiles [Whiskers]), and individual patient data for (A) Bispectral Index (BIS), and composite A-Line ARX Index (cAAI) at different levels of the University of Michigan Sedation Scale (UMSS).*

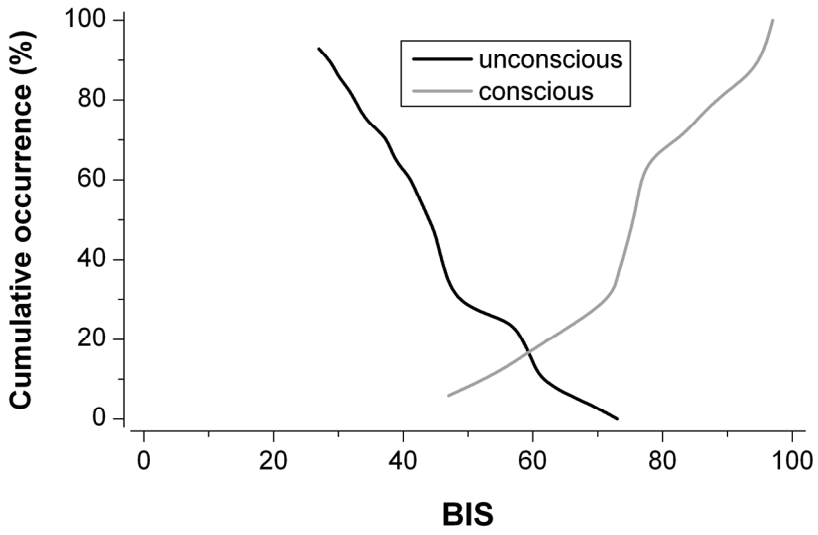

Figure 2 *Cumulative occurrences for consciousness and unconsciousness as a function of the University of Michigan Sedation Scale for the Bispectral Index (BIS).*

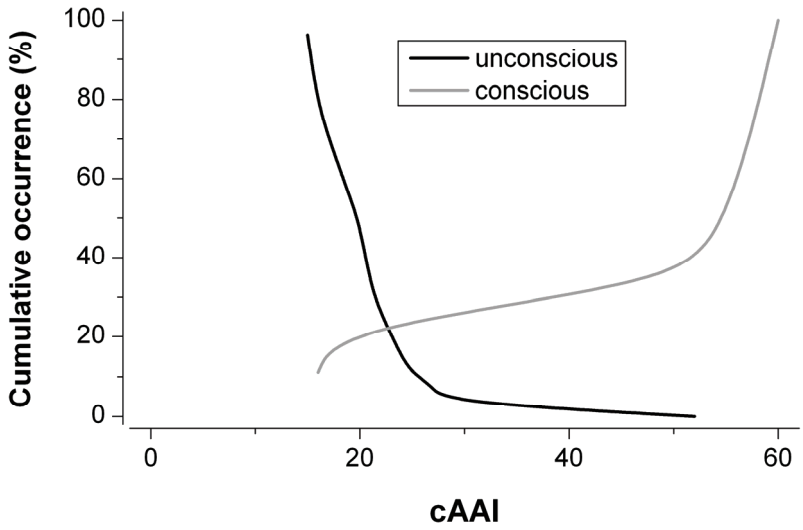

Figure 3 *Cumulative occurrences for consciousness and unconsciousness as a function of the University of Michigan Sedation Scale for the composite A-Line ARX Index (cAAI).*

DISCUSSION

This study was conducted to compare the performance accuracy of BIS and cAAI, which are both independent variables used to measure hypnosis depth, in pediatric patients. Both monitors performed equally in predicting sedation levels, as evaluated by the UMSS. Also, P_K values comparing overall relative performance were equal between the two monitors. However, it is noteworthy to mention that P_K values are only one single performance parameter for comparing depth of anesthesia monitors and that, therefore, caution must be taken not to misinterpret our results as being indicative for equal performance of the cAAI and the BIS.

Not surprisingly, we observed higher P_K values during the induction period than during emergence for both indices. This is in accord with previously published work by Klockars *et al.*[25] Overall P_K values for both monitors, *i.e.*, from preanesthetic wakefulness until postoperative ROC, were higher than P_K values during either the induction or emergence phases (table 2). This finding may at least partly be explained by the fact that intraoperatively all UMSS scores were 4, because patients who did not respond to surgical stimuli were assigned to this level.

Our results are in contrast to a previous study by Ironfield *et al.*[19] comparing BIS and cAAI in children aged 0 - 12 yr undergoing cardiac catheterization. In that study, during steady state concentrations of sevofluranebased anesthesia, cAAI was a poor predictor of depth of anesthesia compared with BIS. In the 2- to 12-yr-old group, the P_K for BIS (0.89) was significantly higher than the P_K for cAAI (0.53). In contrast, in the 0- to 1-yr-old group, there was no evidence of a significant difference between P_K for BIS (0.74) and the P_K for cAAI (0.53). An explanation for the discrepancies between our findings and the results of Ironfield *et al.* may be differences in anesthesia technique. Our study was performed with non-steady state concentrations of isoflurane, because of the pharmacokinetic profile of isoflurane,[26] whereas Ironfield *et al.* used steady state concentrations of sevoflurane. In addition, Ironfield *et al.*[19] correlated electroencephalographic parameters with end-tidal sevoflurane concentrations, which will have a variable relation with arterial and effect site concentration depending on the amount of ventilation-perfusion mismatch, and a variable clinical effect depending on the pharmacodynamic susceptibility of the patient to the achieved effect site concentration. In our study, we correlated electroencephalographic parameters with clinical signs, thereby circumventing the problems caused by interindividual pharmacokinetic and pharmacodynamic differences.

The findings in our study show considerable overlap in both BIS and cAAI values for each level of the UMSS. The large interindividual variation we observed in cAAI values was also reported by Weber *et al.*[27] for the former A-Line monitor during sevoflurane anesthesia in children.

The ideal monitor of anesthetic depth should have 100% sensitivity (no false-negative results) and 100% specificity (no false-positive results) in distinguishing different levels of hypnotic depth. Not surprisingly, neither of the monitors in our study was found to be ideal, because no variable provided perfect sensitivity-specificity. To reach a 100% certainty of unconsciousness, a BIS value of less than 17 and a cAAI value of less than 12 were required. To undoubtedly ascertain consciousness, BIS values greater than 78 and cAAI values above 52 were required. Positive predictive values, or precision rates, were poor during emergence but comparable for both monitors (tables 3 and 4).

Table 3 Specific sensitivity or specificity of different 'cut-off' BIS levels to describe consciousness for different phases

Variable	Cut-off Value	Specificity	Sensitivity	Negative Predictive Value	Positive Predictive Value
BIS Overall	90	100	37	99	100
	80	100	60	99	100
	78	100	62	99	100
	70	98	68	100	43
	60	89	69	99	10
	50	93	73	99	7
	40	55	94	100	3
	30	24	96	100	2
	20	3	98	99	2
	17	2	100	100	2
BIS Induction	90	100	43	98	100
	80	100	63	99	100
	70	100	64	99	99
	60	92	64	99	24
	50	84	68	99	14
	40	59	93	100	8
	30	31	96	100	5
	20	8	98	99	4
	17	7	100	100	4
BIS Emergence	90	100	12	99	94
	86	100	12	99	30
	80	96	22	99	10
	70	61	85	100	4
	60	26	93	100	2
	50	11	99	100	2
	48	9	100	100	2
	40	5	100	100	2
	30	2	100	100	2
	20	0	100	100	2

Data are presented as percentages. BIS = Bispectral Index; BIS Emergence = BIS during Emergence Phase; BIS Induction = BIS during Induction Phase; BIS overall = BIS during overall study period.

Table 4 Specific sensitivity or specificity of different 'cut-off' cAAI levels to describe consciousness for different phases

Variable	Cut-off Value	Specificity	Sensitivity	Negative Predictive Value	Positive Predictive Value
cAAI Overall	60	100	56	98	95
	52	100	73	99	85
	50	99	76	99	85
	40	99	80	99	76
	30	94	84	99	36
	20	62	93	100	9
	12	3	100	100	4
	10	1	100	100	4
cAAI Induction	60	100	54	96	94
	52	100	73	98	93
	50	99	75	98	93
	40	99	79	98	85
	30	92	83	98	48
	20	58	93	99	17
	12	4	400	100	9
	10	2	100	100	9
cAAI Emergence	60	100	0	98	-
	50	75	89	100	7
	40	71	96	100	6
	30	62	97	100	5
	20	39	97	100	3
	14	9	100	100	2
	10	0	100	100	2

Data are presented as percentages. cAAI = composite A-Line ARX Index; cAAI Emergence = cAAI during Emergence Phase; cAAI Induction = cAAI during Induction Phase; cAAI overall = cAAI during overall study period.

One possible explanation for this observation might be that ROC after general anesthesia is much more difficult to determine than LOC during induction. Furthermore during emergence, only for cAAI was an on-off phenomenon observed in the majority of our patients. That means intraoperative cAAI values remained constant during emergence until the moment of ROC and then within seconds increased to 60. In addition, there is a

theoretical chance that patients regained consciousness before being reassessed by the UMSS within a 2-min period.

The cumulative occurrence data in figures 2 and 3 show a remarkable overlap between "conscious" and "not conscious" data. This means BIS and cAAI data within the commonly accepted target ranges for general anesthesia do not always indicate an unconscious patient. This does also apply for the conscious patient, who may present with index values usually associated with deep levels of anesthesia. Our findings correspond with findings previously reported in adults, indicating some overlap of both monitors during propofol anesthesia.[16]

In our study, cAAI distinguished the transition from consciousness to unconsciousness faster than BIS. This may be explained by the faster signal processing of the AEP Monitor/2 compared with BIS. In daily practice, this time delay in processing is an important factor, because clinicians respond to the real-time indices observed on the monitor.

In this study, we observed frequent fluctuation between AEP-derived and electroencephalogram-derived cAAI values. Unfortunately, the AEP Monitor/2 only exports cAAI values without distinguishing between AEP or electroencephalogram derivation. Therefore, it is noteworthy to emphasize that cAAI data do not necessarily mean that the index is solely MLAEP derived.

We used the pediatric four-sensor BIS® probe, which, according to the manufacturer, removes electrical artifact that is interpreted as EMG by the BIS® monitor. The performance of the four-sensor probe may thus be somewhat different from the three-sensor probe, particularly in situations with significant EMG contamination such as emergence. To our knowledge, all previously published studies in children investigated the performance of BIS using the three-sensor probe; it may therefore be inappropriate to compare our results.

A shortcoming of this and the majority of other studies dealing with the evaluation of depth of anesthesia monitoring systems is the lack of an ideal tool for assessing the patient's hypnotic state. We selected the UMSS because it correlates well with clinical reflections of the hypnotic component of anesthesia and has been validated in children.[21] However, subjective clinical scoring systems, such as the UMSS, are only indicative for a specific moment and by their nature introduce potential error *via* individual implementation and interpretation. Furthermore, depending on the intensity of potentially distressing painful physical stimulation, they could be measuring spinal reflexes as well as cortical activity. Therefore, we cannot expect total agreement between the UMSS and BIS and cAAI scores. In addition, unconsciousness is likely to be associated with stage 2 of the UMSS, and assignment to this stage requires tactile stimulation. Because the transition from

unconsciousness to consciousness after inhalational anesthesia is frequently accompanied by excitation phenomena, additional external stimuli could significantly increase the risk of developing laryngospasm.

Unfortunately, awake data were not obtainable in all children. Some children were agitated when sensors were applied, and in other children, parents did not allow the sensors to be applied before induction of anesthesia. The number of children who accepted sensor placement before anesthesia induction would have been higher had we chosen to premedicate with midazolam. Based on the fact that benzodiazepines have a known impact on the electroencephalogram,[28] we decided not to premedicate our patients.

In summary, we found that BIS and cAAI to perform equally in distinguishing different hypnotic conditions in the particular setting of isoflurane anesthesia in children. Because of faster signal processing, the cAAI seemed to be superior to the BIS in the prediction of LOC. However, both monitors showed notable interindividual variability and overlap between the different hypnotic states. It is important to note that these results should not be extrapolated to other anesthesia techniques in children.

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6

Bispectral index and composite auditory evoked potential index as measures of the electroencephalographic effects of isoflurane in children

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ABSTRACT

Background

Bispectral Index (BIS), derived from the EEG, and the composite A-line autoregressive index (cAAI), derived from both the EEG and auditory evoked potentials, have been promoted as anesthesia depth monitors. The aim of this study was to compare the performance of BIS and cAAI in distinguishing different levels of anesthesia and to study the relationship between BIS and cAAI and non-steady state end-tidal concentration of isoflurane (ET_{iso}) in children.

Methods

Twenty children aged 3 - 16 years, undergoing standardized isoflurane anesthesia for cardiac catherization, were enrolled. The relationship between BIS and cAAI and the University of Michigan Sedation Scale (UMSS) was calculated using prediction probability during induction and emergence of anesthesia. Furthermore the relationship between ET_{iso} and BIS and cAAI was analysed using NONMEM.

Results

Prediction probabilities for BIS and cAAI versus UMSS were 0.82 and 0.88 ($p < 0.001$) for induction, and 0.88 and 0.86 for emergence ($p < 0.001$). Non-linear mixed effects modelling demonstrated a pharmacodynamic correlation between non–steady state end-tidal concentration of isoflurane versus BIS and cAAI. The EC_{50} was 1.0% for BIS and 0.35% for cAAI.

Conclusions

When comparing BIS and cAAI in children with the level of consciousness as defined by the UMSS, both indices performed equally. An inhibitory sigmoid E_{max} model demonstrated a lower EC_{50} for cAAI compared to BIS.

INTRODUCTION

Various monitors based on the EEG or mid-latency auditory evoked potentials (MLAEP) are proposed for measuring depth of anesthesia. The most widely adopted monitor is the Bispectral Index (BIS). The recently developed AEP monitor/2 extracts MLAEPs from the EEG after an acoustic stimulus, and calculates the composite A-Line ARX Index (cAAI) from the MLAEP and EEG.[1] Adult studies comparing BIS and cAAI demonstrated that both indices were comparable indicators of anesthetic depth.[2,3] In children, however, only two studies investigating cAAI have been published.[4,5] Weber *et al*. demonstrated less propofol consumption and shorter recovery times during cAAI guided anesthesia.[5] Furthermore, cAAI was a poor predictor of anesthetic depth compared to BIS during sevoflurane-based anesthesia.[4]

Our aim was to compare the performance of both BIS and cAAI in distinguishing different hypnotic states, evaluated by the University of Michigan Sedation Scale (UMSS).[6] Second aim was to determine the relationship between end-tidal isoflurane concentrations (ET_{iso}) and BIS and cAAI.

METHODS

Patients

The study was approved by the Institutional Ethics Committee (Erasmus University Medical Centre, Rotterdam, the Netherlands), and written informed parental consent was obtained. Patients aged between 2 and 16 years old, with ASA I or II status, undergoing anesthesia for cardiac catherization were enrolled in the study. Exclusion criteria were hypacusis or deafness, any neurological disease, allergy to adhesives, medication affecting the central nervous system or any contraindication to the protocol.

Anesthesia

All patients received a standardized anesthetic regimen. No sedative premedication was administered prior to induction. Anesthesia was induced with fentanyl (2 µg/kg) and propofol (3 - 5 mg/kg), followed by rocuronium (0.6 mg/kg) to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane in an air/oxygen mix (30% O_2), which was adapted according to routine clinical practice by the attending anesthesiologist who was blinded to BIS and cAAI monitoring. The patients were mechanically ventilated and ventilation was titrated to normocapnia (end-tidal carbon dioxide 35 - 40 mmHg). Local anesthesia infiltration was used prior to cannulation of the femoral vessels by the pediatric cardiologist. At the end of the catherization procedure, isoflurane was discontinued, and the tracheal tube was removed when sufficient spontaneous breathing had returned and patients responded to verbal commands.

Data collection

BIS and cAAI were simultaneously recorded with a BIS monitor (A-2000, version 3.2; Aspect Medical Systems, Newton, M.A.) and an AEP monitor/2 (Danmeter A/S, Odense, Denmark; software version 1.6). Before induction of anesthesia, a four sensor pediatric BIS probe (BIS Pediatric Sensor, Aspect Medical Systems, De Meern, the Netherlands) was attached to the left side of the patient's forehead for BIS registration. For the AEP monitor/2, a headphone for auditory stimuli and three disposable electrodes (auditory evoked potential electrodes; Danmeter A/S) were positioned at the mid-forehead (+), right forehead (reference), and right mastoid (-). The sensors and headphone were removed after patients regained consciousness.

During the procedure, the attending anesthesiologist, blinded to BIS and cAAI monitoring, assessed the patient's level of consciousness using the UMSS (see Table 1). Data collection started just before induction of anesthesia and was continued until the return of consciousness (ROC) of the patient. ROC was defined as eye opening, purposeful movement, or age-appropriate phonation. The BIS is ranged from 0 to 99. According to the manufacturer, values above 90 indicate wakefulness and the target range for a patient under general anesthesia is 40 to 60. cAAI levels higher than 45 indicate wakefulness, whereas levels between 15 and 25 are considered to reflect surgical anesthesia.

The following specific case milestones were defined a priori: awake, loss of consciousness (LOC; defined as loss of eye lash reflex), start and end of the cardiac catherization, stop of isoflurane supply, and ROC. The attending anesthesiologist determined LOC and ROC. UMSS was assessed when patients were awake, and at start of catherization insertion. During emergence, the UMSS was assessed every 2 min.

In addition to BIS, cAAI, and ET_{iso}, electrocardiogram, heart rate, non-invasive blood pressure, end tidal carbon dioxide, oxygen saturation via pulse oximetry, and rectal temperature were monitored continuously during anesthesia. All data were collected in 5-s intervals (Rugloop, Demed, Temse, Belgium) and synchronized (Labgrab, Demed) on a laptop computer.

Table 1 University of Michigan Sedation Scale (UMSS)

Score	Responsiveness
0	Awake and alert
1	Minimally sedated; tired/sleepy, appropriate response to verbal conversation or sound
2	Moderately sedated; somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated; deep sleep, arousable only with significant physical stimulation
4	Unarousable

Statistics

Data were tested for normality with the Kolmogorov-Smirnov method. For data sets that followed a normal distribution, parametric tests were used. For all other data sets appropriate non-parametric tests were applied. Data were analysed using SPSS V12.0.1 (SPSS Inc., Chicago, IL) and MedCalc V 9.3.1 (MedCalc Software, Mariakerke, Belgium). A *p* value smaller than 0.05 was considered statistically significant.

Prediction probability

In order to compare the observed sedation level of the patient using ordinal values as provided by the UMSS and continuous measurements of BIS and cAAI prediction probabilities, P_k, were calculated. Pk compares the performance of indicators having different units of measurements or different data types (i.e. continuous versus ordinal or categorical data) and provides a better way to investigate the overall relative performance of the different indicators in describing a sedation level. P_k was calculated using a custom spreadsheet macro, the PK-MACRO, described and provided by Smith *et al*.[8,9] A P_k value of 1.0 means that the parameter (e.g. depth of hypnosis indicator such as BIS or cAAI) predicts the states (e.g. the hypnotic state) correctly 100% of the time. A P_k value of 0.5 means that the prediction is no better than chance alone. A P_k value of < 0.5 indicates an inverse relationship. P_k analysis was based on the available paired BIS and cAAI data for every individual patient.

To assess the relationship between BIS and cAAI versus UMSS, P_K analysis was calculated during 2 periods:

1. induction of anesthesia: the period from the induction of anesthesia until the administration of rocuronium, and
2. emergence from anesthesia: from termination of anesthesia until return of consciousness.

A Mann-Whitney-U test was used to evaluate whether the P_K for BIS differed from that of cAAI.

Population pharmacodynamic model

To determine the pharmacodynamic relation between end-tidal isoflurane concentration, BIS, and cAAI, non-linear mixed effect modelling was applied (NONMEM VI, Globomax LLC, Hanover, MD).[7] NONMEM estimates the population pharmacodynamic parameters of the population (typical values) and the interindividual (η) and residual (intraindividual, ε) variability, minimizing the objective function (-2 log likelihood). All analyses were performed with the first-order conditional estimation (method 1) with η-ε interaction. For visualization of the data S-plus (version 6.2, Insightful software, Seattle, WA) was used.

Model development was performed in four steps:

1. choice of structural pharmacodynamic model (including inter-individual variability assessment),
2. choice of residual error model,
3. covariate analysis and
4. internal validation of the model.

Discrimination between different models was made by comparison of the objective function. A value of $p < 0.005$, representing a decrease of 7.8 points in the objective function was considered statistically significant. In addition, goodness-of-fit plots, including observations versus individually predicted, observations versus population predicted, time versus weighted residuals, and population predicted versus weighted residuals were used for diagnostic purposes of the pharmacodynamic data. Finally, the confidence interval of the parameter estimates, the correlation matrix and visual improvement of the individual time versus concentration plots were used to evaluate the model.

For the pharmacodynamic analysis, data were used from 15 minutes after administration of propofol. By this time it was assumed that the effect of propofol was not of relevance for the EEG indices any more. An inhibitory sigmoid E_{max} model was used:

$$PD_{ij} = PD_0 - \frac{(E_{max,i} \cdot c_{1,ij}^{r})}{EC_{50,j}^{r} + c_{1,ij}^{r}} \quad (1)$$

where PD_0 is the baseline BIS or cAAI value, $E_{max,i}$ is the maximum possible effect of isoflurane on BIS or cAAI in the *i*th subject, ($C_{1,ij}$) is the individual predicted end-tidal concentration, γ is the Hill coefficient representing the steepness of the end-tidal concentration *versus* response relation, and EC_{50} is the end tidal concentration (%) at half the maximum score of the BIS or cAAI. Pharmacodynamic parameters were assumed to be log-normally distributed. The interindividual variability (η_i) was assumed to be symmetrically distributed with mean zero and variance ω^2. The residual error for BIS was best characterized by an additive error model.

$$Y_{ij} = PD_{pred,ij} + \varepsilon_{ij} \quad (2)$$

The residual error for cAAI was best characterized by an proportional error model.

$$Y_{ij} = PD_{pred,ij} \cdot (1 + \varepsilon_{ij}) \quad (3)$$

In both models Y_{ij} represents the observed BIS or cAAI effect in the *i*th subject at the *j*th time point, $PD_{pred,ij}$ represents the population prediction at the *j*th time point in he *i*th individual, and ε_{ij} is the residual error.

For the covariate analysis, the following covariates were tested: bodyweight, age, gender. Potential covariates were separately incorporated into the model and considered statistically significant if the objective function decreased 7.8 points and the 95% confidence interval of the additional parameter did not include 0 (assuming normal distribution).

The internal validity of the pharmacodynamic model was assessed by the bootstrap resampling method (repeated random sampling to produce another data set of the same size but with a different combination of individuals). Parameters obtained with the bootstrap replicates were compared to the estimates obtained from the original data set.

RESULTS

Twenty-five patients were recruited for the study. Datasets of three children were excluded from the study because of anesthesia protocol violations. For two children no data were collected as a result of software failure. Analyses were conducted on the 20 remaining children. Their characteristics are shown in table 2.

In 15 patients, BIS and AEP sensors were applied before induction to obtain awake BIS and cAAI values; in 5 children, either the parents did not allow the sensors to be applied before induction of anesthesia, or the children were afraid and agitated. In the remaining children who were awake data acquisition was more difficult with BIS than with cAAI (31% vs. 69% available data). Awake BIS values varied between 95 and 98 (median 94), awake cAAI values were between 39 and 60 (median 60). The transition from AWAKE to LOC occurred at a median BIS value of 67 (interquartile range 27 - 92), and at a median value of 26 for cAAI (interquartile range 18 - 60). With increasing sedation (increase in UMSS score from level 0 to level 4), median BIS and cAAI values decreased significantly (t-test, $p < 0.01$) from 94 to 49, and from 60 to 18, respectively. Of the 20 children, there were 19 complete datasets for awakening. Awakening data for one patient who remained anesthetized were missing because of a transfer to the cardiac surgery theatre. ROC occurred at a median BIS value of 75 (interquartile range 70 - 90), and a median value of 60 for cAAI (interquartile range 32 - 60).

Table 2 Patient characteristics

Variable	**n = 20**
Age (year)	5.3 (3.3 - 16)
Weight (kg)	19.5 (14 - 65)
Gender	11 M, 9 F
Procedure	
ASD closure	4
Diagnostic	12
Balloon dilatation of coarctation	2
Balloon dilatation of native stenosis	1
PDA closure	1

Data are presented as median (range).

Table 3 Prediction probabilities of Bispectral Index (BIS) and composite A-line ARX Index (cAAI) for induction and emergence of anesthesia using the University of Michigan Scale as gold standard

	BIS	cAAI	P-value
Induction	0.82 ± 0.09	0.88 ± 0.06	$p < 0.001$
Emergence	0.88 ± 0.02	0.86 ± 0.02	$p < 0.001$

Data are presented as mean ± SE. 305 paired data sets are included.

For P_k analysis, 305 paired data sets for both BIS and cAAI versus UMSS were available. The P_K values for induction and emergence are shown in table 3. The performance of cAAI to distinguish between awake and loss of consciousness was better compared to BIS ($p < 0.001$). During emergence BIS performed better than cAAI in distinguishing different levels of anesthesia ($p < 0.001$).

In the pharmacodynamic model, both BIS and cAAI were modelled using separate E_{max} models for the two endpoints. The total dataset for the pharmacodynamic model included 3527 BIS, and 3515 cAAI observations of 20 patients.

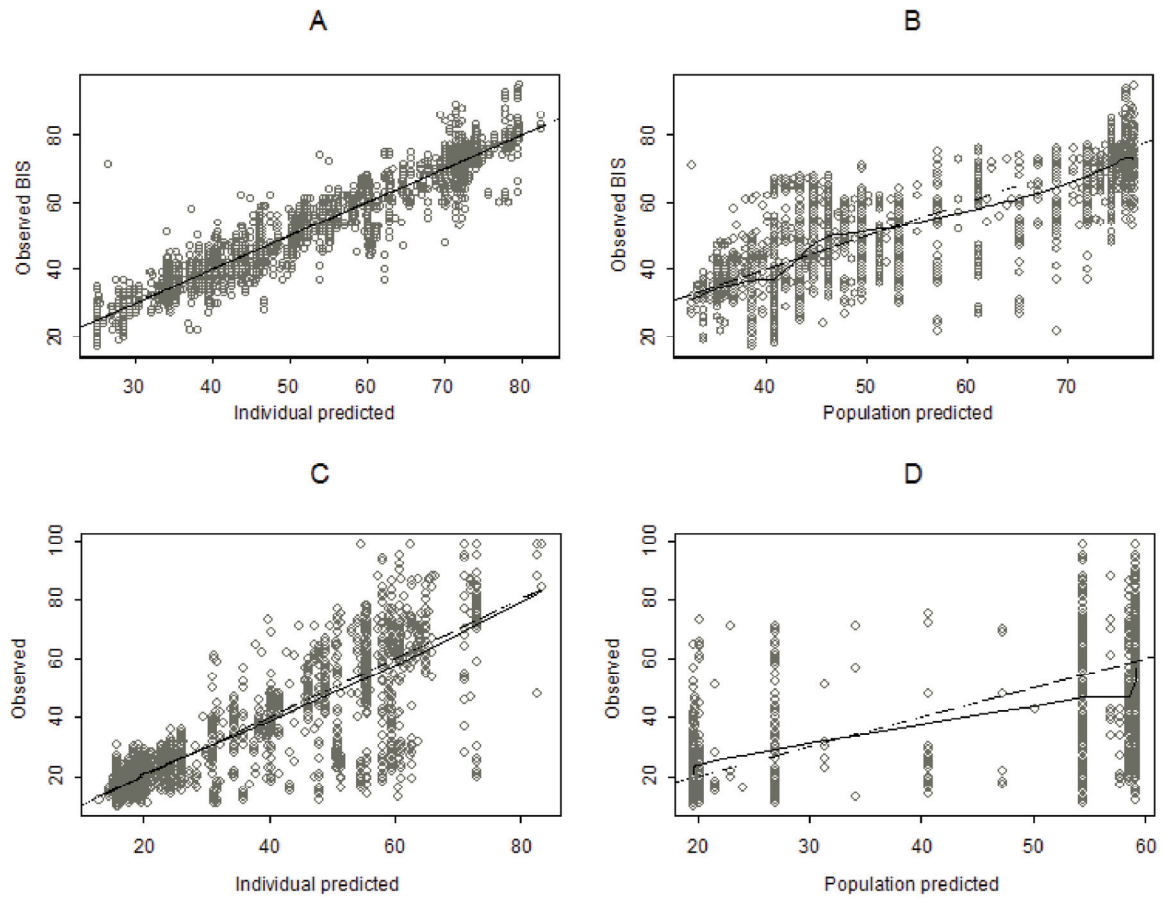

Figure 1 *Diagnostic plots of the final pharmacodynamic model using Bispectral Index (BIS) and composite A-Line ARX Index (cAAI), including (A and C) observations versus individual-predicted end-tidal isoflurane concentrations, (B and D) observations versus population end-tidal isoflurane concentrations. The dashed line indicates the trend line, the solid line represents the line of identity, x = y*

The parameters of the final pharmacodynamic model are reported in Table 4, with values for EC_{50} of 1.0 % for BIS and 0.35 % for cAAI. Interindividual variability on the baseline was larger using the BIS compared to cAAI (5.7 vs 17.2%, respectively), whereas interindividual variability on EC50 was similar (33 vs 31%, resp). Although age on EC_{50} for BIS resulted in a significant drop in objective function, only minimal improvements in individual and diagnostic plots were observed, with worse results in some of the subjects diagnostic plots did not improve. Therefore in the final pharmacodynamic model no covariates were used. No hysteresis was found for the pharmacodynamic model. In Figure 1 the diagnostic plots for BIS and cAAI are shown. In Figure 2 BIS and cAAI values versus time in a representative patient are presented. In Figure 3 the concentration effect relationship for BIS and cAAI as a function of end-tidal isoflurane concentration is presented.The bootstrap validation (300 replications) confirmed the stability of the model for BIS. For cAAI, however, bootstrap validation demonstrated large deviations from the parameter estimations (see table 4). In Figure 4 the variability in response to ET_{iso} is presented using the BIS as an endpoint.

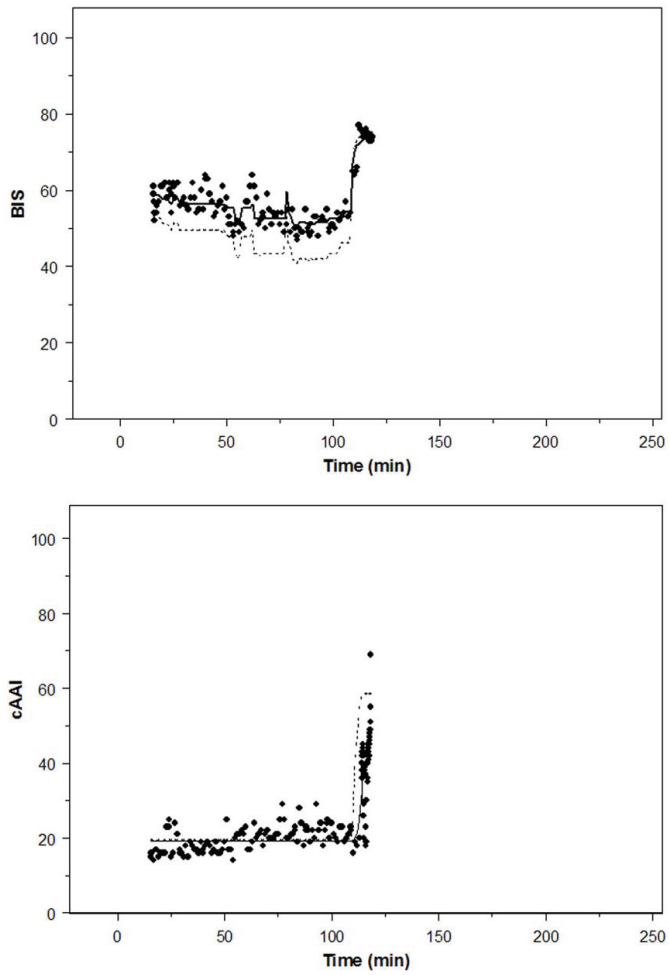

Figure 2 *BIS (A) and cAAI (B) versus time (minutes) in a representative patient. The solid circles represent the observations, the solid lines represent the individual predicted concentration or depth of anesthesia and the dashed line represents the population predicted concentration or depth of anesthesia*.

Table 4 Parameter estimates of the final pharmacodynamic BIS and cAAI models and the stability of the parameters using the bootstrap validation (300 times)

	Final Model Mean (CV%)	**Bootstrap Final Model Mean (Final/BS*100%)**
Fixed effects BIS		
Baseline	76.6 (1.7)	77.5 (99.0)
E_{max}	53.2 (2.3)	53.2 (100.0)
EC_{50}	1.0 (7.6)	0.9 (109.5)
Gamma	2.6 (16.2)	2.8 (91.8)
Fixed effects cAAI		
Baseline	59.2 (5.3)	73.7 (80.3)
E_{max}	39.6 (3.0)	42.1 (117.2)
EC_{50}	0.35 (7.0)	0.86 (40.9)
Gamma	12.1 (20.4)	4.3 (283.8)
Interindividual variability BIS (%)		
Baseline	5.7 (46.5)	8.8 (42.4)
EC_{50}	33.17 (37.5)	55.4 (35.8)
Gamma	65.6 (36.0)	56.7 (133.5)
Interindividual variability cAAI (%)		
Baseline	17.2 (37.2)	4.7 (1328.5)
E_{max}	9.8 (35.5)	37.1 (7.0)
EC_{50}	31.4 (37.6)	41.6 (57.2)
Gamma	86.5 (42.6)	52.2 (275.4)
Residual error		
e1, BIS units	20.6 (17.2)	20.9 (98.8)
e1, cAAI %	22.9 (17.9)	9.3 (575.7)
Performance measures (-2LL)		
BIS	14458.8	14500 (100.3)
cAAI	16526.8	14800 (111.6)

BS = bootstrap validation; BIS = Bispectral index; cAAI = composite A-Line ARX index; Gamma = the Hill coefficient representing the steepness of the concentration versus response relation; EC_{50} = end-tidal isoflurane concentration at half maximum effect; ; E_{max} = maximum possible effect of propofol on BIS or cAAI; interindividual variability = square root of the exponential variance of η minus 1; ε1 = residual error additive; ε2 = residual error additive;-2LL = objective function. Values in parentheses are coefficient of variation (CV) of the parameter values.

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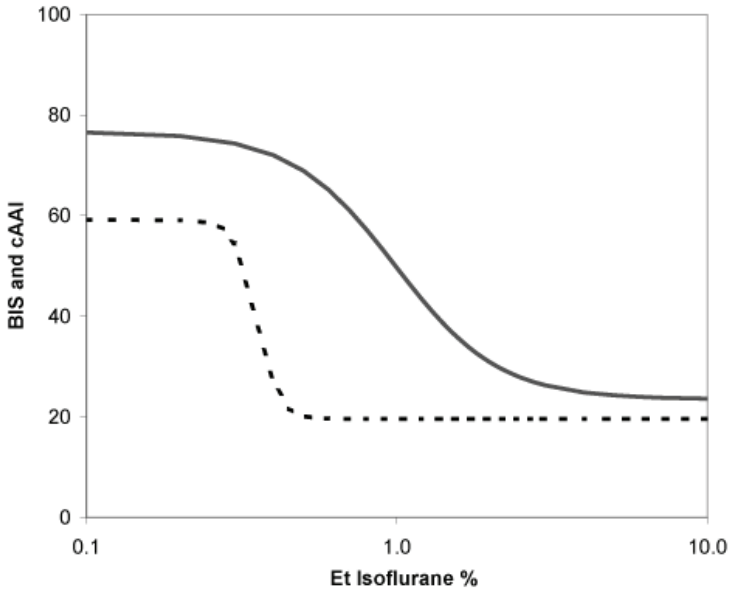

Figure 3 *The concentration effect relationship for BIS (solid black line) and cAAI (dashed line) as a function of end-tidal (Et) isoflurane concentration.*
For BIS, the EC_{50} was 1.0 % and the Hill coefficient was 2.6. For cAAI, the EC_{50} was 0.35% and the Hill coefficient was 12.1.

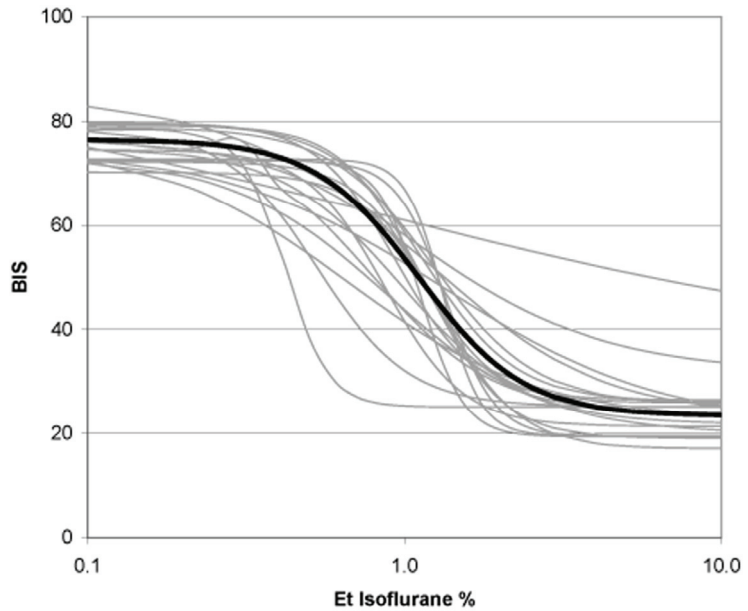

Figure 4 *Individual concentration - response curves for end-tidal isoflurane and Bispectral Index (BIS). The thick black line represents the population concentration -response curve.*

DISCUSSION

This study was conducted to compare the performance of BIS and cAAI to differentiate between different hypnotic states during isoflurane anesthesia in children, using the UMSS as gold standard. Furthermore, the dose-response relationship was studied between BIS and cAAI and non-steady state end-tidal isoflurane concentration (ET_{iso}). Significant differences were demonstrated during induction, where cAAI performed better in measuring sedation levels (P_K 0,88 vs. 0.82, $p < 0.001$), and emergence, where BIS was superior (P_K 0,88 vs. 0.86, $p < 0.001$). However, these differences appear to not be of clinical relevance in our daily practice.

Furthermore, the pharmacodynamic relation between BIS and cAAI versus ET_{iso} could be described using NONMEM (see figure 1) In the pharmacodynamic model different EC_{50}'s and Hill coefficients were found for BIS and cAAI. For cAAI, the EC_{50} was smaller (0.35% versus 1.0%), indicating that cAAI is more sensitive to differences in ET_{iso} than BIS (figure 3). The steeper Hill coefficient (12.1 versus 2.6) for cAAI supports our clinical observations that the process of awaking from isoflurane anesthesia was associated with an 'on-off' cAAI response rather than a gradual progression to awake levels, which was previously reported by White et al.[10]

Previous findings of Ironfield *et al.* in children aged 0 - 12 years undergoing cardiac catherization suggested that cAAI is a poor predictor of depth of anesthesia compared to BIS during steady-state concentrations of sevoflurane-based anesthesia.[4] In the 2 - 12 year-old group, the P_K for BIS (0.89) was significantly higher than the P_K for cAAI (0.53). An explanation for the discrepancies between our findings and the results of Ironfield *et al*. may be differences in anesthesia technique. Our study was performed with non-steady-state concentrations of isoflurane, because of the pharmacokinetic profile of isoflurane,[17] whereas Ironfield *et al.* used steady-state concentrations of sevoflurane. In addition, Ironfield *et al.* correlated EEG parameters with end-tidal sevoflurane concentrations, which will have a variable relationship with arterial and effect-site concentration depending on the amount of ventilation-perfusion mismatch, and a variable clinical effect depending on the pharmacodynamic susceptibility of the patient to the achieved effect-site concentration. In our study we therefore also correlated EEG parameters with clinical signs, thereby circumventing the problems caused by interindividual pharmacokinetic and pharmacodynamic differences.

To date, the concentration-response relationship between EEG derived indices and ET_{iso} has only been studied for the BIS monitor and not for cAAI. Several studies in adults demonstrated that an inhibitory sigmoid E_{max} model adequately described the pharmacodynamic relationship between BIS and ET_{iso}.[11-13] In 30 children with a median age of 3.2 yr, Whyte *et al.* reported an inverse correlation between 6 steady state end-tidal

isoflurane concentrations and BIS.[14] The EC_{50} in their study was 0.85%, which is less compared to our results ($EC_{50,BIS}$ 1.1%). cAAI on the other hand, has not been previously related to end-tidal concentrations of isoflurane in children. An inhibitory sigmoid E_{max} model described the dynamic relationship between cAAI and ET_{iso} (Figure 1C). In the model lower cAAI values where adequately described, whereas at higher cAAI values a larger range was demonstrated (see Figure 1C). However, at higher cAAI values all patients were awake.

Both BIS and cAAI decreased with increasing concentration of isoflurane (i.e. as depth of anesthesia increases). In some patients, however, we observed increased BIS and cAAI values at increasing ET_{iso}. Detsch *et al.* previously described in adults a paradoxically increased BIS at increasing isoflurane concentrations.[15] It was suggested by Detsch *et al.* that the possibility of a paradoxical increase was related to continuous pre-burst EEG patterns consisting of high frequency activity. Previous findings in children aged 6 months to 12 years undergoing sevoflurane anesthesia have also demonstrated that BIS paradoxically increased at high end-tidal sevoflurane concentrations.[16] As our study was not designed to systematically investigate the effects of low and high isoflurane concentrations on BIS and cAAI, we cannot provide the reason why both BIS and cAAI paradoxically increased at high end-tidal isoflurane concentrations.

We selected cardiac catherization patients, because of the absence of painful stimuli, and correlated the end-tidal concentration of isoflurane under non-steady state conditions with BIS and cAAI. One might argue that steady state concentrations are more reliable. As previous findings have demonstrated that it takes 40 min for the brain tissue concentration to equal arterial isoflurane concentration for 1% inspired isoflurane concentration,[18] we decided not to wait for an equilibrium between alveolar and cerebral tissue partial pressures. Furthermore, our study patients had a heterogeneous selection of complex congenital heart conditions, with attendant variable pulmonary blood flow, making it difficult to guarantee the time course of alveolar-brain equilibration.

In conclusion, when comparing BIS and cAAI in children with the level of consciousness as defined by the UMSS, we found both indices to perform equally. The concentration-relationship between ET_{iso} versus BIS and cAAI was described using an inhibitory sigmoid E_{max} model.

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Population PK/PD model-based dosing optimization of propofol-remifentanil anesthesia in children and adolescents

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ABSTRACT

Background

Adolescent scoliosis surgery with an intraoperative wake-up test is often performed with propofol-remifentanil anesthesia because of desirable pharmacokinetic and pharmacodynamic properties. To avoid inadequate anesthesia and predict return of cognition during the intraoperative wake-up test, so as to allow for immediate neurological evaluation, propofol pharmacokinetics and pharmacodynamics were characterized in adolescents undergoing propofol-remifentanil anesthesia.

Methods

Fourteen adolescents (9.8 - 20.1 years) were evaluated during standardized propofol-remifentanil anesthesia, using Bispectral index (BIS) and composite A-Line ARX index (cAAI) as pharmacodynamic endpoints. NONMEM was applied for population pharmacokinetic and pharmacodynamic modeling.

Results

A two-compartment model best described propofol pharmacokinetics. No covariates were identified. Total clearance was 1.37 l/min, central volume 3.6 l, intercompartmental clearance 1.15 l/min and peripheral volume 76.8 l. In the pharmacodynamic model, BIS and cAAI were simultaneously modeled using separate E_{max} models for the two endpoints and a similar effect-compartment equilibrium rate constant between the central and effect compartment (k_{eo}). Values for k_{eo} were 0.25 and 0.066 min^{-1}, during infusion and bolus administration, respectively. The EC_{50} was 3.17 mg/l for BIS and 1.41 mg/l for cAAI. The Hill coefficient was 1 for BIS and 5.3 for cAAI.

Conclusions

To achieve BIS values between 40 and 50, adolescents should receive, after an induction dose of 175 mg, 480 mg/h during the first 30 minutes, 420 mg/h during one hour, followed by 350 mg/h. cAAI values are then expected to be 16. For reanesthesia after a wake-up test, a bolus dose of 75 mg propofol is recommended, followed by 350 mg/h.

INTRODUCTION

Spinal cord injury with neurological sequelae is a rare but feared complication in adolescents undergoing correction of idiopathic scoliosis. To reduce the risk of motor deficit or paraplegia, an intraoperative wake-up test is applied, which consists of waking up patients during and immediately after completion of spinal procedures.[1] The performance of wake-up tests requires an anesthetic regimen that provides both predictable and fast recovery and return of cognition, so as to allow for immediate neurological evaluation. Total intravenous anesthesia with propofol and remifentanil is widely used for adolescents undergoing this type of surgery because of desirable pharmacokinetic and pharmacodynamic (PK/PD) properties. Both agents have rapid onset of action, are easy titratable and are cleared rapidly by redistribution and metabolism. Nevertheless, concentrations are often suboptimal in clinical practice because pharmacokinetics between and within individual patients show great variability. As a consequence, potential problems may arise from under- or overdosing, such as intraoperative awareness, longer wake-up times, or hemodynamic instability. For optimal dosage strategies, comprehensive knowledge of the PK/PD properties of propofol in combination with remifentanil is of importance. However, propofol PK/PD data in combination with remifentanil adolescents are limited.

The propofol-remifentanil PK/PD properties have been widely studied in adults.[2-5] This has allowed the determination of the optimal dose to obtain adequate anesthesia with the fastest recovery in this population.[6] Appropriate propofol-remifentanil dosing regimens for children have also been characterized.[7,8]

A cerebral pharmacodynamic feedback, such as Bispectral Index (BIS), derived from the electroencephalogram (EEG), and the composite A-Line ARX index (cAAI), derived from auditory evoked potentials (AEP) and the EEG, may help the anesthesiologist to adjust propofol dosing to maintain optimal anesthesia. So far, however, data on electroencephalographic response to propofol-anesthesia in children are limited[9-11] and in adolescents lacking.

In the current study, propofol PK/PD properties in adolescents are investigated using population PK-PD modeling with BIS and cAAI as pharmacodynamic endpoints. The final aim is to optimize propofol dosing for adequate anesthesia and predict recovery and return of cognition, so as to allow for immediate neurological evaluation during propofol-remifentanil anesthesia for scoliosis.

MATERIALS AND METHODS

The study was approved by the Medical Ethics Review Board of the Erasmus University Medical Center. Written informed consent of parents and patients was obtained. Eligible

subjects were patients with American Society of Anesthesiologists physical status I or II undergoing correction of idiopathic scoliosis between January 2005 and January 2007. Exclusion criteria were hypacusis or deafness, any neurological disease, medication affecting the central nervous system, or any contraindication to the anesthesia protocol.

Anesthesia protocol

Patients received a standardized anesthetic regimen without premedication. Anesthesia was induced with remifentanil 1 µg/kg/min, followed by a bolus propofol (4 mg/kg), and rocuronium (0.6 mg/kg) to facilitate endotracheal intubation. The lungs were mechanically ventilated to normocapnia (end-tidal carbon dioxide 35 - 40 mmHg). A central venous catheter and an arterial line were inserted for invasive continuous measurement of central venous pressure, arterial blood pressure and for arterial blood sampling.

Anesthesia was maintained with propofol by continuous infusion (2 - 10 mg/kg/h) and remifentanil (0.2 - 1 µg/kg/min), no further doses of neuromuscular blocking agents were administered. The attending anesthesiologist was blinded to BIS and cAAI values and conducted anesthesia in order to maintain heart rate and mean arterial pressure within 20% of baseline values obtained before induction of anesthesia. During the operation intrathecal morphine (5 µg/kg) was administered by the surgeon for both intra- and postoperative pain treatment. For the wake-up test, propofol and remifentanil infusions were stopped. The anesthesiologist in charge then repeatedly asked the patients to move their fingers, i.e. at least every 30 seconds until they responded, and thereafter to wiggle their toes. After the wake-up test, patients were reanesthetized with an IV bolus of propofol (3 - 5 mg/kg) and maintenance of anesthesia was continued as previously described. Thirty minutes before the estimated end of surgery, 100 µg/kg morphine was administered intravenously. At the end of surgery, propofol and remifentanil infusions were discontinued, and patients were extubated when sufficient spontaneous breathing had returned and they responded to verbal commands. Thereafter, patients were transferred to the Pediatric Surgical Intensive Care Unit.

In addition to continuous BIS and cAAI monitoring, electrocardiogram, heart rate, noninvasive and invasive arterial blood pressure, central venous pressure, end tidal carbon dioxide, oxygen saturation via pulse oximetry, and rectal temperature were continuously monitored, collected at 5-sec. intervals using Rugloop (Demed, Temse, Belgium), and synchronized with Labgrab software (Demed).

Electroencephalographic and Auditory Evoked Potential recording

The attending anesthesiologist was blinded to BIS and cAAI values throughout the study. BIS and cAAI were measured before induction of anesthesia until return of consciousness of the patient, defined as spontaneous eye opening. In the Pediatric Surgical Intensive Care Unit only BIS was registered.

Values were recorded with a BIS™ monitor (A-2000, version 3.2; Aspect Medical Systems, Newton, M.A.) and an AEP monitor/2 (Danmeter A/S, Odense, Denmark; software version 1.6). A four-sensor BIS probe (BIS Pediatric Sensor, Aspect Medical Systems International BV, De Meern, The Netherlands) was attached to the patient's left forehead. The BIS is ranged from 99 to 0. Values above 90 indicate wakefulness and the target range for a patient under general anesthesia is 40 to 60. For the AEP monitor/2, a headphone for auditory stimuli and three disposable electrodes (auditory evoked potential electrodes; Danmeter A/S, Odense, Denmark) were positioned at the mid-forehead (+), right forehead (reference), and right mastoid (-). The cAAI is ranged from 99 to 0. cAAI levels higher than 45 indicate wakefulness, whereas levels between 15 and 25 are considered to reflect surgical anesthesia.

Blood sampling and analysis

Venous samples (1 ml) were taken before induction of anesthesia, and at approximately 15 or 30 min after the start of propofol infusion. After an arterial line was placed, arterial samples (1 ml) were taken at approximately 45 or 60, 120 or 180, 240 or 360 min after the start of the propofol infusion; at 5 - 10 or 10 - 15 min after stopping propofol infusion for the wake-up test; at the time of patient movement to a verbal command during the wake-up test; just before and 1 h after each dose adjustment; just before stopping; and 15 or 30, 45 or 60, and 120 min after the end of the infusion after surgery. The maximum amount for blood sampling was 25 ml per patient.

Blood samples were collected in oxalate tubes and stored at 4°C until analysis (within 1 month). Propofol concentrations were measured in whole blood using high-performance liquid chromatography with fluorescence detection.[12] The limit of quantification was 0.005 mg/l. Inter- and intra-assay coefficients of variation were less than 6.7% and 3.3%, over the concentration range 0.5 - 20 mg/l.

Data analysis

NONMEM VI (Globomax LLC, Hanover, MD) with Splus (version 6.2; Insightful software, Seattle, WA) for the visualization of the data, was used for the sequential population pharmacokinetic and pharmacodynamic analysis.[13,14]

Model development was performed in four steps:

1. choice of structural pharmacokinetic or pharmacodynamic model (including inter-individual variability assessment),
2. choice of residual error model,
3. covariate analysis, and
4. internal validation of the model.

Discrimination between different models was made by comparison of the objective function. A value of $p < 0.005$, representing a decrease of 7.8 points in the objective function, was considered statistically significant. In addition, goodness-of-fit plots, including observations versus individually predicted, observations versus population predicted, time versus weighted residuals, and population predicted versus weighted residuals, were used for PK-PD data diagnostic purposes. Finally, the confidence interval of the parameter estimates, the correlation matrix, and visual improvement of the individual time versus concentration plots were used to evaluate the model.

Covariate analysis

Covariates were plotted independently against the individual post-hoc parameter estimates and the weighted residuals to visualize potential relationships, as described before.[10] The following covariates were tested: bodyweight, age, gender, height, body surface area, body mass index and body mass index for children (based on weight-for-height percentiles),[15] muscle relaxants, remifentanil infusion rates, and temperature.

Potential covariates were separately incorporated into the model and considered statistically significant if the objective function decreased 7.8 points and the 95% confidence interval of the additional parameter did not include 0 (assuming normal distribution).

Validation

The internal validity of the population pharmacokinetic and pharmacodynamic models was primarily assessed by the bootstrap resampling method (repeated random sampling to produce another data set of the same size but with a different combination of individuals). Parameters obtained with the bootstrap replicates were compared to the estimates obtained from the original data set. Deviations up to 5 - 10 % were accepted for PK and 15% for PD.

Additionally, numerical predictive distribution errors (NPDE) were computed.[16,17] All observations of the dataset were simulated a 1000 times with Monte Carlo simulation using the final parameter estimates. Four tests were sequentially performed to compare the distribution of the NPDE to the expected standard normal distribution: the Wilcoxon signed rank test is performed to test whether the mean is significantly different from 0; the Fisher test to test whether the variance is significantly different from a normal distribution variance; the Shapiro-Wilks test to test if the distribution is significantly different from a normal distribution and the Kolmogorov-Smirnov test to test the departure from a N(0, 1) distribution. *p*-values computed in these test should be > 0.05 to confirm a normal distribution. Visual inspection of the plots as well as the results of the tests was evaluated.[16,17]

Pharmacokinetic model

For the pharmacokinetic analysis, propofol concentrations were log transformed. The propofol pharmacokinetics were best described by a two-compartment model (NONMEM ADVAN 3 TRANS 4) in which the parameters, clearance (CL), central volume of distribution (V_1), inter-compartmental clearance (Q) and the peripheral volume of distribution (V_2) were independently estimated by NONMEM.

The individual value (post hoc value) of clearance (CL) of the ith subject was modeled by

$$CL_i = CL_{tv} * e^{\eta i} \quad (1)$$

where CL_{tv} is the mean estimated of the typical population clearance value and η_i is a random variable with mean zero and variance ω^2, assuming lognormal distribution of clearance in the population.

The residual error (or intraindividual variability), resulting from assay errors, model misspecifications, and other unexplained sources, was best described by a proportional error model. This means for the jth observed log transformed propofol concentration of the ith individual (Y_{ij}) the relation

$$Y_{ij} = \log c_{pred,ij} + \varepsilon_{ij} \quad (2)$$

where c_{pred} predicted log transformed propofol concentration and ε_{ij} is the random variable with mean zero and variance σ^2.

Pharmacodynamic model using Bispectral Index and composite A- Line ARX Index as end point

BIS and cAAI data were described by a sigmoidal E_{max} model linked to the propofol concentration in the central compartment with a first-order equilibration constant k_{e0}.

$$PD_{ij} = PD_0 - \frac{(E_{max,i} \cdot c^{r}_{1,ij})}{EC_{50,j}^{r} + c_{1,ij}^{r}} \quad (3)$$

where PD_0 is the baseline BIS or cAAI value, $E_{max,i}$ is the maximum possible effect of propofol on BIS or cAAI in the *i*th subject, ($C_{1,ij}$) is the individual predicted propofol concentration at the central volume, γ is the Hill coefficient representing the steepness of the concentration *versus* response relation, and EC_{50} is the propofol concentration (mg/l) at half the maximum score of the BIS or cAAI. Pharmacodynamic parameters were assumed to be log-normally distributed. The interindividual variable (η_i) was assumed to be symmetrically distributed with mean zero and variance ω^2. The residual error was best characterized by an additive error model.

$$Y_{ij} = PD_{pred,ij} + \varepsilon_{ij} \quad (4)$$

where Y_{ij} represents the observed BIS or cAAI effect in the *i*th subject at the *j*th time point.

RESULTS

Pharmacokinetics

The pharmacokinetic model was based on 225 blood samples from 14 adolescents during propofol-remifentanil anesthesia for scoliosis surgery with an intraoperative wake-up test. Patient characteristics are provided in Table 1. The pharmacokinetics of propofol were better described with a two compartment model than a three compartment model, and demonstrated little interindividual variance for all parameters (Table 2). The fits of 1000 bootstrap replicates of the data set demonstrated the stability of the model, and results from the numerical prediction distribution errors computation demonstrated a normal distribution of errors, while no trend was observed in the graphs. Figures 1 A and 1 B show the diagnostics of the final model. Figure 2 A shows a representative individual time versus log transformed plasma concentration plot.

In the pharmacokinetic model, none of the explored covariates (bodyweight (BW), age, sex, height, body surface area (BSA), body mass index (BMI) and body mass index for children) was identified significant, although there was a trend towards a positive allometric correlation between body weight and clearance. In the equation: $CL_i = CL_{pop} \bullet (BW_i/51)^b \bullet e^{\eta i}$, where BW_i is the bodyweight of the ith individual and 51 is the median bodyweight in kilograms in this population, b was estimated to be 0.76, while there was no significant change in objective function compared to a fixed allometric scaling factor of 0.75.[12,18] Although this equation on the predictive value of bodyweight on clearance resulted in a significant decrease in objective function, only minimal improvements in individual and diagnostic plots were observed, with worse results in some of the subjects. This significant decrease in objective function can be explained by one single subject with considerable overweight. Finally no covariates were used in the final pharmacokinetic model.

Pharmacodynamic model using the Bispectral index and composite A-Line ARX Index as end points

The total data set for the pharmacodynamic model included a median of 100 (60 - 141) observations for BIS and 97 (56 - 141) for cAAI per patient. In the pharmacodynamic model, both BIS and cAAI were modeled simultaneously using separate E_{max} models for the two endpoints and a similar effect-compartment equilibrium rate constant between the central and effect compartment (k_{eo}). This simultaneous approach was preferred over separate pharmacodynamic models for BIS and cAAI. While estimates for k_{eo}, EC_{50} and Hill coefficients were largely comparable when using two separate models versus a simultaneous model, the simultaneous analysis resulted in improved statistical power and a successful internal validation procedure. The simultaneous approach resulted in values for k_{eo} of 0.25 and 0.066 min^{-1} during infusion and after bolus injection, respectively, while separate pharmacodynamic modeling of the two endpoints resulted in k_{eo} values of 0.18 and 0.055

min^{-1}, for BIS and 0.28 and 0.070, respectively, for cAAI, which provides the basis for one k_{eo} for two different endpoints within the final model.

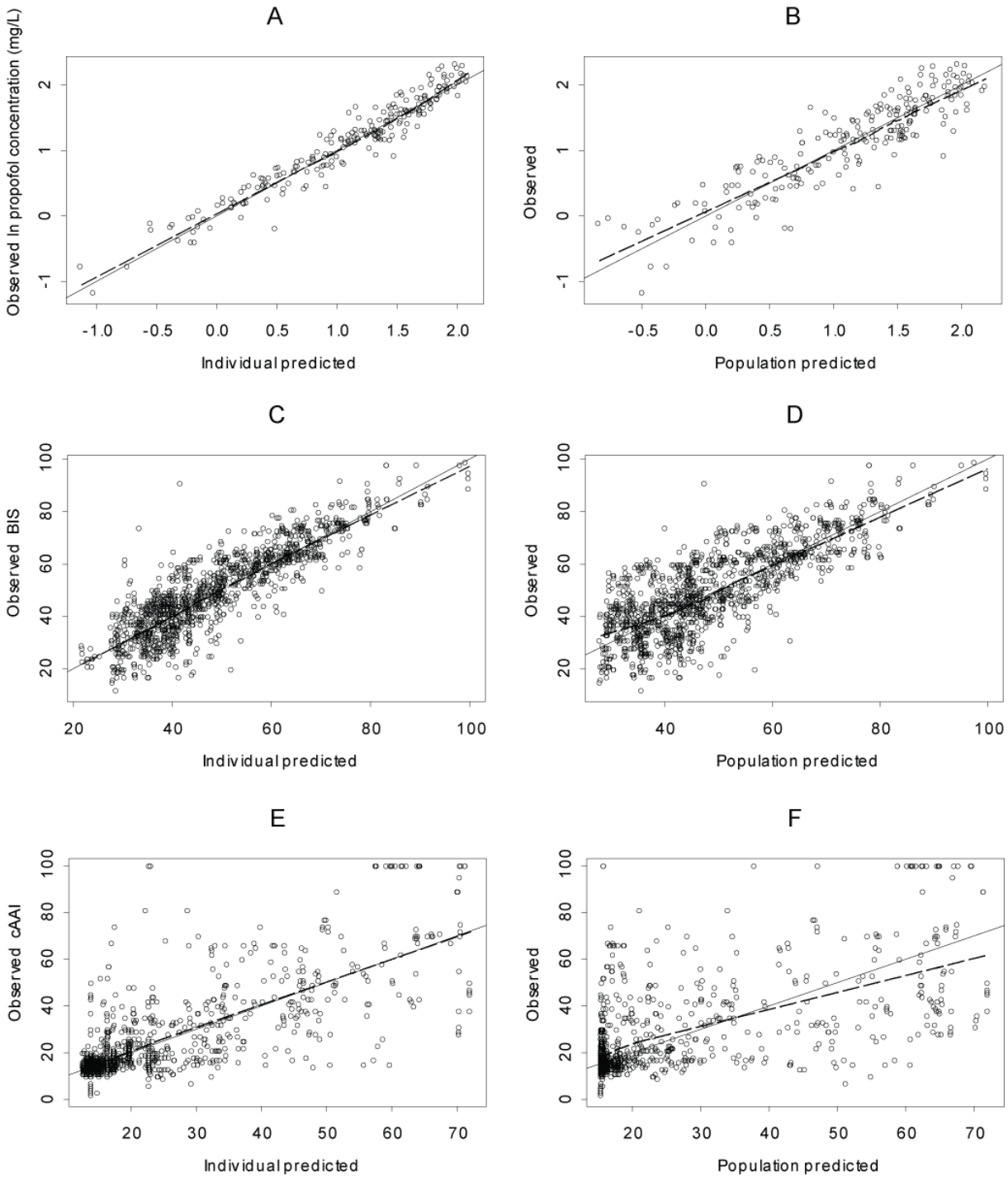

Figure 1 *Diagnostic plots of the final pharmacokinetic (A and B) and pharmacodynamic models using Bispectral Index (BIS; C and D) and composite A-Line ARX Index (cAAI; E and F), including (left) observations versus individual-predicted propofol concentrations, and (right) observations versus population concentrations. The dashed line indicates the trend line, the solid line represents the line of identity, x = y*

Table 1 Patients' and data characteristics (n = 14)

Gender (M / F)	2 / 12
Age (years)	14.7 (9.8 - 20.1)
Bodyweight (kg)	51 (36.6 - 82)
Height (cm)	162.5 (142 - 183)
BMI (kg/m^2)	18.7 (16.3 - 37.9)
BMI for children (kg/m^2)	39.0 (10.0 - 99.0)
BSA (m^2)	1.54 (1.20 - 1.85)
Number of blood samples per patient	16 (6 - 22)
Number of BIS events per patient	100 (60 - 141)
Number of cAAI events per patient	97 (56 - 141)
Duration of propofol infusion (minutes)	410.0 (200 - 460)
Length of wake-up test (minutes)	21.5 (7.6 - 42.4)
ROC after propofol infusion (minutes)	52.2 (22.6 - 116.33)

F = Female; BMI = Body Mass Index; BSA = Body Surface Area; M = Male; BIS = Bispectral Index; cAAI = composite A-Line ARX Index; ROC = Return of consciousness. The length of wake-up test is defined as the length of time propofol infusion was stopped during the intraoperative wake-up test. Data are presented as a median (minimum-maximum).

The inclusion of two different k_{eo}'s for bolus and infusion in the model resulted in a significant decrease of 226 points in objective function ($p < 0.001$). The EC_{50} was 3.17 mg/l (CV = 28%) for BIS and 1.41 mg/l (CV = 38%) for cAAI. No covariates could be identified although there was a trend towards an influence of age on the EC_{50} ($p > 0.05$). When a separate EC_{50} for the youngest individual was estimated, the objective function decreased ($p < 0.001$). The Hill coefficient was not significantly different from 1 (CV = 30%) for BIS, and 5.3 for cAAI. The population parameters of the basic and final pharmacodynamic models are reported in Table 3. The bootstrap validation (300 replications) confirmed the stability of the model. Results from the numerical prediction distribution errors computation demonstrated that the graphs did not show any trend, although the normality tests did not entirely confirm a normal distribution of errors, as previously described by Comets *et al*.[17] Figures 1 C, D, E and F show the diagnostics of the final model. In Figures 2 B and 2 C, BIS and cAAI values versus time in a representative adolescent are presented. Figures 1 and 2 show that the model describes both BIS and cAAI observations in an adequate manner during induction, wake-up test, reinduction and emergence of anesthesia until return of consciousness. However, during the wake-up test, the final pharmacodynamic model was not entirely able to describe the cAAI observations (Figure 2).

In Figure 3 the concentration effect relationship for BIS and cAAI is presented, with an EC_{50} of 3.17 mg/l and a Hill coefficient of 1 for BIS, and an EC_{50} of 1.14 mg/l and a Hill coefficient of 5.3 for cAAI. In Figure 4 the individual propofol concentration - response curves for BIS and cAAI are presented.

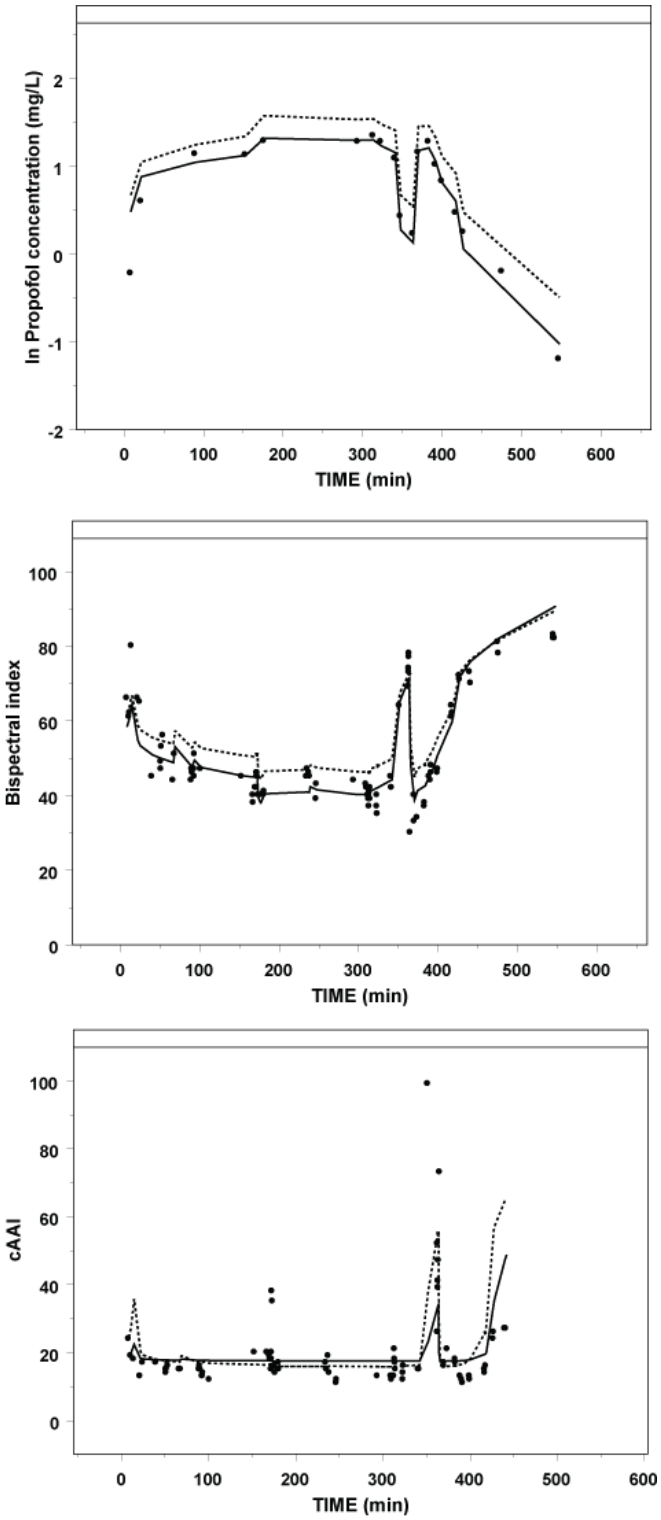

Figure 2 *Log transformed propofol concentrations (A), Bispectral Index (BIS; B) and composite A-Line ARX Index (cAAI; C) versus time (minutes) in a representative adolescent. The solid circles represent the observations, the solid lines represent the individual predicted concentration or depth of anesthesia and the dashed line represents the population predicted concentration or depth of anesthesia.*

Table 2 Parameter estimates of the basic pharmacokinetic model and the stability of the parameters using bootstrap validation

Parameter	Covariate Model Mean (CV%)	Basic Model (final) Mean (CV%)	BS Basic Model Mean (CV%)
Fixed effects			
CL (l/min)	1.33 (5.1)	1.37 (7.0)	1.38 (5.1)
Q (l/min)	1.14 (10.2)	1.15 (29.4)	1.16 (44.1)
V_1 (l)	3.59 (30.4)	3.6 (10.2)	3.45 (11.3)
V_2 (l)	77.2 (5.1)	76.8 (5.0)	77.3 (5.0)
Interindividual variability			
ω2 of CL in %	16.4 (24.0)	22.1 (28.7)	21.4 (25.7)
Residual error			
σ2	18.8 (11.9)	19.0 (11.9)	18.4 (12.5)
Performance measures			
(-2LL)	-463	-452	-464.7

BS = bootstrap validation; CL = clearance; Q = intercompartmental clearance; V_1 = central volume; V_2 = peripheral volume; ω^2 = variance, the square root of the exponential variance of η-1 is the percentage of the interindividual variability in the pharmacokinetic parameters; σ^2 = proportional individual variance; -2LL = objective function. Values in parentheses are coefficient of variation (CV) of the parameter values.

Simulations

The simulations using the PK/PD model demonstrated that, for a BIS between 40 - 50, adolescents should receive, after an induction dose of 175 mg, 480 mg/h during the first 30 minutes, 420 mg/h during one h, followed by 350 mg/h. cAAI values are then expected to be 16. After the wake-up test, a bolus dose of 75 mg propofol is recommended, followed by 350 mg/h for reanesthesia (Figure 5).

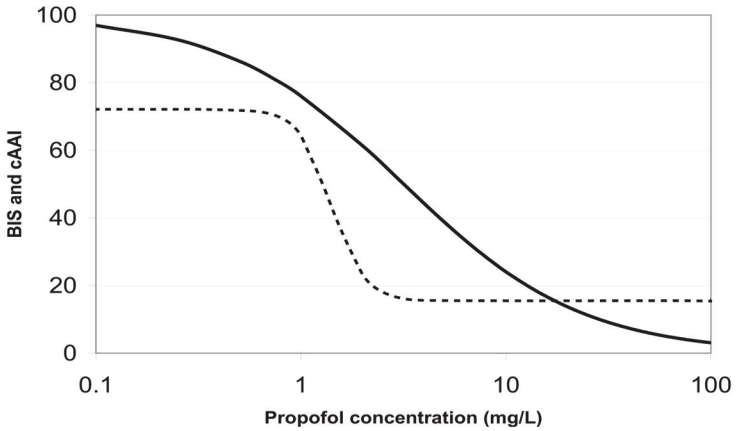

Figure 3 *The concentration effect relationship for Bispectral Index (BIS; solid black line) and composite A-Line ARX Index (cAAI; dashed line) as a function of propofol concentration (mg/l). BIS = Bispectral index; cAAI = composite A-Line ARX index; EC_{50} = propofol concentration (mg/l) at half maximum effect. The EC_{50} for cAAI is estimated at 1.41 mg/l propofol with a Hill coefficient of 5.3. The EC_{50} for BIS is estimated at 3.17 mg/l propofol with a Hill coefficient of 1.*

Table 3 Parameter estimates of the basic and final pharmacodynamic BIS and cAAI models and the stability of the parameters using the bootstrap validation (300 times)

Parameter	Basic Model Mean (CV%)	Final Model Mean (CV%)	BS Final Model Mean (Final/BS*100%)
Fixed effects BIS and cAAI			
k_{e0} (min^{-1})	0.089 (12.4)		
k_{e0} bolus (min^{-1})		0.066 (12.4)	0.066 (100.1)
k_{e0} infusion (min^{-1})		0.25 (12.8)	0.24 (100.3)
Fixed effects BIS			
Baseline	100 FIX	100 FIX	100 FIX
E_{max}	100 FIX	100 FIX	100 FIX
EC_{50} (mg/l)	3.44 (6.8)	3.17 (7.9)	3.22 (98.6)
Gamma	1 FIX	1 FIX	1 FIX
Fixed effects cAAI			
Baseline	70.3 (7.3)	72.1 (9.4)	72.0 (100.2)
E_{max}	54 (8.3)	56.5 (11.4)	56.4 (100.1)
EC_{50} (mg/l)	1.78 (11.2)	1.41 (13.3)	1.45 (97)
$EC_{50,individual}$ (mg/l)		4.26 (7.4)	4.08 (104.5)
Gamma	6.71 (52.2)	5.3 (27.7)	6.02 (88.1)
Interindividual variability BIS (%)			
EC50 (mg/l)	26.9 (46.1)	27.8 (53.2)	27.8 (99.8)
Gamma	37.1 (40.0	29.6 (40.1)	30.1 (96.7)
Interindividual variability cAAI (%)			
E_{max}	7.6 (49.0)	6.0 (53.6)	5.75 (107.7)
EC_{50} (mg/l)	52.4 (35.1)	37.9 (36.6)	37.3 (102.9)
Residual error			
ε_1, BIS units	8.4 (9.8)	7.8 (10.1)	7.8 (101.6)
ε_2, cAAI units	12.6 (23.5)	12.3 (24.9)	12.2 (101.7)
Performance measures			
(-2LL)	15070.6	14833.5	14853 (99.9)

BS = bootstrap validation; BIS = Bispectral index; cAAI = composite A-Line ARX index; Gamma = the Hill coefficient representing the steepness of the concentration versus response relation; EC_{50} = propofol concentration (mg/l) at half maximum effect; $EC_{50,\ individual}$ = propofol concentration (mg/l) at half maximum effect of the youngest adolescent; E_{max} = maximum possible effect of propofol on BIS or cAAI; k_{e0}, = first-order equilibration constant; k_{e0} bolus = first-order equilibration constant during the bolus; k_{e0} infusion = first-order equilibration constant during the infusion; interindividual variability = square root of the exponential variance of η minus 1; ε1 = residual error additive; ε2 = residual error additive; -2LL = objective function. Values in parentheses are coefficient of variation (CV) of the parameter values.

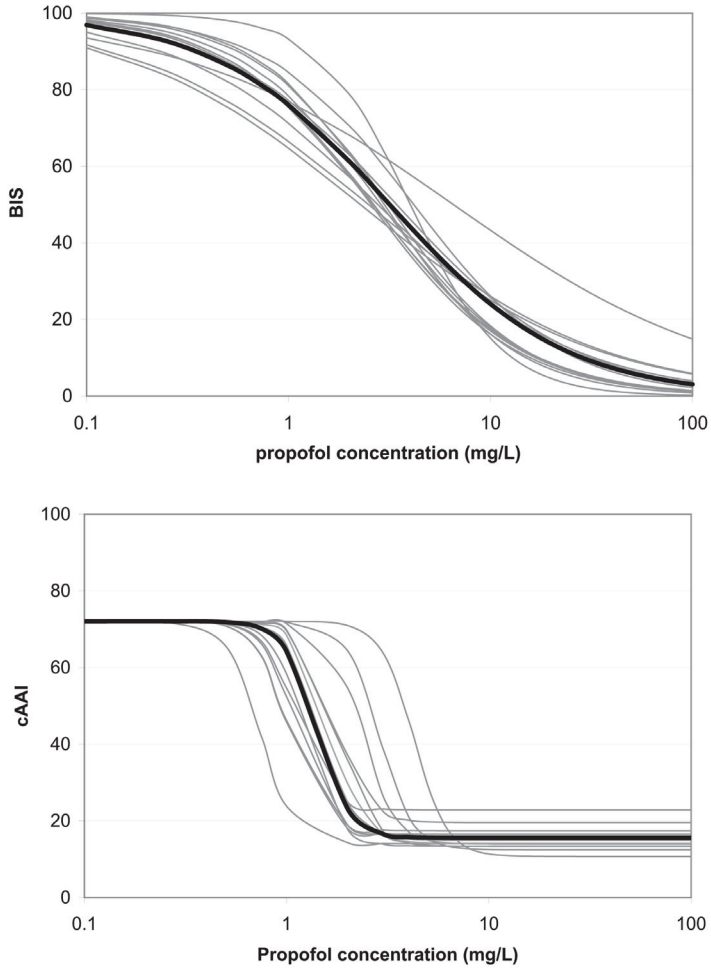

Figure 4 *Individual propofol concentration - response curves (thin lines) for Bispectral Index (BIS) and composite A-Line ARX Index (cAAI). The thick black lines represent the population concentration – response curves.*

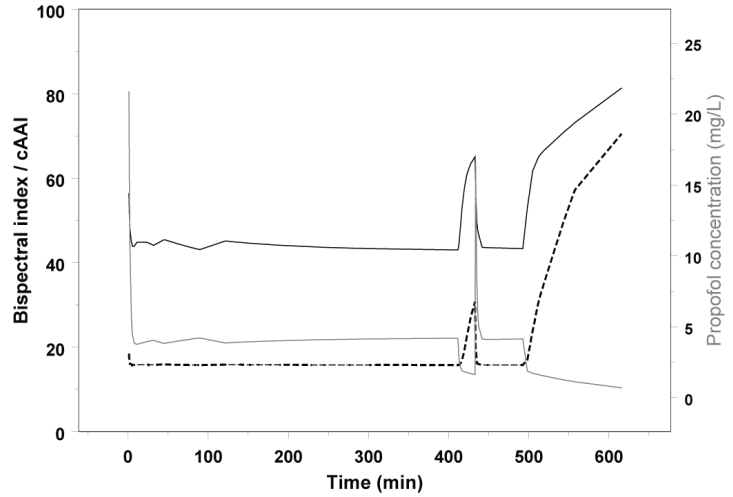

Figure 5 *Model based predictions of Bispectral Index (BIS; solid black line) and composite A-Line ARX Index (cAAI; dashed line) values and propofol concentrations (grey line), following the recommended propofol dosing of 175 mg induction bolus, followed by 480 mg/h during the first 30 minutes, 420 mg/h during one h and 350 mg/h until the wake-up test. After the wake-up test, 75 mg propofol, followed by 350 mg/h for reanesthesia, is administered*.

DISCUSSION

To optimize propofol dosing for adequate anesthesia during propofol-remifentanil anesthesia in adolescents undergoing idiopathic scoliosis surgery, a population model for propofol pharmacokinetics and pharmacodynamics was described, using BIS and cAAI as pharmacodynamic endpoints.

Our pharmacokinetic model for propofol in adolescents adequately described the observations for induction of anesthesia, the intraoperative wake-up test, reinduction and emergence from anesthesia. It showed little variance for all pharmacokinetic parameters. The central volume and clearance found in this study (3.6 l and 1.37 l/min) are consistent with previously reported findings in adults during propofol-remifentanil anesthesia. On the other hand, our estimation of the peripheral volume of distribution (76.8 l) was larger than the earlier reported volume of 31.7 l.[2,3] This larger estimate may be a result of longer duration of propofol administration in our study, during which more extensive tissue distribution may have occurred.

Also the pharmacodynamic model adequately described BIS and cAAI observations during induction of anesthesia, the intraoperative wake-up test, reinduction and emergence from anesthesia. In the final pharmacodynamic model different EC_{50}'s and Hill coefficients were estimated for BIS and cAAI. For cAAI, the EC_{50} was smaller (1.41 mg/l versus 3.17 mg/l), and the Hill coefficient was steeper (5.3 versus 1) compared to BIS, indicating that cAAI is more sensitive to differences in propofol concentration than BIS. The steeper Hill coefficient for cAAI supports our clinical observation that the awaking from propofol-remifentanil anesthesia was associated with an 'on-off' cAAI response rather than a gradual progression to awake levels, as previously described by White *et al*.[19] Because of the relatively small amount of available awake data points in the present study, it was not possible to estimate baseline and E_{max} for BIS. Therefore, in the final pharmacodynamic model both parameters for BIS were fixed to 100. For cAAI, baseline was estimated at 72.1, and E_{max} at 56.5. Interestingly, fixing the E_{max} for cAAI to 100 gave a similar EC_{50} value, indicating a minimal influence on the EC_{50}.

Interestingly, limited interindividual variability was observed in the pharmacokinetic and pharmacodynamic analysis. We do not have an explanation for this observation. Yet it seems an important deviation from previous published data that needs to be explored in future studies. For the time being, however, it would seem that a bodyweight-independent propofol dosing regimen is suitable for this specific age group.

Although the pharmacodynamic model in general correctly predicted BIS ad cAAI values during emergence from anesthesia, the model was not entirely able to describe the peak

cAAI observations (Figure 2 C). A possible explanation is that patients during the wake-up test were, apart from the fact that surgery continued, stimulated by verbal commands to move their fingers and toes, whereas after the procedure patients spontaneous recovery was awaited. As these intraoperative stimuli during the wake up test were not accounted for in the final PD model, model based predictions following the recommended propofol dosing regimen will therefore predict cAAI and BIS values without a stimulus to move legs or arms and may therefore underestimate peak cAAI values (Figure 2 C) and to a lesser extent BIS values (Figure 2 B) if the wake-up test is accompanied by verbal stimulation.

No covariates for the pharmacokinetics nor the pharmacodynamics of propofol could be identified in the present study, although age tended to influence the EC_{50} ($p > 0.05$). There was insufficient statistical power to estimate a continuous influence of age on EC_{50}. Yet, when a separate EC_{50} for the youngest subject was estimated, a significant decrease in the NONMEM objective function was observed. Future studies in younger individuals will have to explore whether age is of influence to the EC_{50}.

The k_{e0} for infusion (0.25 min^{-1}) in the present study is consistent with that reported in adults[20,21] whereas the k_{e0} for bolus (0.066 min^{-1}) is smaller than that previously reported. Comparison with other studies may be misleading, however, as estimation of the k_{e0} may depend on many factors, such as dose, rate of administration, study design and the underlying pharmacokinetic model used.[9,20,21] We do think that our estimates for this parameter in adolescents are valid. For one thing, because the k_{e0} for bolus and infusion could be estimated from data during induction of anesthesia, intraoperatively during a prolonged infusion time (6 - 8 hours), a wakeup test, reinduction of anesthesia and spontaneous return of consciousness. Furthermore, validity is confirmed by the results of the internal validations of the model.

According to clinical practice, propofol and remifentanil dosing in the present study was based on linear bodyweight functions, and both agents were adjusted at the discretion of the anesthesiologist. Thus, propofol dosing widely varied between all individual patients (e.g. intraoperative range 300 - 700 mg/h). Furthermore, the median duration of the wake-up test was 21.5 minutes and the period until return of consciousness 52.2 minutes. Comparing the simulated dosing regimen based on our PK/PD model to the doses used during the study, the new dosing regimen will overall reduce continuous intraoperative propofol infusion by 100 mg/hour during 2.5 to 6.5 hours (from 450 to 350 mg/h). This seems important as BIS values intraoperatively in general were very low, with values approaching burst suppression. Based on the simulations, the spontaneous return of consciousness during the intraoperative wake-up test (without stimulus to move arms or legs) is then estimated to take 21 minutes. As in this simulation model no external stimuli were incorporated, the duration of the wake-up test is therefore expected to be shorter. A

prospective study evaluating the new dosing regimen will have to demonstrate whether the recommended dosing regimen will actually result in shorter duration of the wake-up test and earlier return of consciousness.

Based on PK/PD population modeling, our results demonstrate that a bodyweight independent propofol dosing regimen is suitable during propofol-remifentanil anesthesia in adolescents. Future studies will need to confirm whether bodyweight is indeed not a covariate for propofol dosing in adolescents**.** As a recent review by Tod *et al*. demonstrated that advanced validation of population models was carried out in only 16% of pediatric studies,[22] we would like to emphasize that our PK/PD models were internally validated using advanced techniques.

In conclusion, based on our population pharmacokinetic and pharmacodynamic model, to achieve a BIS between 40 - 50, adolescents should receive, after an induction dose of propofol of 175 mg, a propofol infusion rate of 480 mg/h during the first 30 minutes, 420 mg/h during one hour, followed by 350 mg/h until the intraoperative wake-up test. cAAI values are then expected to be 16. After the wake-up test, we recommend a bolus dose of 75 mg propofol, followed by 350 mg/h for reanesthesia.

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8

General discussion

Prologue

The studies in this thesis aimed to improve the knowledge on intraoperative awareness, monitoring depth of anesthesia, and pharmacokinetic and pharmacodynamic profiles of different anesthetics in children. This final chapter evaluates the main findings in relation to other studies and provides suggestions for further research.

Intraoperative awareness in children: is it for real?

The possibility of intraoperative awareness in children was long ignored for a variety of reasons. For one, children's testimonies were considered to be unreliable. Furthermore, the general reluctance of children to report adverse events may have added to a perception that awareness occurs rarely in children. Alternatively, it may have been thought to be no different from awareness in adults and thus requiring no particular attention.[1] Attitudes have changed, however, and the possibility of intraoperative awareness in children is now increasingly recognized. In a recent survey of pediatric anesthesiologists through the British and French Pediatric Anesthesia Societies, 60% of the respondents indicated that awareness is a problem in children and 27% reported to have encountered at least one case of awareness. Interestingly, the majority underestimated the incidence and indicated it was about 1:1000.[2] So far, however, no more than two large studies have addressed this problem.[3,4]

Two illustrative cases of intraoperative awareness in our hospital, described in **chapter 2,** triggered a systematic evaluation to study the incidence of awareness in children aged 5 - 18 years in our hospital. Definite awareness was identified in 6 out of 928 children (0.6%), but specific risk factors could not be identified. The 0.6% incidence is comparable with the incidences reported in the earlier mentioned large studies (around 1%),[3,4] and appears to be higher than that reported in adults (0.1 - 0.2%) undergoing anesthesia for non-high risk surgery.[5,6] (**chapter 3**)

Importantly, although no formal post hospitalization behavior follow-up was applied and the number of awareness cases was small, the children who reported awareness in our study did not seem to be traumatized on the short term. In both earlier studies, too, the awareness children did not seem to be upset about their experiences.[3,4] One prospective follow-up study in seven children aged 8 - 16 years found no evidence for post-traumatic stress disorder one year after an episode of awareness.[7] These children claimed not to have experienced major pain, terror or helplessness during surgery. Although the sample size in that study is small, it would seem that children suffer less psychological sequelae than adults following intraoperative awareness. These children reported less frightening intra-operative sensations and may be assumed to have had less understanding of the anesthesia procedure as compared with adults. Both factors may have influenced their appraisal of their awareness and have protected them from the full impact of this potentially traumatic

experience.[8] Nevertheless, it is still possible that some children will develop posttraumatic stress disorder, judging from a case series of adults with post traumatic stress disorder after awareness under anesthesia. Some of these adults had experienced awareness as a child.[9] A follow-up study in our institution is planned to explore the long-term consequences of awareness.

The nature of awareness in children is often different to that described in adults. In adults it is a varied experience ranging from intense pain associated with helplessness and immobility to just vague recollections of beeping noises. In children, awareness is in many cases not associated with paralysis and there are no obvious signs of light anesthesia, mishap or intentional underdosing. Yet, it is also possible for children to experience 'adult-like' awareness. This was demonstrated in **chapter 2** through the occurrence of paralysis, helplessness and anxiety. No psychological symptoms for posttraumatic stress disorder were found in these children. Children's awareness experiences therefore seem to be more benign, with fewer negative thoughts.

The crucial element in awareness studies is the manner in which awareness is revealed and ascertained. In all studies of intraoperative awareness in children and adults so far there is reason for concern on this point. The diagnosis may be subjective, repeated questioning could have induced false memories, or patients would confuse memories of events in the operating room and with those in the recovery room. Confirming that a recollection is true awareness relies on the richness of memory and inevitably involves a subjective assessment. Assessing awareness in children can be difficult as children are still developing their memory consolidation and search strategies. Between the ages of 4 and 8 years, however, children gain skills in encoding and retrieving memory, mainly due to steadily increasing myelination and speed of processing, the adoption of better mechanisms of memory management, and greater overall understanding.

When interviewed, open ended, complex or temporally inconsistent questions may confuse children and as a consequence awareness can be missed. Besides, children have poorer source monitoring and are more likely to confuse the origin or temporal context of the memory. This is particularly so if leading questions are used. The interview technique used might therefore be responsible for possible under or over reporting.[1]

Our results indicate that children may not report awareness spontaneously as only one of the six patients reported this to the medical staff. It would be the best strategy, therefore, to ask all children from 5 years of age for awareness recollections directly after recovery from anesthesia. For these interviews, specialized interviewing skills[1] and semi-structured questionnaires, adapted to cognitive abilities, are recommended.

How to deal with it?

In 2004, the US Joint Commission on Accreditation of Healthcare Organizations (JCAHO) set forth recommendations to prevent and manage intraoperative awareness in patients of all ages, both adults and children.[10] Specific recommendations included: identification of individuals at higher risk for intraoperative awareness, appropriate follow-up after general anesthesia, and identification, management and, if appropriate, referral of those who reported awareness. This Sentinel Event Alert also referred to children, which stirred up the pediatric anesthesia community. The recommendations clearly were seen lacking any scientific background related to intraoperative recall and the role of monitoring anesthesia depth in the care of infants and children.

In the meantime we have to come to realize that children indeed may experience awareness, as pointed out above. Evidence for the different causes and consequences of awareness in children is now beginning to emerge.[3,4] As numbers of cases are still relatively small, quantifying the risk of psychological sequelae is virtually unrealizable. Consequently, evidence based management of awareness in children is almost impossible. Nevertheless, some recommendations can be made on how to manage awareness in children. First, it is important to show compassion to all children who have experienced awareness, and to take time to reassure both them and their parents, and suggest psychological support if necessary.[1,8] Second, adverse consequences may emerge not until at a later stage, so parents should be informed about this possibility and the child should be followed. Third, we must not overlook the possibility that the anesthesiologist may also need debriefing. Finally, it is most important that health care providers are aware of this complication, so that suspected awareness cases can be adequately treated after referral to the anesthesia department.

It has been suggested that the anesthesiologist should inform patients at risk for awareness about the potential occurrence. This practice should be restricted, however, to adults at a relatively high risk, for example those undergoing cardiac surgery and trauma patients.[11] Considering their young life experience and different expectations of anesthesia, it is inadvisable to alarm children.[12]

How to prevent it?

Prevention of awareness should be a priority for all anesthesiologists. In this regard, autonomic responses such as tachycardia, hypertension, sweating, lacrimation, and pupillary dilatation, are unreliable indicators of depth of anesthesia. As paralyzed patients cannot express themselves, the use of neuromuscular blockers should be avoided whenever possible.[12] This, however, does not guarantee prevention of awareness, as our study in **chapter 3** has identified patients with awareness experience under non-relaxant anesthesia.

The first major step in the prevention of awareness in children is to continue to educate anesthesiologists about this complication. Furthermore, good knowledge of pharmacology in

children is advisable in order to maintain an adequate concentration of anesthetics. Yet, 'safe' concentrations of inhalational or intravenous hypnotic drugs have never been established. As short-acting agents are often used in pediatric anesthesia, close monitoring and frequent check of vaporizers and pumps, just as in adults,[11] is recommended. Moreover, because hypnotic drugs are rapidly redistributed in children as a result of their high cardiac output, supplemental doses of these agents should be given before initiating strong stimuli such as laryngoscopy and intubation.[4,12] End-expiratory anesthetic gas concentration should be monitored routinely.[12]

There is some evidence that BIS monitoring reduces awareness in adults at high risk.[13] A recent study, however, demonstrated that BIS-guided anesthesia in patients with high risk of awareness did not result in a lower incidence of awareness than did end-tidal agent measurement based anesthesia.[14] This study led to significant controversy on this subject.[15-18] Current evidence in adults is insufficient to justify a standard, guideline, or absolute requirement that depth of anesthesia monitors should be used to reduce the occurrence of intraoperative awareness in high-risk patients undergoing general anesthesia.[11] In children, it is at this moment unclear whether EEG monitoring could prevent awareness. The nature of awareness in children is quite different from that in adults, and therefore separate trials of awareness prevention strategies (including EEG monitoring) are needed.

Will monitoring depth of anesthesia help?

Intraoperative awareness cannot be measured during the intraoperative phase of general anesthesia, because the recall component of awareness can only be determined postoperatively by obtaining information directly from the patient. Therefore, the intraoperative assessment of anesthesia brain effect is crucial to ensure anesthesia is adequate. As pointed out above, one reason to monitor depth of anesthesia is the prevention of awareness. Other desirable aspects are the prevention of too deep levels of anesthesia, minimization of dosing of anesthetics, more rapid recovery from anesthesia, shortening of recovery time, and ideally reduction of costs.

Applications outside the operation room include the use of brain function monitors for adequate and safe procedural sedation and to guide sedation in the intensive care unit.[19,20] As the pharmacology of anesthetics changes with children's ages, it is plausible that depth of anesthesia monitors could guide accurate drug delivery in children for both inhalational and intravenous anesthetics. However, in infants under the age of 6 months, these monitors should be used very cautiously.[21] Furthermore, there is growing evidence that these monitors shorten recovery times and decrease anesthetic drug consumption in children.[22-24] Whether monitoring depth of anesthesia could prevent the occurrence of awareness in

children needs to be evaluated in a separate, well-powered clinical trial before these monitors can be advocated as standard of care in children.

Which monitor to choose?

In this thesis, both the BIS and the AEP/2 monitor were studied in children using indirect measures such as the University of Michigan Sedation Scale (UMSS) and anesthetic drug concentration during three different settings:

1. isoflurane anesthesia with caudal block for inguinal hernia surgery (**chapter 4**),
2. isoflurane anesthesia for cardiac catheterization (**chapter 5**), and
3. propofol-remifentanil anesthesia for scoliosis surgery (**chapter 6**).

In all three settings, the two monitors performed equally in distinguishing different UMSS levels. Furthermore, a dose-response relationship was described for BIS, cAAI and end-tidal concentrations of isoflurane. Although BIS was better correlated to anesthetic concentrations than cAAI, there is at this stage too little evidence to suggest any one device is substantially superior to any other.

What about total intravenous anesthesia?

Propofol is often used in children for induction and maintenance of anesthesia because of desirable pharmacokinetic and pharmacodynamic properties. Nevertheless, large inter- and intraindividual variability is often demonstrated in clinical practice. Next to this, real time monitoring of propofol blood concentrations is not possible. Consequently, adequate propofol dosing is often uncertain, leading to possible over or under dosing potentially responsible for prolonging delay of recovery or perioperative awareness. Additional brain function monitoring is therefore recommended during total intravenous anesthesia to individualize propofol dosing. In **chapter 7** a new PK/PD based dosing regimen for propofol was developed to prevent inadequate anesthesia during adolescent scoliosis surgery. BIS and cAAI were used as PD endpoints. A prospective study evaluating the new dosing regimen will have to demonstrate whether our recommended dosing regimen will actually result in shorter duration of the wake-up test and earlier return of consciousness.

What to do next?

As we have seen, evidence has emerged that intraoperative awareness under general anesthesia is an important clinical problem in pediatric anesthesia. Although this thesis has added some evidence on incidence, causes and consequences, much work still needs to be done. Further progress in the identification, prevention or management of intraoperative awareness in children first of all requires efforts to clarify the possible causes. A logical first step is including awareness as an outcome measure of anesthetic procedures in order to allow future meta-analysis. Every single case can help add to our understanding of the causes of awareness. Besides, multi-center studies will have to throw further light on the causes of this complex phenomenon. Once we have sufficient understanding of the possible

causes, the next step would be finding ways to prevent this complication as much as possible.

Next to the causes, we need to learn more about the psychological consequences of awareness, preferably on the longer term. Improved understanding could lead to evidence-based management of this complication. Studies on monitoring of anesthesia depth as a means of preventing awareness in children are recommended. As awareness is a rare complication, a large sample size is needed to demonstrate a reduction in the incidence from 1.0% to 0.1%. A multi-center approach is therefore indispensable.

Several depth of anesthesia monitors have been developed in the past few years. Of these monitors, BIS remains the most widely studied. Nevertheless, the number of pediatric studies is still limited. Several studies, though, have demonstrated an emerging role for the use of BIS in children older than 2 years. At present the use of BIS in infants cannot be recommended however. For the younger children it appears to be necessary to develop a special "neonatal BIS algorithm". Next to BIS, also other depth of anesthesia monitors should be studied more extensively in children. Furthermore, randomized controlled pediatric trials looking at other relevant outcome parameters than the prevention of awareness, such as anesthetic requirements or speed of recovery, are urgently needed.

As depth of anesthesia indices are regarded as pharmacodynamic measures of cerebral drug effect, they may be considered as an integral part of anesthetic pharmacology. Finally, new PK/PD studies integrating other potential relevant factors, such as pharmacogenetic profiles of patients, should lead to optimization of anesthetics administration and thus avoid potential deleterious consequences of too light or too deep levels of anesthesia. There is every reason to be confident that the findings from all such studies will even further improve pediatric anesthesia excellence.

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9

Summary

Samenvatting

SUMMARY

In view of the potential hemodynamic side effects of anesthetics, the act of balancing between deep and light anesthesia is one of the major challenges in pediatric anesthesia. Overdosing and underdosing have both clinical and economic consequences. Overdosing results in a deep hypnotic state which may lead to hypotension, longer wake-up times, and longer stay in the recovery room. Underdosing, on the other hand, may lead to hypertension, tachycardia, and even awareness. Awareness is defined as explicit recall of events during a procedure performed under general anesthesia. To avoid potential problems from under- and overdosing, children should be administered individualized doses of anesthetics to maintain optimal levels of anesthesia. The studies in this thesis aimed to improve the knowledge on intraoperative awareness and monitoring of depth of anesthesia in children. Furthermore, in response to the clinical need for safe and adequate dose administration, pharmacokinetics and pharmacodynamics of different anesthetics were studied. Better understanding of these effects might prevent too deep or too little levels of anesthesia.

Awareness in children

In **Chapter 2** two cases of awareness are described, which triggered a systematic approach to study the incidence of awareness in children in our hospital. In **chapter 3** the incidence of awareness in our hospital is evaluated. Data from 928 consecutive pediatric patients, aged 5 - 18 yr, were collected prospectively over a 12-month period. Interviews using a structured questionnaire were scheduled at three time points: within 24 hours after the operation, and 3 - 7 and 30 days postoperatively. Twenty-six reports of suspected cases were sent to four independent adjudicators with long term experience in pediatric anesthesia. For six cases they were unanimous in the conclusion that the case could be classified as a true awareness case, resulting in a 0.6% incidence. No specific causes for the occurrence of awareness were identified. Auditory and sensory perceptions were the sensations most reported by these six children. Pain, anxiety and paralysis were less often mentioned. The children in general did not report awareness as stressful. We concluded that the results from our study add to the validity of the previously reported findings. Intraoperative awareness during pediatric anesthesia therefore appears to be a phenomenon with an estimated incidence around 10 cases per 1000, irrespective of geographic location, institution or anesthetic practices.

Monitoring depth of anesthesia in children

Reliable monitoring of depth of anesthesia could help anesthesiologists to maintain optimum levels of anesthesia and prevent problems caused by underdosing and overdosing. Many anesthesiologists rely on somatic signs (motor responses, changes in respiratory pattern) and autonomic signs (tachycardia, hypertension, lacrimation, sweating) to guide the dosage of anesthetic agents. However, these clinical signs do not always correlate with

depth of anesthesia and are often masked by the use of drugs such as neuromuscular blockers. A number of EEG-processed monitors have been proposed to objectively measure the hypnotic state of a patient. In this thesis we studied the BIS monitor (BIS; index: BIS), and the Auditory Evoked Potential Monitor (AEP; index: cAAI). Anesthesia depth is a poorly defined, abstract concept and there is no gold standard measure of anesthetic depth with which to compare indices derived from depth of anesthesia monitors. This is why indirect measures such as anesthetic drug concentration and sedation scales must be used.

In **chapter 4** the performances of BIS and cAAI in distinguishing different hypnotic states, as evaluated by the University of Michigan Sedation Scale (UMSS), were compared in children and adolescents during propofol-remifentanil anesthesia for scoliosis surgery with an intraoperative wake-up test. Furthermore, postoperative explicit recall was evaluated. Twenty patients (aged 10 - 20 years) were enrolled. During the wake-up test they were instructed to remember a color. Patients were interviewed for explicit recall. We demonstrated significant differences between the monitors in distinguishing different levels of anesthesia, but these differences do not appear to be clinically meaningful. We therefore concluded that both monitors performed equally. Both indices increased during the wake-up test, indicating a higher level of consciousness. No explicit recall was demonstrated.

In **chapter 5** the performances and reliabilities of BIS and cAAI in distinguishing different hypnotic states in children, as evaluated with the UMSS, were compared. Thirty-nine children (aged 2 - 16 years) scheduled for elective inguinal hernia surgery were studied. For all patients, standardized isoflurane based anesthesia was used. With respect to indicate consciousness or unconsciousness, 100% sensitivity was reached at cut-off values of 17 for BIS and 12 for cAAI. 100 % specificity was associated with a BIS of 71 and a cAAI of 60. To ascertain consciousness, BIS values greater than 78 and cAAI values above 52 were required. We concluded that BIS and cAAI were comparable indicators of depth of hypnosis in children. Both indices, however, showed considerable overlap for different clinical conditions.

In **chapter 6** the performances of BIS and cAAI in distinguishing different levels of anesthesia during cardiac catherization were compared in twenty children aged 3 - 16 years, using the UMSS as gold standard. When comparing BIS and cAAI in children with the level of consciousness as defined by the UMSS, both indices performed equally well.

Pharmacokinetics and pharmacodynamics of anesthetics in children

In **Chapter 6** the dose-response relationships between BIS, cAAI and non-steady state end-tidal concentration of isoflurane in 20 children undergoing cardiac catherization were studied. The concentration-relationship between isoflurane end-tidal concentrations versus BIS and cAAI was described using an inhibitory sigmoid E_{max} model. The EC_{50} for BIS was

1.0%, with a Hill coefficient of 2.6. For cAAI, the EC_{50} was 0.35%, with a Hill coefficient of 12.1.

In **chapter 7** pharmacokinetics and pharmacodynamics of propofol during standardized propofol-remifentanil anesthesia to avoid inadequate anesthesia and predict return of cognition, were characterized in 14 adolescents, using BIS and cAAI as pharmacodynamic endpoints. NONMEM was applied for population pharmacokinetic and pharmacodynamic modeling. No covariates were identified. To achieve BIS values between 40 and 50, we recommend an induction dose of 175 mg propofol, 480 mg/h continuous propofol infusion during the first 30 minutes, 420 mg/h during one hour, followed by 350 mg/h until the wake-up test. cAAI values are then expected to be 16. For reanesthesia after a wake-up test, a bolus dose of 75 mg propofol is recommended, followed by 350 mg/h.

In **Chapter 8** the results of our studies are discussed with a view on future perspectives.

SAMENVATTING

Omdat de toediening van anesthetica kan leiden tot verstoring van de hemodynamiek, is het vinden van het juiste omslagpunt tussen te diepe en te lichte anesthesie één van de grote uitdagingen in de kinderanesthesie. Overdosering kan leiden tot een diepe hypnotische staat en hypotensie. Voorts kan de uitleiding van anesthesie langer duren, en heeft de patiënt meer tijd nodig om bij te komen. Onderdosering daarentegen kan leiden tot hypertensie, tachycardie en "awareness". Bij awareness – of wakker worden tijdens een operatie – herinnert men zich duidelijk bepaalde gebeurtenissen tijdens de operatie, ondanks dat men onder algehele narcose was gebracht. De gedachte leeft dat dit soort problemen kan worden voorkomen door de gewenste dosering van anesthetica per patiënt te bekijken. Een deel van de onderzoeken in dit proefschrift is uitgevoerd om meer inzicht te krijgen in deze awareness bij kinderen. De andere onderzoeken houden daar verband mee. Die gaan over het bewaken van de diepte van anesthesie bij kinderen, alsmede de zogenaamde farmacokinetische en farmacodynamische eigenschappen van verschillende anesthetica.

Awareness bij kinderen

In **hoofdstuk 2** zijn de ervaringen met awareness van twee kinderen beschreven. Deze vormden de aanleiding voor verder onderzoek naar dit fenomeen. In **hoofdstuk 3** is de incidentie van awareness bij kinderen in ons ziekenhuis onderzocht. Gedurende 12 maanden werden gegevens van 928 kinderen in de leeftijd van 5 - 18 jaar verzameld. We stelden alle kinderen dezelfde vragen op drie tijdstippen: binnen 24 uur na de operatie, en 3 - 7 en 30 dagen na de operatie. Van alle "verdachte" gevallen werd een rapport gestuurd naar een onafhankelijke beoordelingscommissie, bestaande uit vier ervaren kinderanesthesiologen. Als deze unaniem van mening waren dat het ging om awareness, werd het betreffende voorval gedefinieerd als 'echte awareness'. De commissie kreeg 26 van deze rapporten, en zes daarvan kregen het predikaat 'echte awareness'. De incidentie bedraagt derhalve 0.6%. De onderzoekers vonden geen specifieke oorzaken voor het optreden van awareness. Het horen en voelen van dingen werd het meest gerapporteerd door deze zes kinderen. Pijn, angst en verlamming werden minder vaak genoemd. In het algemeen vonden de kinderen in het onderzoek hun awareness ervaring niet stressvol. De resultaten van ons onderzoek versterken de waarde van eerder gepubliceerde bevindingen bij kinderen. Over het algemeen, dus onafhankelijk van de geografische locatie, ziekenhuis of anesthesiologische praktijk, komt intraoperatieve awareness bij ongeveer 10 op de 1000 kinderen voor, meer dan bij volwassenen.

Meten van de diepte van anesthesie bij kinderen

Als de diepte van de anesthesie op betrouwbare wijze zou kunnen worden gemeten, dan zouden anesthesiologen problemen door te lichte of te diepe anesthesie wellicht kunnen voorkomen. Nu letten anesthesiologen meestal op zogenaamde klinische tekenen bij de

patiënt, zoals bewegingen, veranderingen in ademhalingspatroon, tachycardie, hypertensie, tranen, zweten. Deze klinische tekenen correleren helaas niet altijd met de diepte van de anesthesie. Bovendien worden ze vaak gemaskeerd door gelijktijdig gebruik van andere middelen, zoals spierverslappers. Een objectievere methode is het gebruik van een zogenaamde hersenfunctiemonitor, gebaseerd op het elektro-encefalogram (EEG). In dit proefschrift zijn twee van die monitoren onderzocht, de BIS monitor (BIS; index: BIS) en de Auditory Evoked Potential Monitor (AEP; index: cAAI). Het begrip 'diepte van anesthesie' is nogal abstract begrip, en er is geen gouden standaard om de waarden van deze monitors mee te vergelijken. Daarom moeten we onze toevlucht nemen tot indirecte maatstaven, zoals de concentratie van het anestheticum in het bloed, en observatieschalen.

In **hoofdstuk 4** is onderzocht in hoeverre de BIS en de AEP monitor het onderscheid tussen waak en slaap kunnen aangeven, en of ze daarin verschillen. Dit werd onderzocht bij twintig kinderen en adolescenten (10 - 20 jaar) die onder narcose waren met propofol en remifentanil tijdens scoliose chirurgie met een intraoperatieve wake-up test. Als gouden standaard werd gebruik gemaakt van een observatieschaal, de University of Michigan Sedation Scale (UMSS). Daarnaast werd onderzocht of de patiënten expliciete herinneringen hadden aan de wake-up test. Gedurende de wake-up test werden ze geïnstrueerd een kleur te onthouden. Na de operatie werden ze geïnterviewd met behulp van een gestructureerde vragenlijst om na te gaan of ze zich dit, of andere dingen, konden herinneren. De beide monitors bleken significant te verschillen in het onderscheidend vermogen tussen waak en slaap, maar voor de praktijk lijkt dit irrelevant. Geen van de patiënten had expliciete herinneringen aan de wake-up test.

In **hoofdstuk 5** is onderzocht in hoeverre de BIS en de cAAI onderscheid kunnen maken tussen de verschillende stadia van anesthesie, en of ze daarin verschillen. Dit werd gedaan bij 39 kinderen (2 - 16 jaar) tijdens een liesbreukoperatie. Allen kregen gestandaardiseerde anesthesie met isofluraan en een caudaal blok. Ook hier diende de UMSS als gouden standaard. Voor het onderscheid tussen 'waak' en 'slaap' werd 100% sensitiviteit bereikt bij de afkapwaarde 17 voor de BIS en 12 voor de cAAI. 100 % specificiteit was geassocieerd met een BIS van 71 en een cAAI van 60. Bewustzijn werd vastgesteld als de BIS hoger was dan 78 of de cAAI hoger dan 52. Uit dit onderzoek werd geconcludeerd dat BIS en cAAI vergelijkbare indicatoren zijn voor het weergeven van de diepte van anesthesie, echter met een aanzienlijke overlap voor de verschillende stadia.

In **hoofdstuk 6** is hetzelfde onderzoek als beschreven in hoofdstuk 5 uitgevoerd bij 20 kinderen (3 - 16 jaar) die een hartkatheterisatie ondergingen. Alle kinderen kregen gestandaardiseerde anesthesie met isofluraan. Het onderscheidend vermogen van beide indices tussen de verschillende stadia van anesthesie, weergegeven door de UMSS, was gelijk.

Farmacokinetiek en farmacodynamiek van anesthetica bij kinderen

In **hoofdstuk 6** is ook de farmacodynamische relatie beschreven tussen 'non-steady state' end-tidal isofluraan concentraties en BIS en cAAI beschreven bij 20 kinderen die een hartkatheterisatie ondergingen. Dit werd gedaan door middel van een sigmoïde E_{max} model. De EC_{50} voor BIS was 1.0%, met een Hill coëfficiënt van 2.6. Voor cAAI was de EC_{50} 0.35% met een Hill coëfficiënt van 12.1.

In **hoofdstuk 7** zijn de farmacokinetische en -dynamische eigenschappen van propofol onderzocht tijdens anesthesie met propofol en remifentanil bij 14 kinderen en adolescenten (10 - 20 jaar) die geopereerd werden voor een idiopathische scoliose. De BIS en de cAAI dienden als farmacodynamische eindpunten. Om BIS waarden tussen 40 - 50 te verkrijgen, wordt de volgende gewichtsonafhankelijke propofoldosering geadviseerd: inductiedosis 175 mg, gevolgd door continue infusie van 480 mg/uur gedurende de eerste 30 minuten, 420 mg/uur gedurende 1 uur, gevolgd door 350 mg/uur tot aan de wake-up test. De cAAI waarden worden dan geschat op 16. Na de wake-up test wordt een bolus van 75 mg propofol geadviseerd, gevolgd door continue infusie van 350 mg/uur.
Een nieuwe studie zal uit moeten wijzen of dit doseringsadvies daadwerkelijk leidt tot een snellere wake-up test en eerder ontwaken van patiënten.

In **hoofdstuk 8** worden de resultaten van alle studies en de toekomstperspectieven besproken.

A

Appendices:

Dankwoord
List of publications
Curriculum Vitae
Abbreviations

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Het is gelukt! Dit proefschrift was niet tot stand gekomen zonder de hulp van heel veel mensen, van wie ik een aantal in het bijzonder wil noemen.

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PUBLICATIONS

Publications related to the thesis

HJ Blussé van Oud-Alblas, AT Bösenberg, D Tibboel. Awareness in children: another two cases. Paediatr Anaesth. 2008 Jul;18(7):654-657.

HJ Blussé van Oud-Alblas, JWB Peters, TG de Leeuw, D Tibboel, J Klein, F Weber. Comparison of Bispectral index and composite Auditory Evoked Potential index for monitoring depth of hypnosis in children. Anesthesiology. 2008 May;108(5):851-857.

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Intraoperative awareness during pediatric anesthesia. NVA Wetenschapsdag 2008, Amsterdam.

Population PK-PD model based optimization of propofol-remifentanil anesthesia in adolescents. NVA Wetenschapsdag 2008, Amsterdam.

Bispectral Index and composite Auditory Evoked Potential Index as measures of the electroencephalographic effects of isoflurane in children. FEAPA 2008, Athens.

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Comparison of Bispectral index and cAAI for monitoring depth of hypnosis in children. FEAPA 2007, Amsterdam.

Comparison of cAAI and Bispectral index during propofol-remifentanil anesthesia for adolescent scoliosis surgery with intraoperative wake-up test. FEAPA 2007, Amsterdam.

Awareness in children: does it exist? Jackson Reese Symposium 2006, Rotterdam.

CURRICULUM VITAE

Heleen Blussé van Oud-Alblas was born on September 2nd 1975 in Rotterdam, the Netherlands. After graduating from the Erasmiaans Gymnasium in Rotterdam in 1993, she studied pharmacology at the University of Utrecht, the Netherlands. In 1996 she started her medical training at the University of Utrecht. During her study, she spent four months in South Africa to do research on tuberculosis in HIV positive children at the Tygerberg Hospital in Cape Town.

After obtaining her medical degree in 2003, she worked as a resident at the pediatric department of the Medisch Centrum Rijnmond-Zuid Hospital in Rotterdam (Supervisors: Dr. A. Brandsma, Dr. A. Oudesluys). From 2004 onwards, she was a research fellow at the departments of Anesthesiology (Prof. dr. J. Klein) and Pediatric Surgical Intensive Care (Prof. dr. D. Tibboel) in the Erasmus MC-Sophia Children's Hospital in Rotterdam, working on the research presented in this thesis. In 2008 she started her training in anesthesiology at the Erasmus MC department of Anesthesiology (Supervisor: Dr. R.J. Stolker). She is married to Derk Schep; they have a beautiful daughter Frédérique (2007).

List of Abbreviations

AEP	Auditory evoked potentials
ASA	American Society of Anesthesiologists
BIS	Bispectral Index
cAAI	composite Auditory Evoked Potential Index
EEG	Electroencephalogram
HR	Heart rate
LMA	Laryngeal mask airway
LOC	Loss of consciousness
MAP	Mean arterial blood pressure
MLAEP	Mid-latency auditory evoked potentials
P_K	Prediction probability coefficient
ROC	Return of consciousness
SD	Standard deviation
SE	Standard error
TIVA	Total intravenous anesthesia
UMSS	University of Michigan Sedation Scale