

Spectral Entropy as a Measure of Hypnosis and Hypnotic Drug Effect of Total Intravenous Anesthesia in Children during Slow Induction and Maintenance

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ABSTRACT

Background: We evaluated whether spectral entropy (SpE) can measure the depth of hypnosis and the hypnotic drug effect in children during total intravenous anesthesia.

Methods: Sixty healthy children, aged 3–16 yr, were studied. Anesthesia was induced with an increasing target controlled infusion of propofol, and maintained by a stable remifentanyl infusion and variable concentrations of target controlled infusion propofol. Depth of hypnosis was assessed according to the University of Michigan Sedation Scale (UMSS). Estimated plasma (C_p) and pseudo effect site (C_{eff}) propofol concentrations reflected the hypnotic drug effect. Patients were stratified to three age groups. The correlations between SpE versus UMSS, C_p , and C_{eff} were analyzed by Prediction Probability (P_k). The pharmacodynamic relationship between SpE and C_p , and the differences of SpE values between the age groups at the corresponding UMSS levels, were studied.

Results: Respective mean P_k values for the youngest, middle, and oldest age groups were: 1) during induction: SpE versus UMSS 0.87, 0.87, and 0.93; SpE versus C_p 0.92, 0.95, and 0.97; and SpE versus C_{eff} 0.88, 0.94, and 0.95; 2) during maintenance: SpE versus C_{eff} 0.86, 0.75, and 0.81. The pharmacodynamic analysis determined an association between SpE and C_p that followed the E_{max} model closely. There were

What We Already Know about This Topic

- Monitors for assessment of depth of sedation/hypnosis are widely validated for use in adults
- Data on the relationship between electroencephalography measures and plasma propofol concentrations are scarce

What This Article Tells Us That Is New

- In 60 patients (age: 3–16 yr) spectral entropy (SpE) was related to the level of hypnosis as assessed by the University of Michigan Sedation Scale in an age-dependent manner
- Younger children (3–6 yr) showed higher SpE values for deep sedation and surgical anesthesia when compared to older ones

significant differences in SpE values between age groups at corresponding UMSS sedation levels.

Conclusions: SpE measures the level of hypnosis and hypnotic drug effect in children during total intravenous anesthesia. There is an age dependency associated with SpE. Anesthesia should not be steered solely on the basis of SpE.

THE need and indications for measurement of the level of hypnosis and hypnotic drug effect in children may be even more important than in adults. First, there is recent evidence that awareness during anesthesia is four to eight times more common in children than in adults.^{1–5} Second, there are emerging laboratory animal data that suggest various common anesthetics may be toxic for the developing brain.^{6–8} Moreover, the “brain growth spurt” continues for several years after birth,⁹ meaning the ability to optimize and minimize the use of hypnotic anesthetics may also be valuable in older children. Third, the interindividual variation of drug effects is larger because of pharmacokinetic changes during childhood.¹⁰ This challenges the steering of pediatric anesthesia, which might thus benefit from the use of hypnosis monitors.^{11–14}

A thorough validation of depth of hypnosis (DoH) monitors is necessary before outcome studies in children are justified.¹⁵ At the moment DoH monitors seem to be valid for use in older children, but not in younger children.¹⁵ Further validation studies of DoH monitors are still needed in different pediatric age groups and with different anesthetics.^{15,16}

Spectral entropy (SpE) measures the depth of hypnosis by analyzing the regularity of the electroencephalogram signal

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with a published algorithm.¹⁷ This is used in the SpE Module (M-Entropy; GE Healthcare, Waukesha, WI). SpE has been validated in adult patients, but in children this has been limited to investigations made only during inhalation anesthesia, and show only reasonable SpE performance.^{18–20} The data concerning DoH monitors during total intravenous anesthesia (TIVA) in pediatric anesthesia are scarce, and data on SpE in children were nonexistent until this study.

The primary goal was to evaluate whether SpE reliably measures the depth of hypnosis and the intravenous hypnotic drug effect in children during TIVA. Second, the pharmacodynamic relationship between entropy and the estimated plasma propofol concentration (C_p) was investigated. Third, we characterized several clinical aspects of target-controlled infusion (TCI) propofol anesthesia and SpE monitoring. The differences of the SpE values between the age groups at the corresponding University of Michigan Sedation Scale (UMSS)²¹ levels were also investigated. Our hypothesis was that response entropy (RE) and state entropy (SE) values would have a strong relationship with the UMSS, C_p , and C_{eff} values.

Materials and Methods

Institutional ethics committee approval (for the Hospital for Children and Adolescents, Helsinki University, Helsinki, Finland), along with written informed consent of parents or

patients, when appropriate, were obtained. Sixty children and adolescents, aged from 3 to 16 yr whose weights ranged between 15 to 61 kg, were studied. The age and weight criteria were set by the TCI-pump and the Kataria pharmacokinetic model.²² American Society of Anesthesiologists class 1 and 2 patients were scheduled for elective surgery with an estimated duration of 1–5 h and requiring general anesthesia. Patients were excluded when either they had a disease or medication that affected the central nervous system or when the surgery affected the head or the neck.

Anesthetic Regimen

The anesthetic regimen is illustrated in figure 1 and is a representative patient case. All patients received a standardized anesthetic regimen. No regional anesthesia or neuromuscular blocking agents were used in this study. EMLA[®] local anesthetic cream (AstraZeneca; AstraZeneca AB, Södertälje, Sweden) was topically applied over at least two large predefined superficial veins approximately 1 h before and premedication with 0.3 mg/kg (maximum 15 mg) oral midazolam was administered approximately 30 min before the estimated induction of anesthesia. A well-functioning peripheral intravenous catheter was inserted, which was connected to one-way valves along with drug and infusion lines, and acetated Ringer's solution infusion was then commenced. In order to minimize the injection pain of propofol,

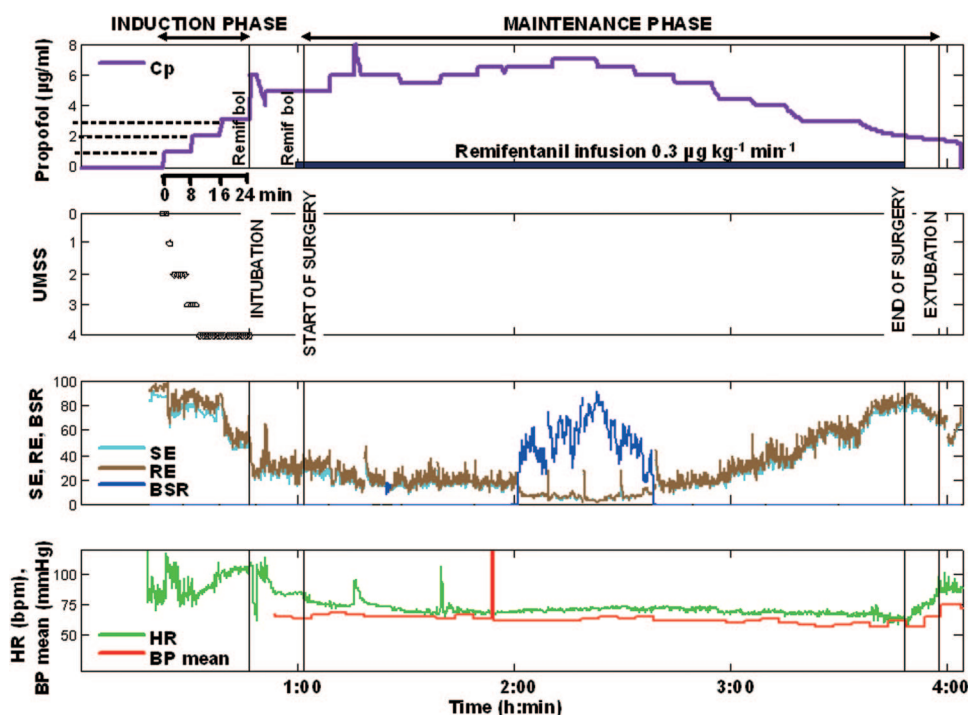


Fig. 1. The graph shows the registration of a representative patient (age 5 yr) with the following parameters: estimated plasma concentration of propofol, the University of Michigan Sedation Scale scores, response entropy, state entropy, heart rate, and mean arterial blood pressure (blood pressure mean). The annotations: induction and maintenance phases, the time intervals of induction (0–8–16–24 min), start and end of surgery, intubation and extubation, administration of remifentanil boluses, and infusion. BP = blood pressure; BSR = burst suppression ratio; C_p = estimated plasma concentration of propofol; HR = heart rate; RE = response entropy; SE = state entropy; UMSS = University of Michigan Sedation Scale scores.

a venous stasis was applied and intravenous lidocaine 0.5 mg/kg was administered and allowed to take effect for 45 s before opening the venous stasis. Immediately after this, propofol 20 mg/ml (Propofol-Lipuro 2%; B. Braun Melsungen A G, Melsungen, Germany) TCI at C_p of 1 $\mu\text{g}/\text{ml}$ commenced by TCI-pump (Alaris Asena; Alaris Medical Systems, Basingstoke, United Kingdom), according to the pharmacokinetic model described by Kataria *et al.*²² This C_p was maintained for 8 min, after which the C_p was increased to 2 $\mu\text{g}/\text{ml}$ for another 8 min and thereafter to 3 $\mu\text{g}/\text{ml}$ for a third 8-min period. Increased fraction of inspired oxygen was given when needed during this stepwise propofol induction.

After induction the C_p was increased to 6 $\mu\text{g}/\text{ml}$ and remifentanyl 1.5 $\mu\text{g}/\text{kg}$ was concomitantly infused for more than 1 min, followed 1 min later by orotracheal intubation. Patients were under controlled ventilation with oxygen-air mixture, to aim at normocapnia until the end of surgery. Approximately 5 min before the start of surgery, the C_p of TCI-propofol was set to 5 $\mu\text{g}/\text{ml}$. Approximately 1 min before the start of surgery, a remifentanyl bolus 1.5 $\mu\text{g}/\text{kg}$ was given, and remifentanyl 0.3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was infused until the end of surgery.

During surgery the remifentanyl infusion was kept stable. After the induction phase the level of anesthesia was adjusted by changing the C_p as clinically indicated by the anesthesiologist in charge, blinded to the SpE values. The anesthesiologist took the decision to increase or decrease the C_p by 0.5–1 $\mu\text{g}/\text{ml}$ over approximately 10-min intervals when clinically possible in order to achieve different levels of hypnotic drug effect for study measurements. Remifentanyl 1.5 $\mu\text{g}/\text{kg}$ boluses were used as secondary rescue analgesic therapy.

Approximately 10 min before the end of surgery, C_p was targeted to 2–3 $\mu\text{g}/\text{ml}$. Immediately before the end of surgery, intravenous acetaminophen 20 mg/kg and/or ketoprofen 1 mg/kg were given for postoperative analgesia. At the end of surgery, C_p was set to 0 $\mu\text{g}/\text{ml}$ and remifentanyl infusion was discontinued. The patient was manually ventilated, and when spontaneous ventilation was considered sufficient, the patient was extubated.

Electroencephalogram Acquisition and Other Monitoring

Before the anesthetic induction, the forehead skin was wiped with an alcohol swab and allowed to dry. A disposable adult self-adhesive entropy sensor (GE Healthcare) was placed according to the manufacturer's instructions. Electrode impedances were checked before the start of induction and automatically during anesthesia. SpE values (RE, SE), including the burst suppression ratio (BSR), were measured every 5 s with a M-Entropy module of the S/5 Anesthesia Monitor (GE Healthcare). SpE indices with all other measured parameters were collected into a laptop computer (Acer; Acer Group, New Taipei City, Taiwan) using the Rugloop software (Demed, Temse, Belgium). Baseline measurements were obtained before proceeding to anesthesia induction, and the data collection continued until the extubation of the patient.

We relied on the M-Entropy module on the detection of burst suppression (BS). The occurrence of BS was defined as the BSR of the M-Entropy exceeding 1%, and the disappearance of BS was interpreted as the moment when the BSR was again back at the value of 0%.

To detect possible lighter levels of hypnosis (indicated by higher SpE values) during maintenance and emergence (= the last 15 min of surgery), occurrences of SpE index values, between 50–60 and above 60, were registered and analyzed as percentage of corresponding overall maintenance duration of the individual patients.

The pharmacokinetic data (C_p) of the propofol TCI-pump, noninvasive arterial blood pressure, and heart rate (HR) of the S/5 monitor were collected in parallel with the SpE data. Blood pressure measurements were taken at baseline and every 5 min during anesthesia maintenance but not during induction. In addition to study monitoring, routine anesthesia monitoring was carried out including: end-tidal oxygen concentration, pulse oximetry saturation, capnography, and nasopharyngeal temperature.

Study Periods and Measurements

This study was divided into two phases: 1) the induction phase (lasting 24 min), from the start of induction until the increase of C_p to 6 $\mu\text{g}/\text{ml}$ just before intubation, and 2) the maintenance phase, from the start of surgery to the extubation of the patient.

A member of the research team who was blinded to the SpE monitor's output estimated the level of consciousness by using the UMSS²¹ (table 1). UMSS scores were taken at baseline before induction and then during the induction phase at 1-min intervals. The UMSS scores were stored as annotations with a timestamp accuracy of 1 s in a computer file. The annotations were subsequently synchronized with the data files obtained from the S/5 monitor and the drug-related data from the Rugloop system.

The estimated TCI-propofol C_p was considered to be in pseudo-steady state with the effect site concentration (C_{eff}) when the C_p had been stable for 7 min. Seven minutes was approximately four times that of^{1,2,23,24} the plasma effect site equilibration rate constant (k_{e0}) half-life (1.7 min),²⁵ which allowed enough time for C_{eff} to equilibrate with C_p .

The moment that UMSS 2 score changed to UMSS 3 or 4 was determined as the moment of loss of consciousness. Loss of consciousness were determined by means of the timestamps of "UMSS 2" and "UMSS 3 or 4" annotations. The moment of loss of responsiveness (LOR) was defined as the moment when a patient state for the first time was annotated as "does not open eyes or squeeze the hand of the UMSS evaluator when asked." This moment was determined as being the mean of the timestamps of the annotations "obeys commands" and "does not obey commands."

The use of extra remifentanyl boluses and vasoactive drugs were recorded.

Table 1. The University of Michigan Sedation Scale

Score	Patient State	
0	Awake and alert	—
1	Minimally sedated	Tired/sleepy, appropriate response to verbal conversation, and/or sound
2	Moderately sedated	Somnolent/sleeping, easily aroused with light tactile stimulation, or a simple verbal command
3	Deeply sedated	Deep sleep, aroused only with significant physical stimulation
4	Unarousable	—

Statistical Analysis

The patients were stratified into three age groups based on the recommendations of the European Medicines Evaluations Agency²⁶: 3–6 yr (youngest), 7–11 yr (middle), and 12–16 yr (oldest). Comparisons between the results for different age groups were carried as outlined below. The normality of the distributions of variables was assessed using the Lilliefors²⁷ test. Depending on its outcome we performed one-way ANOVA or Kruskal-Wallis tests for comparison between age groups. A significance level $P < 0.05$ was used in all tests to accept or reject hypotheses.

Prediction probabilities (P_k)²⁸ were calculated during induction between: RE, SE *versus* UMSS; RE, SE *versus* C_p , C_{eff} and RE, SE *versus* HR to assess the relationships between these variables. During maintenance the P_k values between RE, SE *versus* C_{eff} and also RE, SE *versus* HR, and arterial blood pressure were analyzed. A P_k value of 1.0 would indicate that a parameter such as RE was perfectly following changes in the sedation level, whereas a P_k -value of 0.5 would indicate that the prediction was no better than chance alone. In some cases, variables changed inversely to one another such as SpE values increasing with decreasing UMSS values. In such cases a P_k close to 0 indicated a strong but opposite directional relationship. Consequently, those results were presented as $1 - P_k$ in order to allow easy comparison with other variables' associations.

The mean of the two SpE values recorded in the 10 s immediately preceding each UMSS annotation were used to generate (SpE, UMSS) pair values for calculation of the P_k between SpE and UMSS. The same approach was used to calculate (HR, UMSS) and (C_p , UMSS) and (C_{eff} , UMSS) pairs. We identified the steady state and nonsteady-state periods during the induction for the three increasing steps of propofol. The mean SpE and C_p/C_{eff} values for each propofol step for each patient were calculated to compare SpE values and HR values with C_p and C_{eff} . Thus, for each patient we had three (SpE, C_p/C_{eff}) pairs for the P_k calculation. All the obser-

vation pairs from all patients were then pooled into one dataset to obtain a mean P_k and its corresponding SE.

All annotations available for each patient were pooled into one large dataset to calculate the prediction probability in order to obtain the associations between SpE and the change of "obeys commands" to "does not obey commands." The relationships between SpE and UMSS 2 *versus* UMSS 3 annotations were obtained by calculating mean values of SpE at each level for each patient then pooling all data.

We detected those periods in the maintenance phase during which C_p had not changed more than $0.01 \mu\text{g/ml}$ for 7 min or more for the maintenance analysis. The mean of the variables over those stable periods was then calculated to create (SpE, C_{eff} *etc.*) pairs for each patient. Again all data pairs for all patients were pooled within the appropriate age group to calculate the final P_k values.

The pharmacodynamic relationship between SpE values and C_p was evaluated by employing the E_{max} model.²⁹

$$E = E_0 - \frac{E_{max} \cdot C^\gamma}{EC_{50}^\gamma + C^\gamma}$$

where E is the recorded entropy value and C the propofol concentration. E_0 is the value at a drug concentration of 0, whereas E_{max} is the maximum (suppressive effect) value for E . EC_{50} is the drug concentration that corresponds to the half-maximal effect of entropy. γ (γ) is a measure that describes the steepness of the drug concentration-effect relationship (the Hill coefficient).

All C_p and SpE data obtained from all patients during the maintenance phase were pooled and a nonlinear least squares fit using the E_{max} model as reference function was calculated using Matlab's function `nlinfit()`. This was done separately for the three specified age groups.

E_0 and E_{max} were specified as 100 for RE and as 91 for SE¹⁷. The results of the fit were the estimated values of EC_{50} and γ together with their 95% CIs and plotted as curves of the equations calculated from these data, in addition to the 95% CIs for predicted values of SE and RE, were calculated when new observations of drug concentrations were obtained in a simulated data range of 0–10 $\mu\text{g/ml}$ with increasing steps of $0.01 \mu\text{g/ml}$.

Our main aim was the validation of SpE during TIVA; consequently we did not perform a pre hoc power analysis for detecting SpE differences between age groups at equal sedation or equal C_p levels. The means and standard deviations of entropy at different UMSS levels were calculated. The Kruskal-Wallis test was used to compare the distributions of SpE values among age groups at each UMSS level. For these tests, for each patient one SpE value per UMSS level was used, calculated as the average SpE value observed at that UMSS level. To investigate a possible relationship between EC_{50} and age, additional individual fits were performed for the data of each subject separately, again using Matlab's `nlinfit()` function. Linear correlation and regression analysis was performed to assess possible presence of a relationship.

Table 2. Patient Demographics

Age Group	3–6 yr	7–11 yr	12–16 yr
Number of patients	20	20	20
Male/female	13/7	11/9	12/8
Age, yr (ranges)	4.8 ± 0.9 (3–6)	9.5 ± 1.5 (7–11)	13.7 ± 1.1 (12–16)
Weight, kg (ranges)	21.4 ± 3.4 (15–28)	37.4 ± 9.3 (23–59)	51.2 ± 6.2 (40–60)
Duration of surgery, min (ranges)	108 ± 68 (17–288)	74 ± 37 (24–142)	72 ± 46 (21–198)
Type of surgery			
Orthopedics	9	16	17
Bone	5	9	10
Soft tissue	3	2	0
Arthroscopy, osteosynthesis material removal	1	5	7
Gastrointestinal	3	3	2
Laparotomy	3	2	1
Laparoscopy	0	1	1
Urology	8	1	1
Laparotomy	2	1	0
Other	6	0	1

Data are presented as number of patients, mean ± SD (range), where appropriate.

Results

All patients were included in the analyses. During induction and the maintenance phases all patients had missing data for very short periods. The mean lengths of these missing data were 95, 80, and 75 s per patient for the youngest, middle, and oldest age groups, respectively. The corresponding mean percentages of missing data as a proportion of total recording per age group were 3.2, 2.7, and 2.2%.

The average total doses of propofol in mg/kg/h per age group were (SD; ranges): the youngest 15.9 (1.8; 12.0–18.9), the middle 15.9 (2.2; 13.2–21.3), and the oldest 15.1 (2.0; 11.9–18.0). These doses include both the induction and maintenance doses, and should be interpreted together with the duration of surgery (table 2).

A representative patient case with relevant data are shown in figure 1. Patient demographics are shown in table 2.

The Lilliefors test indicated that the distribution of all the hemodynamic variables could not be assumed to be normal, and thus nonparametric tests were used for further analysis. The length of surgery was not statistically different between age groups analyzed (Kruskal–Wallis test, $P = 0.09$).

The baseline SpE data collection from all patients was successful. The median baseline values of RE and SE with ranges per age group were: the youngest 97 (89–98) and 88 (83–90), the middle 95 (87–99) and 88 (83–90), and the oldest 97 (92–99) and 88 (85–91), respectively. There were no significant differences in SpE baseline measurements between any age groups ($P = 0.70$ for SE and $P = 0.34$ for RE).

The box plots of RE and SE versus UMSS in the induction phase are shown in figure 2. The P_k values during the induction and the maintenance phase in each age group are shown in tables 3 and 4, respectively, for: RE, SE, HR, C_p , C_{eff} versus UMSS; RE, SE, HR versus C_p ; RE, SE, HR versus C_{eff} ; RE, SE, HR, arterial blood pressure versus C_{eff} . Tables 3 and

4 also include the relationship with hemodynamic variables expressed as prediction probabilities.

The pharmacodynamic relationship between SpE indices and C_p concentrations data for each age group during maintenance are shown in figure 3. The estimations of TCI propofol EC_{50} and γ with 95% CIs are shown in table 5. Based on the relative paucity of C_{eff} data as compared to C_p data, we used C_p data to perform the fits.

Figure 4 shows the age dependency of EC_{50} values. An associated linear relationship using least mean squares regression is drawn for RE: $EC_{50} = -0.0826 \cdot \text{age}(\text{yr}) + 3.17$, and

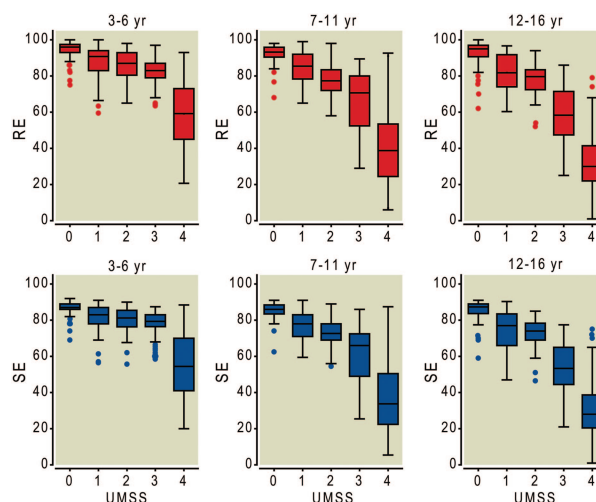


Fig. 2. The box plot analysis shows the relationship between the University of Michigan Sedation Scale scores and response entropy and state entropy during the induction phase for each age group. Each box has lines at the lower quartile, median, and upper quartile values. The whiskers are lines extending from each end of the box to show the extent of the rest of the data. Outliers are data with values beyond the ends of the whiskers. RE = response entropy; SE = state entropy; UMSS = University of Michigan Sedation Scale scores.

Table 3. Prediction Probabilities (P_k) and Standard Error during Induction

Age Group	3–6 yr	7–11 yr	12–16 yr
RE vs. UMSS	0.87 (0.01)	0.87 (0.01)	0.93 (0.01)
SE vs. UMSS	0.86 (0.01)	0.87 (0.01)	0.93 (0.01)
HR vs. UMSS	0.63 (0.02)	0.58 (0.02)	0.68 (0.02)
C_p vs. UMSS	0.90 (0.01)	0.89 (0.01)	0.91 (0.01)
C_{eff} vs. UMSS	0.89 (0.03)	0.82 (0.04)	0.87 (0.03)
RE vs. C_p	0.93 (0.02)	0.94 (0.02)	0.96 (0.02)
SE vs. C_p	0.91 (0.03)	0.95 (0.02)	0.97 (0.01)
HR vs. C_p	0.66 (0.06)	0.58 (0.07)	0.65 (0.06)
RE vs. C_{eff}	0.89 (0.03)	0.94 (0.02)	0.94 (0.02)
SE vs. C_{eff}	0.87 (0.03)	0.93 (0.03)	0.95 (0.02)
HR vs. C_{eff}	0.60 (0.06)	0.54 (0.06)	0.51 (0.06)
RE “obeys commands vs. does not obey”	0.90 (0.01)	0.92 (0.01)	0.98 (0.01)
SE “obeys commands vs. does not obey”	0.88 (0.01)	0.91 (0.01)	0.97 (0.01)
RE UMSS 2 vs. UMSS 3 and 4	0.83 (0.03)	0.85 (0.02)	0.96 (0.01)
SE UMSS 2 vs. UMSS 3 and 4	0.80 (0.03)	0.84 (0.02)	0.96 (0.01)

Standard error in parenthesis. A P_k -value of 1.0 indicates a perfect concordance between two variables, whereas a P_k -value of 0.5 indicates that the agreement in changes between the two is no better than chance alone.

C_{eff} = the estimated (pseudo) effect site propofol concentration; C_p = the estimated plasma propofol concentration; HR = heart rate; RE = response entropy; SE = state entropy; UMSS = the University of Michigan Sedation Scale.

for SE. $EC_{50} = -0.0788 \cdot \text{age}(\text{yr}) + 3.19$. For RE the correlation coefficient between age and EC_{50} is -0.363 ($P = 0.004$), and for SE the correlation coefficient is -0.347 ($P = 0.008$). The results show that for both RE and SE there were significant differences between age groups at UMSS levels 2, 3, and 4, but not at levels 0 and 1. The figure 5 shows the age dependency of the SpE by the plots of SpE values *versus* age of the patient at equal UMSS levels.

The P_k analyses of the specificity of SpE to differentiate between moderate (UMSS 2) and deep sedation (UMSS 3 and 4) and to measure LOR are shown in table 3. Moreover, 55/60 (83%) of patients had BS as defined by the BSR being greater than 1%. The median C_p at appearance and disappearance of BS are shown in table 6, and there is a significant difference (using the ANOVA test) between age groups for appearance ($P = 4 \times 10^{-13}$) as well as disappearance ($P = 5 \times 10^{-20}$) of BS. Table 7 shows the mean C_p with SD and 95% CIs at loss of consciousness and LOR (the significance levels using ANOVA: at loss of consciousness, $P = 0.04$ and at LOR, $P = 0.08$). The mean RE and SE with their SD and 95% CIs at LOR are shown in table 8. The means of SpE indices at LOR between age groups are

significantly different (for RE, $P = 3 \times 10^{-6}$ and for SE, $P = 2 \times 10^{-5}$). The incidence of higher SpE values for RE and SE, between 50–60 or above 60, during maintenance are shown in table 9.

The numbers of patients that received rescue analgesic remifentanyl boluses during the maintenance period were: 3–6 yr: 9 pts 1 dose and 3 pts 2–3 doses; 7–11 yr: 8 pts 1 dose and 1 pt 3 doses; 12–16 yr: 1 pt 1 dose. Four patients received phenylephrine: one patient three times, one patient twice, and two patients once. One patient received atropine twice. The vasoactive dosing did not happen more commonly during burst suppression.

Discussion

This study shows that SpE adequately measures the level of hypnosis and also the hypnotic drug effect in 3 to 16 yr old children during propofol induction and propofol-remifentanyl TIVA. Although the P_k values of other published studies are not strictly comparable,¹⁵ our P_k correlations were generally high, especially during the induction and in the oldest age group.

Induction

During the induction with propofol as the only anesthetic, the P_k values of SpE indices *versus* UMSS were approximately 0.87 in the two younger age groups and 0.93 in the oldest age group. These correlations are high, but as shown by the box plot graphs there were large overlaps of SpE indices with UMSS values at each level of hypnosis.

The concordance of SpE with the hypnotic drug concentration (C_p , C_{eff}) was better with the level of hypnosis as assessed by UMSS. This may be explained by inter- and intraobserver variation of the UMSS estimation.²¹ Surprisingly, the correlations between SpE *versus* C_p were higher

Table 4. Prediction Probabilities and Standard Error during Maintenance

Age Group	3–6 yr	7–11 yr	12–16 yr
RE vs. C_{eff}	0.86 (0.02)	0.75 (0.03)	0.81 (0.02)
SE vs. C_{eff}	0.86 (0.02)	0.75 (0.03)	0.81 (0.02)
HR vs. C_{eff}	0.41 (0.03)	0.41 (0.04)	0.44 (0.03)
BP vs. C_{eff}	0.34 (0.02)	0.49 (0.04)	0.48 (0.04)

Standard error in parenthesis.

BP = arterial blood pressure; C_{eff} = the estimated (pseudo) effect site propofol concentration; HR = heart rate; RE = response entropy; SE = state entropy.

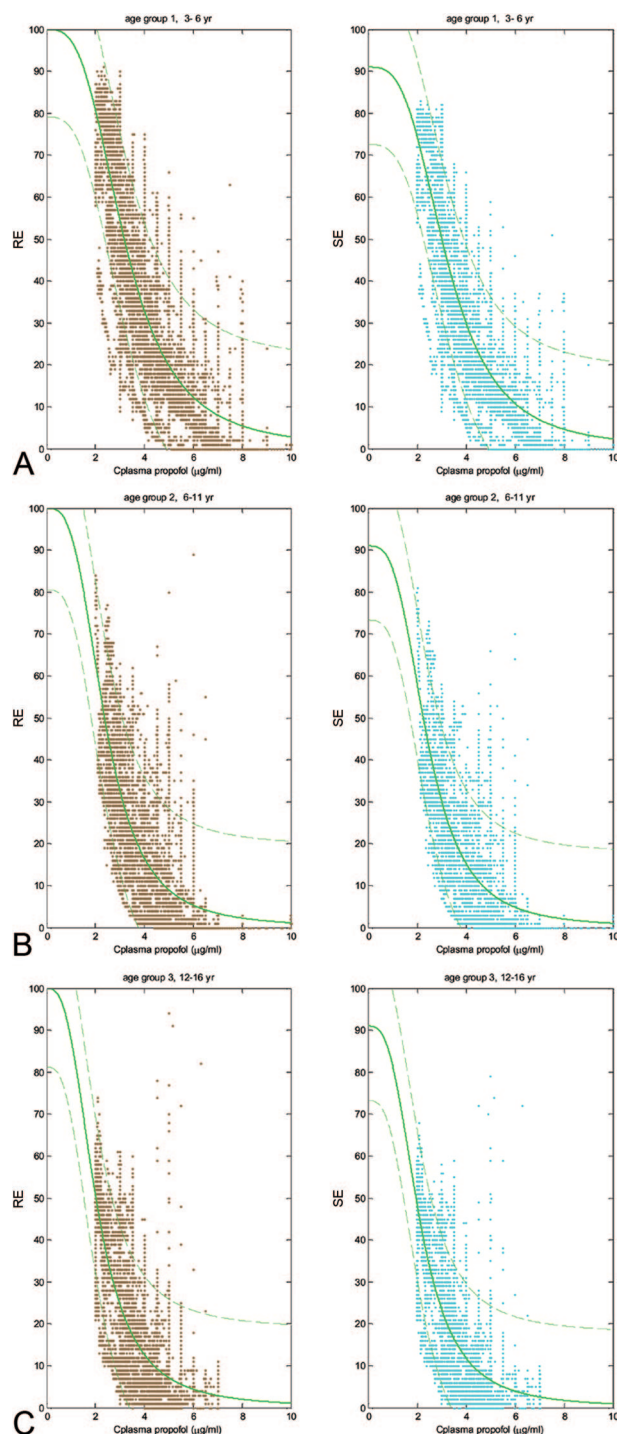


Fig. 3. Plots of the pharmacodynamic association between response entropy and state entropy indices *versus* the estimated plasma concentration of propofol for each age group during maintenance. The continuous line indicates the predicted values, and the dashed lines show the 95% CIs. (A) Age group 3–6 yr; (B) age group 7–11 yr; (C) age group 12–16 yr. C_p = estimated plasma concentration of propofol; RE = response entropy; SE = state entropy.

Table 5. Estimations of the Half-maximal Suppressive Effect of SpE and the Hill Coefficient

	EC_{50}	γ
3–6 yr	—	—
RE	3.18 (3.17–3.19)	3.08 (3.05–3.11)
SE	3.21 (3.20–3.22)	3.20 (3.17–3.22)
7–11 yr	—	—
RE	2.37 (2.36–2.39)	3.10 (3.05–3.15)
SE	2.40 (2.39–2.42)	3.14 (3.09–3.19)
12–16 yr	—	—
RE	2.02 (2.00–2.03)	2.82 (2.78–2.86)
SE	2.09 (2.08–2.11)	2.93 (2.89–2.97)

Data are presented as mean; 95% CI in parenthesis.

γ = the Hill coefficient; EC_{50} = estimations of the half-maximal suppressive effect of SpE; RE = response entropy; SE = state entropy; SpE = spectral entropy.

than those between SpE *versus* C_{eff} . It was expected that the (pseudo) effect site concentration would reflect the hypnosis better than the plasma concentration data. This finding may be because of statistical reasons (number of correlation pair observations) and interindividual pharmacokinetic or pharmacodynamic variations. The correlations of C_p and C_{eff} *versus* UMSS were higher than SpE *versus* UMSS for the

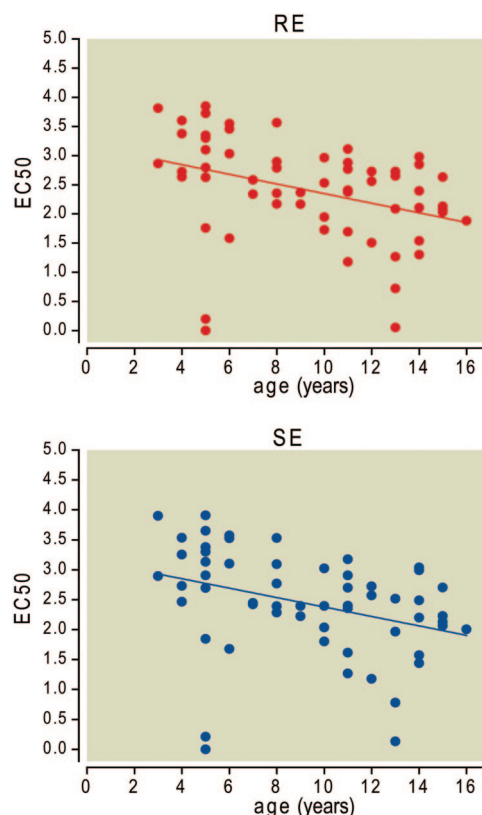


Fig. 4. Estimations of the half-maximal suppressive effect of response entropy and state entropy values as estimated from separate cases *versus* patients' age together with linear relationship as obtained *via* least-squares fitting. EC_{50} = estimations of the half-maximal suppressive effect; RE = response entropy; SE = state entropy.

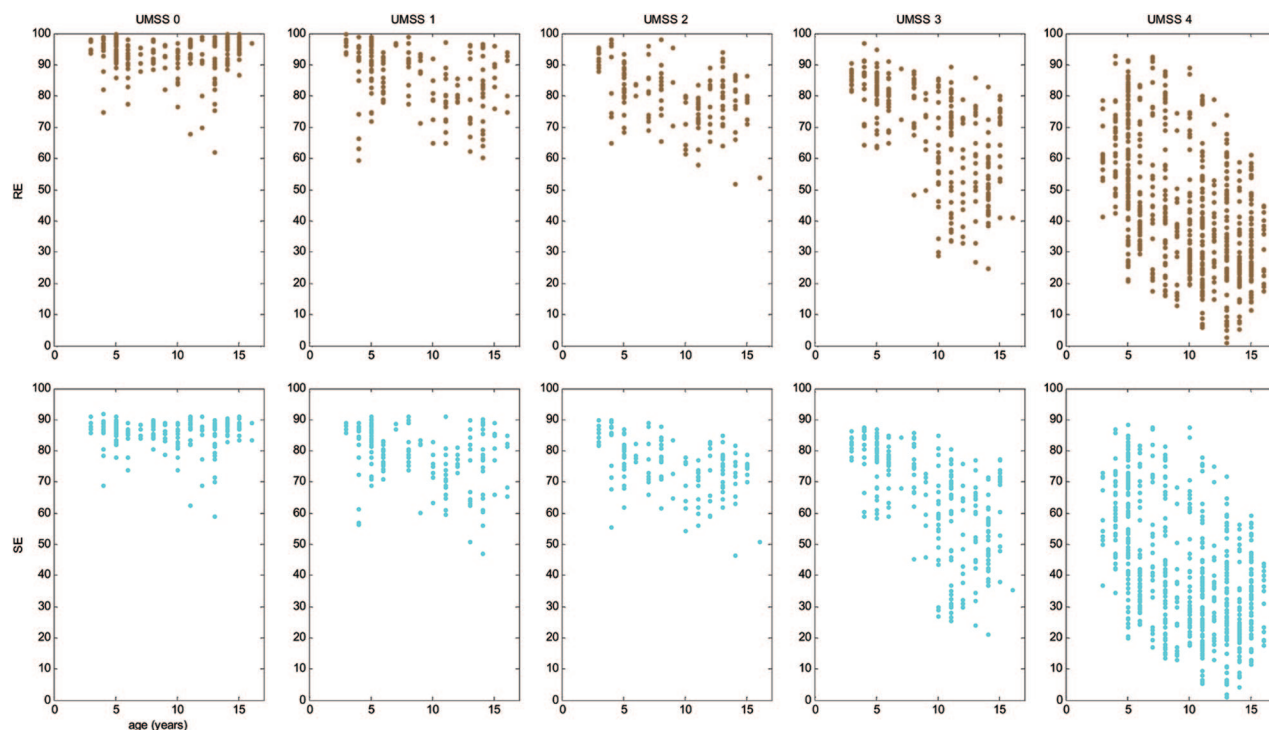


Fig. 5. Response and state entropy values *versus* age at the different University of Michigan Sedation Scale levels. RE = response entropy; SE = state entropy; UMSS = University of Michigan Sedation Scale levels.

youngest age group, but lower for the two older age groups. This may support the speculation that the younger the child, the poorer the performance of the DoH monitor.²⁰

Maintenance

During the anesthesia maintenance and surgery, only the correlation between SpE indices and C_{eff} were calculated for simplicity and statistical reasons. Theoretically the C_{eff} as a brain effect site concentration, should reflect better the hypnosis as measured by the SpE, even in the pseudo-stable state. The P_k correlations between SpE indices and C_{eff} were much lower than during the induction, 0.86, 0.75, and 0.81 for the youngest, middle and oldest age groups respectively. This is not surprising, as there are several possible reasons for this: the varying surgical stimuli, the combining of a stable remifentanyl infusion not titrated to surgical stimuli, the possible pharmacodynamic interactions, the less standardized anesthetic regimen, and methodology compared with the induction. However, the steering of anesthesia cannot solely rely on SpE values because of the overlapping of SpE indices over a range of different UMSS scores.

Table 6. The Median Estimated Concentration of Plasma Propofol ($\mu\text{g/ml}$) at the Appearance and Disappearance of Burst Suppression

Age Group	3–6 yr	7–11 yr	12–16 yr
Appearance	5.00	4.00	3.50
Disappearance	5.00	4.00	3.50

Pharmacodynamic Relationship

The nonlinear regression analysis (fig. 3) demonstrated an obvious pharmacodynamic relationship between SpE indices and C_p . The fitting of the classic E_{max} model is justified and in practice the validity of the fitted curve is good (table 5). Our estimates of propofol EC_{50} for SpE were 3.2, 2.38, and 2.05 $\mu\text{g/ml}$ for the youngest, middle, and oldest age groups, respectively. Figure 4 indicates the clear dependency of EC_{50} on the patient age. In three subjects the obtained EC_{50} is very low (smaller than 0.5). This is because of the fact that the maintenance data of these cases contain SE and RE values that are below 15, thus leading to an almost flat C_p -Entropy curve that made estimation of the equation parameters very difficult.

We used the C_p data instead of the C_{eff} data for pharmacodynamic modeling because in this study there were only relatively few C_{eff} values at different SpE levels. In contrast, the much higher number of C_p values made the use of C_p more suitable for pharmacodynamic modeling, although the C_{eff} values would probably reflect the real pharmacodynamic effect better, and take into consideration the possible hysteresis.

In two pediatric Bispectral Index® (BIS) studies, Munoz *et al.*³⁰ found TCI propofol (Paedfusor pharmacokinetic model) $\text{EC}_{50(\text{effect site})}$ of 3.65 $\mu\text{g/ml}$ for children aged over 3–11 yr. In contrast, Rigouzzo *et al.*¹² infused TCI propofol (Kataria pharmacokinetic model) and obtained an estimate and a measurement of propofol of EC_{50} of 2.9 and 4.0 $\mu\text{g/ml}$ for children aged 3–10 yr. The variation between these studies

Table 7. The Median Estimated Concentration of Plasma Propofol ($\mu\text{g/ml}$) with SD and 95% CI at the Transition of Loss of Consciousness and Loss of Responsiveness

Age Group	3–6 yr	7–11 yr	12–16 yr
LOC	1.95 (0.39) (1.17–2.72)	1.55 (0.51) (0.55–2.55)	1.76 (0.55) (0.67–2.84)
LOR	1.95 (0.39) (1.18–2.72)	1.60 (0.50) (0.61–2.58)	1.71 (0.58) (0.58–2.83)

SD in first parenthesis; 95% CI in second parenthesis.

LOC = loss of consciousness (University of Michigan Sedation Scale 2 changes to 3 or 4); LOR = loss of responsiveness (“obeys commands” changes to “does not obey commands”).

can partly be explained by differences regarding: the electroencephalogram monitor, the pharmacokinetic model, anesthetic regimen, and the differences in age ranges between the studies. Our study demonstrated none of the paradoxical increases of SpE indices as the hypnosis deepens that has been reported for BIS during sevoflurane inhalation anesthesia in children.³¹

Loss of Consciousness

Detecting the difference between moderate and deep levels of sedation is challenging. We studied the effectiveness of SpE to discriminate between moderate (UMSS 2) and deep sedation/anesthesia (UMSS 3 and 4), and to detect the LOR. The ability of SpE to differentiate between moderate and deep sedation/general anesthesia was high for the oldest age group and moderate in the middle age group. Recently, Malviya *et al.*³² concluded that BIS poorly differentiated between moderate and deep levels of sedation in all age groups in a combined secondary analysis of four independent studies evaluating age- and sedative agent-related differences in BIS in a large sample of children younger than 18 yr. However, the SpE values in the youngest age group tended to be higher at the UMSS 1–3 sedation levels and then fell more steeply with the change from UMSS 3 to 4 when compared with the two older age groups. This indicates a poor discrimination between the light to deep sedation levels (UMSS 1 to 3) in the youngest age group.

Hemodynamics

The relationships between HR *versus* UMSS, C_p and C_{eff} during induction, and those between HR and arterial blood pressure *versus* C_{eff} during maintenance assessed by P_k , were weak. These data suggest that hemodynamic variables do not reflect the level of hypnosis or the hypnotic drug effect on children during TIVA. This has also been previously shown for children undergoing inhalation anesthesia.^{20,33}

The Clinical Aspects of Anesthesia

The incidence of BS was demonstrably and accurately detected by the BSR in another study.³⁴ Without SpE guidance, 83% of the patients in our study reached BS that corresponded to a very deep level of hypnosis. There are preliminary data that suggest deep anesthesia in adults to be associated with a long-term negative outcome.^{35–38} Moreover, laboratory neonatal animal data indicate that toxicity of anesthetics for the developing brain might warrant minimizing the anesthetics dosage. Higher levels of SpE values were not registered during anesthesia maintenance and emergence (last 15 min of surgery) period except for the youngest age group. Our BSR occurrence and disappearance in addition to the higher SpE data suggest that clinically one should not probably aim for propofol C_p levels higher than 3.5–5 $\mu\text{g/ml}$. It should be noted these values depend on the patient's age and also assumes that adequate analgesia has been ascertained. This is in concordance with pediatric pharmacodynamic data^{12,30} and also with the optimal propofol and opioid concentrations in adults proposed by Vuyk *et al.*³⁹

On the other hand, our C_p values at the loss of consciousness or LOR (without surgical stimulus in this study), may hint at the minimum dosing of propofol. Our data suggest a lowest C_p level of approximately 2.9 $\mu\text{g/ml}$, and again this assumes that adequate analgesia by adjuvant methods is used.

Measuring precisely the anesthetic drug concentrations *per se* may prevent awareness as reported by Avidan *et al.*⁴⁰ However, those authors measured end-tidal concentrations of inhalation anesthetics in adults, and their data should not be extrapolated to TIVA and to pediatric patients. Our study data suggest that the TCI is a valuable tool in guiding the level of hypnosis, as the associations of C_p with UMSS were good and equal to the correlations of SpE against UMSS.

The need for rescue boluses of remifentanyl on a clinical basis was quite common in the two youngest age groups, but

Table 8. Mean Values of Response and State Entropy (%) with SD and 95% CI at Loss of Responsiveness

Age Group	3–6 yr	7–11 yr	12–16 yr
RE	82.3 (6.3) (69.9–95.8)	73.9 (9.8) (54.6–93.2)	63.8 (13.4) (37.5–90.1)
SE	77.5 (7.4) (63.–91.0)	70.2 (9.1) (52.4–88.1)	60.4 (13.8) (33.3–87.5)

SD in first parenthesis; 95% CI in second parenthesis. Loss of responsiveness refers to when “obeys commands” changes to “does not obey commands.”

RE = response entropy; SE = state entropy.

Table 9. The Incidence of Higher Response and State Entropy Values during Surgery Maintenance and Emergence in Percentage per Corresponding Time Period of the Individual Patient

Age Group	3–6 yr	7–11 yr	12–16 yr
RE above 60			
Entire surgery except last 15 min	14%	0%	0%
Last 15 min of surgery	38%	3%	1%
RE between 50–60			
Entire surgery except last 15 min	5%	0%	1%
Last 15 min of surgery	11%	8%	12%
SE above 60			
Entire surgery except last 15 min	7%	0%	0%
Last 15 min of surgery	30%	3%	0%
SE between 50–60			
Entire surgery except last 15 min	4%	0%	1%
Last 15 min of surgery	15%	5%	10%

RE = response entropy; SE = state entropy.

rare in the oldest age group. This finding may indicate a different pharmacokinetic and/or pharmacodynamic action of the remifentanyl-propofol combination between the age groups.

The Age Dependency of SpE

Our results show significant differences in SpE values between the age groups at the corresponding UMSS levels 2–4. The patients aged 3–6 yr were deeply sedated (= UMSS 3) at SpE values of 80, and half of them were under general anesthesia (= UMSS 4) at SpE indices over 60. So the higher-than-recommended SpE values for surgical anesthetic depth (for adults) by the manufacturer do not indicate an inappropriate anesthesia in this age group. The younger the patients in the 3–16 yr age group, the higher were their SpE indices at clinically similar sedation scores (fig. 5). This is a clinically important finding and is consistent with previous studies on the age dependency of patients for DoH-monitors.^{31,41–44}

As no *a priori* power calculations were conducted and the age dependent differences in SpE values over the total UMSS scale were not large, statistical power of our study may have been an issue. The current evidence strongly suggests that a calibration of DoH-monitors for patient age is warranted.

Comparison with Previous Studies

This was the first study to assess SpE during TCI and TIVA in children; thus there are no previous results for comparison. SpE has been studied in children during inhalation anesthesia^{18–20} and demonstrated reasonable performance in children but not in infants. A comparative accuracy between SpE and BIS was also found. In a more detailed comparison between our present and previous²⁰ studies, SpE seems to measure the depth of hypnosis better during TIVA than during

inhalation anesthesia. However, this disparity may be caused by differences in patient age selection, as older patients were investigated in the present study, and other methodological issues, such as end-tidal sevoflurane being used instead of effect site sevoflurane in the previous study.

In contrast to studies on SpE in children during TIVA, BIS^{12,30,43,45,46} and Narcotrend index⁴⁴ have been investigated during TCI or TIVA anesthesia in children.

Tirel *et al.*⁴³ assessed the relationship between BIS and C_p of TCI propofol (Kataria pharmacokinetic model), combined with remifentanyl infusion during surgery in 50 children aged 3–15 yr. Their multiple correspondence analysis demonstrated a difference in BIS values between C_p 2 and 4 µg/ml, but not between 4 and 6 µg/ml. An explanation for the difference between the BS data reported by Tirel *et al.*⁴³ and our data might be that their patients probably had already reached BS at the C_p 4 µg/ml level, which would have attenuated the difference in BIS between the two higher propofol levels.

The study by Rigouzzo *et al.*¹² deserves special attention. They compared the estimated TCI propofol plasma pseudo-steady state concentrations (C_p) and measured propofol concentrations of blood samples (C_m) in 45 children aged 6–13 yr using Kataria pharmacokinetic model and the corresponding parameters of 45 adults aged 14–32 yr using Schnider pharmacokinetic model. They found that the pharmacokinetic models of the TCI pumps systematically underestimated the real C_m levels. This bias increased as the concentration of propofol increased. Their pharmacodynamic E_{max} model showed EC₅₀ (estimated/measured) 2.9/4.0 µg/ml in children and 2.6/3.3 µg/ml in adults. They speculated that the higher need for propofol in children compared to adults to reach the same BIS level might be caused by both pharmacokinetic and pharmacodynamic factors. Rigouzzo *et al.* used BIS in their study, whereas SpE was determined in our study. If their results on the real propofol concentrations were to be extrapolated to our study, our E_{max} model curve would be shifted to the right and become more shallow, and the BS would be reached at higher concentrations.

Shortcomings

Various pharmacokinetic and pharmacodynamic factors may cause bias. The main limitation of our study was the lack of measured propofol concentrations of blood samples. The use of estimated plasma and effect site concentrations instead of measured plasma concentrations may have impact especially on the results regarding the pharmacodynamic modeling and the observed age dependency of propofol EC₅₀. The effect of remifentanyl on SpE values is not known, and the possible pharmacokinetic and pharmacodynamic interactions between propofol and remifentanyl cannot be ruled out. Both before mentioned issues may have different effects depending on the age of the patient. Moreover, the data regarding these issues in adults are conflicting and in children even lacking. We assume that interactions between propofol, li-

docaine, and midazolam should not have any major impact on our results. The growth and maturation of the central nervous system and their effects on the electroencephalogram may have impacts on the results between different age groups, although these factors are probably not as important as they are in infants and toddlers.

In addition to known problems in pediatric depth of hypnosis research,⁴⁷ we rely on many surrogate measures. There is no exact definition for anesthesia or level of hypnosis. The UMSS probably represents the best validated sedation scale in pediatrics. As the hypnotic drug effect cannot be precisely defined and the effect site concentrations of hypnotics cannot be measured, we have to estimate those concentrations based on pharmacokinetic modeling. We used the equilibrium time of 7 min, which approximately equals four times the only known estimation of plasma-effect site equilibration half-life in children²⁵ assessed with A-Line ARX-index® (Danmeter A/S, Odense, Denmark).

Future

Probably the most important aim for future studies and for the manufacturers of DoH monitors, initially designed for adults, is the calibration of these monitors for pediatric patients of various ages. Our study among numerous other pediatric studies emphasizes the age dependency aspect of the calculated DoH indices. The ability to steer anesthesia on the basis of a pediatrically validated effect site concentration would be of great scientific and clinical significance. Research attention should be especially paid to the very young age groups for which the benefits of hypnosis monitoring may be of the highest value.

Conclusions

This study found a correlation of SpE indices with the level of hypnosis as assessed by UMSS sedation scale in addition to estimated propofol concentrations during TCI propofol induction and TCI propofol-remifentanyl maintenance in children aged 3–16 yr. There was an age dependency in respect of SpE values. Pediatric anesthesia cannot be steered solely on the basis of SpE values.

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