

ORIGINAL ARTICLE

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EFFECT OF AGE ON THE PERFORMANCE OF BISPECTRAL AND ENTROPY INDICES DURING SEVOFLURANE PEDIATRIC ANESTHESIA. A PHARMACOMETRIC STUDY.

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PERFORMANCE OF BIS AND ENTROPY MONITORS IN PEDIATRIC SURGERY

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ABSTRACT

Background

Bispectral index (BIS) and Entropy monitors have been proposed for use in children, but research has not supported their validity for infants. However, effective monitoring of young children may be even more important than for adults, to aid appropriate anesthetic dosing and reduce the chance of adverse consequences.

This prospective study aimed to investigate the relationships between age and the predictive performance of BIS and Entropy monitors in measuring the anaesthetic drug effects within a pediatric surgery setting.

Methods

We concurrently recorded BIS and Entropy (SE/RE) in 48 children aged 1 month to 12 years, undergoing general anesthesia with sevoflurane and fentanyl. Nonlinear mixed effects modelling was used to characterise the concentration-response relationship independently between the 3 monitor indicators with sevoflurane. The model's goodness of fit was assessed by prediction-corrected Visual Predictive Checks. Model fit with age was evaluated using Absolute Conditional Individual Weighted Residuals ($|CIWRES|$). The ability of BIS and Entropy monitors to describe the effect of anesthesia was compared with prediction probabilities (P_K) in different age groups. Intra operative and awakening values were compared in the age groups. The correlation between BIS and Entropy was also calculated.

Results

$|CIWRES|$ versus age showed an increasing trend in the model's accuracy for all 3 indicators. P_K probabilities were similar for all 3 indicators within each age group, though lower in infants. The linear correlations between BIS and Entropy in different age groups were lower for infants. Infants also tended to have lower values during surgery and at awakening than older children, whilst toddlers had higher values.

Conclusions

Performance of both monitors improves as age increases. Our results suggest a need for the development of new monitor algorithms or calibration to better account for the age specific EEG-dynamics of younger patients.

CLINICAL IMPLICATIONS

What is already known

EEG monitors may be useful tools for the assessment of anesthesia in children. BIS and Entropy are commercialized and commonly used devices in clinical practice, but their limitations in the pediatric setting are not completely understood.

What this article adds

This is the first study to apply a mixed effects model population approach with concurrent BIS and Entropy monitoring to compare their performance and relationship to age in pediatric surgery. In a prospective study with 48 children aged 1 month to 12 years we exposed an age related trend in BIS and Entropy monitors' accuracy. Age related differences in monitors' responses were found, indicating that both monitors are not calibrated for use in younger children.

Keywords

Non-invasive, pharmacodynamics, depth of anesthesia, sevoflurane, child, infant.

Body Text

INTRODUCTION

Assessment of anesthesia depth is crucial to titrate appropriate anesthetic dose and ensure adequate sedation. EEG-guided tools are commonly used for adults but use for children has been less common and less extensively studied (1). Currently, research has validated monitoring tools for use in older children, but does not provide strong support for use in younger children. However, effective monitoring for pediatric depth of anesthesia is of critical importance due to a higher potential for adverse consequences such as: intraoperative awakening(2), anesthesia toxicity, higher variability of responses to anesthetic drugs(3), and increased risk of airway complications(4).

BIS technology uses a private algorithm that processes spectral and temporal analysis from a single-channel EEG. Thus it provides a single value from 0-100 that inversely correlates with the patient's level of hypnosis. Entropy uses a published algorithm to evaluate depth of hypnosis through analysis of the EEG signal's irregularity. Wave patterns regularise as anesthesia deepens, and are processed into two indicators: State Entropy (SE): 0-91 and Response Entropy (RE): 0-100, with different characteristics in frequency bandwidths and temporal window length(5) .

Studies exploring the suitability of these monitors for a pediatric population, have found contrasting results. Earlier studies argued a potential clinical utility for BIS in pediatric surgery(6–9). However, following this early enthusiasm, research evidence questioned the ability of BIS to accurately determine depth of anesthesia in infants(10–13).

This study's goal was to investigate the predictive performance of BIS and Entropy as monitoring tools for measuring sevoflurane effects in routine pediatric surgery. Nonlinear mixed effects modelling was used to characterise the dose-response relationship independently between the 3 indicators (BIS, RE, and SE) with sevoflurane. The hypothesis was that the predictive performance of BIS and Entropy in estimating the sevoflurane effects does not change with age. We tested this in two ways: firstly by examining age-related changes in individual model fit and secondly, using prediction probabilities (P_K) to compare the monitor's

performance in different age groups. Additionally, we asserted the linear correlation between monitors' values and awakening values in different ages.

METHODS

Study population

This study was conducted according to standards set by the Declaration of Helsinki and Good Clinical Practice guidelines. After institutional ethics committee's approval and informed written parental consent, the study was performed in the Pediatric Surgery Unit of the University Hospital of Foggia, Italy.

Eligible patients were aged between 1 month and 12 years old, ASA I or II, scheduled for elective surgery with estimated duration between 20 minutes and 2 hours, undergoing general anesthesia with sevoflurane and fentanyl.

To reduce the confounding factors of other medications, we did not include children who received pre-medication other than acetaminophen, regional anesthesia or neuromuscular-blocking agents. We excluded children with: severe developmental delay, neurological disorders, treatment with anti-epileptic or stimulants, pre-existing lung or cardiac disease, airway abnormalities, or marked skin sensitivity. Children were additionally excluded in conditions where the monitor sensors' placement would interfere with surgical procedures.

Anesthesia protocol

As per hospital standard practice, parental presence was allowed during induction of anesthesia. Anesthesia was induced with sevoflurane at 5% in oxygen, in a tight-fitted facemask, using an open pediatric circle system at high fresh gas flow 5-10 l/min. Subsequently sevoflurane was reduced according to minimal alveolar concentration and vital signs. A peripheral venous catheter was inserted when patients lost eyelash reflex and connected with acetated Ringer at 2-4 ml·Kg⁻¹·hr⁻¹ of maintenance infusion rate. Children received fentanyl 1-3 mcg·Kg⁻¹ intravenously and were manually ventilated with bag and facial mask until laryngeal mask (LMA) was successfully inserted. All patients were ventilated using an S/5 Avance ventilator (Datex-Ohmeda Division, GE Healthcare, Helsinki, Finland). Sevoflurane and carbon- dioxide concentrations were measured continuously and every patient was ventilated to maintain normocapnia. General anesthesia was titrated by an experienced pediatric anesthesiologist blind to the EEG-monitor's screens. Anesthesia was maintained with sevoflurane in 50% oxygen in air with total inflow of 5 l/min, and sevoflurane concentration was adjusted in

response to clinical signs. A second dose of fentanyl $0.5\text{-}1\text{ mcg}\cdot\text{Kg}^{-1}$ was given for surgery over 1 hour. Intravenous acetaminophen $7.5\text{-}15\text{ mg kg}^{-1}$ was given prior to surgery completion for postoperative analgesia. At the end of surgery, sevoflurane inhalation was discontinued and patients were allowed to eliminate anesthetic alveolar gas at a washout rate of 10 L/min. The LMA was removed when patients were breathing spontaneously, according to the anesthesiologist's decision. After LMA removal, 100% oxygen was delivered by face-mask. During sevoflurane elimination, patients were not physically handled until awakening. Awakening was defined as onset of continuous purposeful movement, phonation, or eye-opening as previously described in literature (14,15).

Data measurements

At enrolment, anonymised patients' characteristics and surgery type were recorded in a dedicated database. On arrival at the operating room, all patients were monitored using standard devices for blood pressure, electrocardiogram, pulse-oximeter and temperature.

Immediately after induction of anesthesia, the forehead skin was wiped with an alcohol swab and allowed to dry. Disposable BIS and Entropy self-adhesive electrodes were positioned on the forehead in close proximity as described in literature (14,15). Entropy sensors were placed lower and BIS sensors higher on the forehead, while the sensor's distal leads were placed on opposite temples according to manufacturers' instructions. As standard, electrode impedances and signal quality were automatically checked before and during data acquisition. Impedance values $<7.5\text{ kOhm}$ for BIS and $<10\text{ kOhm}$ for Entropy were acceptable.

A BIS-VISTA™ (Aspect Medical Systems, Norwood, MA, USA) and an E-Entropy™ module (Datex-Ohmeda, GE Healthcare, Helsinki, Finland) were used to measure BIS, RE and SE for the following period until awakening. EEG-monitor values and end-tidal sevoflurane concentrations were sampled at 1 minute intervals and captured on a laptop using S/5 collect software (Datex-Ohmeda, GE Healthcare, Helsinki, Finland).

Population pharmacokinetic-pharmacodynamic (PK-PD) modelling

To characterise the concentration-response relationship between BIS or Entropy (RE/SE) and sevoflurane, we used nonlinear mixed effects modelling with NONMEM VII (ICON Development Solutions, Dublin, Ireland).

Nonlinear mixed population approach is a modelling methodology particularly suitable to estimate inter-subject variability when data are sparse or the number of samples per subject is limited.

First, an effect compartment was added for sevoflurane; we set the end-tidal concentrations (C_{et}) as the pharmacokinetic measure in equilibrium with an effect-site (C_e), using the following first order diffusion equation:

$$dC_e/dt = (C_{et} - C_e) \times K_{eo}$$

Where K_{eo} is the first order rate constant accounting for the delay of influx or efflux from plasma to the brain.

The concentration-response relationship between C_e and EEG-monitors was then modelled independently for BIS and Entropy (RE/SE) using an inhibitory sigmoidal maximal effect model:

$$E = E_0 + (E_{max} - E_0) \times C_e^\gamma / (C_{e50}^\gamma + C_e^\gamma)$$

Where E_0 is the estimated BIS or Entropy value in the absence of sevoflurane, E_{max} is the fractional maximum sevoflurane effect, C_{e50} is the effect-site sevoflurane concentration required to achieve half maximum drug effect and γ is the steepness of the concentration-response curve.

The first order conditional estimation (FOCE) with INTERACTION was used to estimate the parameters and residual standard errors (RSE).

Inter-individual variability was modelled using an exponential model:

$$P_i = P_{TV} \cdot e^{\eta_i}$$

Where P_i is the parameter value (K_{eo} , E_0 , E_{max} , γ or C_{e50}) in the i -th patient, P_{TV} is the typical value of the parameter in the population, and η is a random variable with a mean of 0 and variance of ω^2 .

A non-parametric bootstrap method was used to assess robustness of parameter estimates. The 95% confidence intervals of parameters were obtained from results of 200 bootstrap data sets.

Model evaluation was undertaken using plots of prediction corrected Visual Predictive Check (pcVPC) (16). pcVPC based on 1000 simulations were used to evaluate the final model's predictive performance.

Individual model fitting (independent of covariate effects) across ages was evaluated using absolute conditional individual weighted residuals (CIWRES) plotted against age. CIWRES were calculated as the FOCE approximated difference between an individual's data and the model prediction of that data divided by the root of the covariance of the model generated data (17). We stratified $|CIWRES| > 2$ and compared their proportions among age groups. In the absence of empirical Bayesian estimate (EBE) shrinkage and with a similar number of data points per subject, this diagnostic should not show trends with any covariate, in this case, age.

Statistical analysis

Patients were stratified into 3 age groups: 1-12 months (infants), 13-36 months (toddlers), and 37-144 months (children). The ability of BIS and Entropy monitors to identify changes in sevoflurane concentration in the three age groups was assessed using prediction probabilities (P_k).

P_k represents a measure of performance where an indicator can correctly predict the rank order of an arbitrary pair of distinct anesthetic depths (18). As an ideal anesthetic depth indicator is described by a monotonically decreasing or increasing function, P_k allows a simple interpretation and being a nonparametric measure, is independent from scale units and assumptions on underlying distributions. P_k has a value of 1 when the indicator predicts the anesthetic depth perfectly and 0.5 when the indicator predicts no better than chance.

We computed P_k from pooled data pairs of monitor values (BIS, RE or SE) in absence of surgical stimulation (emergence phase) *versus* end-tidal sevoflurane and *versus* the mathematically predicted effect-site concentrations in the 3 age groups. We used the PK Tool software which provides estimation of standard errors and confidence intervals by bootstrap methodology, and multiple comparison with Bonferroni correction (19).

Results are expressed as number of patients, percentage, mean \pm standard deviation and median (interquartile range-IQR) where appropriate. Data were tested for normality by Shapiro-Wilk test. Comparisons between age group variables were made by ANOVA with Bonferroni correction for multiple comparisons or by Kruskal-Wallis with Dunn's test where appropriate. $|CIWRES|$ were compared among age groups using Cochran–Armitage test for trend. Linear correlation with 95% confident intervals between the three indicators

were also calculated and compared across groups. A P-value less than 0.05 was considered significant. Statistical analysis was performed with GraphPad Prism Software Version 6.01 for Windows 7 (GraphPad Software Inc., San Diego, USA).

RESULTS

50 children were enrolled. Two children were excluded from further analysis, one because surgery lasted under 20 minutes and one where Entropy failed to record >20% of observations. Patient characteristics and surgery data for the 48 enrolled children are summarised in **table 1**. The toddler group had a higher proportion of males. The majority of procedures were abdominal and urologic surgery. Surgery was uneventful for all and there were no significant differences in length of anesthesia between age groups (ANOVA, $P=0.41$).

Mean time delay from induction to starting data recording was 8 ± 3.2 minutes. Surgery time accounted for 71.3% of all total duration of data collection. Data excluded due to low quality index were 2.6% and 3.5% of total data for BIS and Entropy respectively.

The medians of all values recorded during surgery were significantly different among age groups (Kruskal-Wallis test $P<0.0001$ for both BIS and Entropy). At awakening, all indicators' values were significantly different among the age groups (Kruskal-Wallis test $P=0.011$ for BIS, $P<0.0001$ for both RE and SE). The difference of medians between infants and toddlers was 6, 17 and 7 during surgery and 11, 33 and 42 at awaking for BIS, RE and SE respectively. Overall, toddlers displayed highest values compared with other age groups and infants had the lowest value at awakening (**figure 1**).

The pharmacodynamic analysis demonstrated a clear relationship between BIS and Entropy indices *versus* sevoflurane. Both monitors achieved a comparable fit with effect-site sevoflurane concentration using the inhibitory sigmoid Emax model.

The pooled concentration-response curve (**figure 2**) showed an hysteresis loop when plotting monitor's values against end-tidal sevoflurane concentration (C_{et}) in each age group. This hysteresis collapsed once plotting monitor's values or the individual predicted values against effect-site sevoflurane concentration (C_e), resulting from NONMEM PK-PD modelling. **Supplementary figure S1** shows individual PK-PD plots for BIS, RE and SE.

Parameter estimates of the population model and typical values according to age groups are shown in **supplementary table S1**. The population model consisted of a sigmoidal model with inter-individual and residual random variability. A visual predictive check of the final model did not show major differences

between the predictive performance of the 3 indicators (**supplementary figure S2**). Evaluation of the model's goodness-of-fit demonstrated that a patient's age affected the model's performance for each indicator (Chi square test $P < 0.01$). Individual model fit, measured by $|CIWRES|$ improved with age in both monitors (Cochran-Armitage tests for trend $P < 0.0001$ for BIS and RE, $P = 0.0004$ for SE) (**figure 3 and supplementary table S2**).

Table 2 lists the calculated P_K probabilities for the three indicators against sevoflurane (C_{et} and C_e) during the emergence phase. As expected, for both monitors, P_K were found to be higher for effect-site than for end-tidal sevoflurane concentration in all age groups. P_K were not significantly different for all 3 indicators within each age group, and were lower in infants than in older children (ANOVA with Bonferroni correction $P < 0.0001$ for all indicators).

Table 3 shows the inter-monitors correlation in the different age groups. Linear correlations between monitors were significantly lower in the infant group (Fisher r-to-z transformation $P < 0.0001$).

DISCUSSION

This study demonstrated that both BIS and Entropy similarly reflect the effect of sevoflurane anesthesia in children, although age has a profound impact on their accuracy. We used PK to compare the monitor's ability to detect sevoflurane concentration changes during the emergence phase. Within each age group, no differences were found between the 3 indicators in terms of predictive performance.

However, an age related trend in monitor's performance was found where both monitors' accuracy improved as age increased. Our results also confirmed previous research evidence that BIS and Entropy monitors in infants are less linearly correlated (14,20). Low performance and weak inter-monitor correlation indicates that both monitors fail to capture the state of anesthesia and their response to anesthesia induced EEG patterns is essentially different in infants.

We found a difference in average values during surgery and at awakening among age groups. Although depth of anesthesia monitors' values do not have a clear physiological correlate(1), these differences may be clinically relevant in term of anesthesia management.

Comparison, validation, and pharmacodynamic studies assessing EEG-monitor tools in children, especially for youngest ages, are challenging due to methodological and ethical concerns. Firstly, there are ethical considerations around recruiting children for research and secondly, depth of anesthesia is a theoretical construct without an accepted standard for clinical measurement. Finally, whilst extrapolating adult data can be useful in pediatric anesthesia, we must be mindful that adult pharmacokinetic-pharmacodynamic models may not provide equivalent validity for children(3).

There are few studies comparing BIS and Entropy in children, and very little data have covered their performance in younger ages. In the first published study of Entropy in children 1 month - 12 years, Davidson et al(14) demonstrate a significant strong correlation between BIS and Entropy in children and toddlers, but not infants. They observed a less significant difference in values between deep anesthesia and awakening in infants. Subsequently, Davidson et al.(15) found a greater spread of BIS and Entropy values and a less defined relationship at different steady-state sevoflurane concentrations between 1.5% and 2.5% in infants. Klockars et al.(20) studied the relationship between BIS and Entropy using a modified Observer's Assessment of

Alertness/Sedation Scale in 20 infants aged 1 month–1 year and 40 children aged 1–15 years receiving sevoflurane anesthesia. The non-linear regression between monitors and sevoflurane was much less clear for infants. Both these studies questioned the clinical usefulness of BIS and Entropy monitors in infants. More recently, Klockars et al.(21) evaluated Entropy in 60 children aged 3-16 years during total intravenous anesthesia, and found an age dependency effect on the pharmacodynamic relationship. They emphasised that research evidence justifies attention to support appropriate monitor calibration for pediatric patients at different ages(21).

This study's findings consolidate previous evidence that BIS and Entropy monitors are less accurate in infants. As sevoflurane levels were not at steady-state, we applied pharmacological modelling to study the concentration-response relationship between effect-site drug and monitors. The fit of the classical inhibitory Emax model is justified in practice for steady-state and also for not-steady-state(6,13,20,21). To our knowledge, this is the first study applying a mixed effects model population approach with concurrent BIS and Entropy monitoring comparing the model fit characteristics of the concentration-response relationship at different ages in pediatric surgery.

The assumption is that every change in anesthetic effect-site concentration will produce a corresponding sigmoid response in the underlying EEG. We then evaluated the discrepancy between the observed monitor values and the individual model predicted values. In this study we cannot rule out a maturational effect on the pharmacological model itself (i.e. non-sigmoid relationship), in that case, our model would not be appropriate for all ages. Hence the measure of CIWRES is a metric of model goodness-of-fit which should be independent of covariate effects because it is based on individual model predicted values. With rich data that was not unduly affected by EBE shrinkage, our explanation of the observed trend is differences in the nature of the pharmacodynamic endpoint or, in other words, data produced by the EEG-monitors. Our findings suggest that the algorithms processing the EEG in small children misinterpret the EEG information (i.e. do not track minimal EEG changes) because they are not calibrated for these age specific patterns.

Our analysis exposed an age related trend in monitors' accuracy, whilst most other previous studies were only able to observe better performance in children versus infants. Finding a trend rather than a difference between two distinct groups is important as it may help understand why the monitors are less accurate with younger

ages and direct research towards improving monitor's effectiveness. The early years period has the fastest brain development rate, and maturation rates are likely to vary between individuals. Furthermore, developmental EEG under general anesthesia show peculiar characteristics, such as a more 'binary' state of consciousness (9), low anesthesia sensitivity (22) and paradoxical reactions(10). The definition of age groups can impact the ability to observe age-related maturational changes in brain-state dynamics under anesthesia.

Unfortunately, our methodology did not capture raw-EEG data to provide further evidence of age-related differences, which may have exposed some underlying explanation for the worse fit of BIS or Entropy values. Akeju et al.(23), have retrospectively characterised sevoflurane anesthesia-induced EEG features as a function of age in pediatric patients. They found increased total EEG power from infancy up to 6 years, subsequently declining to plateau at approximately 21 years. They also observed larger power in slow-frequencies bands for infants, while children over 1 year had greater power in high-frequency bands, compared with adults. Age-specific EEG-dynamics are likely expression of cortical and sub-cortical networks developmental processes, such as synaptogenesis and myelination , throughout childhood.

Sury et al. (24) analysed the spectral power of infants during emergence from sevoflurane anesthesia and found that infants 3 months and older had peak power in the 5–20 Hz range during maintenance and this power decreased on emergence. Recently Cornelissen et al. (25) compared the EEG dynamics of 2 infant subgroups aged 0-3 and 4-6 months before, during and on emergence from sevoflurane anesthesia. They found that theta and alpha oscillations appear at around 4 months and over, while alpha power increases during anesthesia only in the older group. Interestingly, all infants lacked of frontal alpha predominance and coherence, a feature associated with sevoflurane-induced unconsciousness in adults.

These recent advances indicate that EEG-monitor based algorithms that rely on the frequency components of the EEG need to be adjusted to account for age-related changes in the EEG, specifically in infants.

Shortcomings

This study has a possible limitation in using adult sensors. BIS has recently made available pediatric sensors, although these are not yet available for Entropy. There was limited space on smaller children's forehead for sensor allocation which may have affected the monitor's performance. To accommodate the Entropy sensor,

we placed the BIS sensor slightly higher than recommended by the manufacturer, although research has demonstrated that this introduces minimal bias(5).

Other potential limitations of this study are the presence of surgical stimulation and the lack of a validated clinical score. It must be stressed that the theoretical construct of anesthesia depth is the balance between anesthetic effect-site concentration and painful stimulation. However, clinical measures of consciousness are problematic, especially in small children, with no single preferred validated scoring system able to reliably detect the varying degrees of anesthesia in pediatric patients. As all patients received analgesia according to their need under the anesthetist's decision, we assumed that surgical stimulation was comparable between patients and that anesthetic concentrations reflected the levels of anesthesia.

Future studies

There is potential to explore further options to calibrate these monitors more adequately based on specific characteristics of the EEG data of immature brains and thus provide better support for younger ages.

CONCLUSIONS

This research offers further strong evidence that BIS and Entropy are inadequately calibrated for use in infants, as age itself affects the monitors' performance. The uncertainty of these monitors in predicting young children's levels of anesthesia suggest that the monitor's calibration for adult EEG brain activity patterns during general anesthesia cannot be reliably transferred to developing brains, potentially due to differences in brain-state dynamics under general anesthesia.

The monitor's algorithms require further attention to improve their suitability for younger children. Based on adult patient's benefits from application of BIS and Entropy, this may improve quality of care and outcomes for these youngest and most vulnerable pediatric patients.

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Conflict of interest

Authors declared no conflict of interest.

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TABLES

Table 1. Patient demographicData are presented as number of patients, mean \pm SD (range).

Groups	Infants		Toddlers		Children	
Number of patients	8		22		18	
Age, months	6.6 \pm 3.7	(1-12)	24.9 \pm 8.1	(13-36)	82.2 \pm 33.8	(37-144)
Male/female	4/4		14/8		9/9	
Weight , kgs	7.6 \pm 2.5	(3-10)	13.1 \pm 1.9	(10-18)	29.7 \pm 13.6	(15-58)
Duration of anesthesia , minutes	80.4 \pm 27.1	(39-132)	64.3 \pm 32.4	(20-159)	73.8 \pm 30.4	(28-120)
Type of surgery						
Gastrointestinal	5		9		8	
Urology	2		11		6	
Other	1		2		4	

Table 2. Prediction Probabilities (PK) for the monitor's indices according to age groups

Standard error in parenthesis. A Pk-value of 1.0 indicates a perfect concordance between two variables, whereas a Pk-value of 0.5 indicates that the agreement in changes between the two is no better than chance alone. Cet=end-tidal sevoflurane concentration. Ce= effect-site concentration of sevoflurane.

Age group		BIS				RE				SE			
				95% CI				95% CI				95% CI	
Infants	Cet	0.57	(0.030)	0.52	0.64	0.52	(0.027)	0.50	0.60	0.50	(0.020)	0.50	0.58
	Ce	0.64	(0.007)	0.63	0.65	0.61	(0.009)	0.59	0.63	0.62	(0.010)	0.60	0.64
Toddlers	Cet	0.79	(0.011)	0.77	0.81	0.76	(0.012)	0.73	0.78	0.77	(0.012)	0.74	0.79
	Ce	0.81	(0.003)	0.81	0.82	0.82	(0.003)	0.82	0.83	0.81	(0.003)	0.81	0.82
Children	Cet	0.80	(0.009)	0.78	0.81	0.79	(0.007)	0.77	0.80	0.78	(0.006)	0.77	0.79
	Ce	0.81	(0.004)	0.80	0.81	0.80	(0.008)	0.79	0.82	0.80	(0.009)	0.78	0.81

Table 3 . Correlation coefficient (r) with 95% confidence intervals between monitor's indices among age groups. P value<0.0001 for all correlation coefficients. P values for comparison of correlation coefficients Fisher r-to-z transformation * infants vs toddlers, ** toddlers vs children.

	Infants			Toddlers			Children	
	r	95% CI	*	r	95% CI	**	r	95% CI
BIS vs RE	0.47	0.40-0.53	<0001	0.78	0.76-0.80	0.234	0.76	0.73-0.78
BIS vs SE	0.43	0.36-0.50	<0001	0.76	0.73-0.78	0.101	0.73	0.70-0.75
RE vs SE	0.96	0.95-0.97	<0001	0.98	0.98-0.98	1.0	0.98	0.98-0.98

FIGURES' CAPTIONS

Figure 1. Median (IQR) monitors' values during surgery, and at awakening from anesthesia in the three age groups. Kruskal-Wallis test. Dunn's post-hoc multiple comparisons are included where significant.

*** P<0.05 and ** P<0.01**

BIS: bispectral index. RE: response entropy. SE: state entropy.

Figure 2. Concentration-response curve modelling plots for the three indicators in each age group.

Monitors' values *against* end-tidal sevoflurane concentrations (Cet) - black dots - and *against* effect-site concentration (CE) - blue dots. Red dots are the individual predicted values versus the effect-site concentrations. BIS: bispectral index. RE: response entropy. SE: state entropy.

Figure 3. Absolute Conditional Individual Weighted Residuals (|CIWRES|) versus age for the three indicators.

Dashed lines define the age thresholds (12 and 36 months). BIS: bispectral index. RE: response entropy. SE: state entropy.

SUPPLEMENTAL MATERIAL

Supplementary Figure S1. Individual PK-PD plots for BIS, RE and SE (A,B and C respectively).

Monitors' values *against* end-tidal sevoflurane concentrations (C_{et}) - blue dots - and *against* effect-site concentration (C_E) - red dots. BIS: bispectral index. RE: response entropy. SE: state entropy. Patient's age is numbered in the top of the boxes.

Supplementary Table S1. Model parameters

The estimated pharmacodynamic parameters, inter-individual and random variability for the 3 indicators. Data are given as mean (SD). K_{eo} (min⁻¹) = elimination rate constant from the effect-site compartment. E₀ = value in the absence of sevoflurane. E_{max} = Indicator value at maximal effect. C₅₀ (vol%) = Effect-site sevoflurane concentration associated with 50 % response. γ = Steepness of the concentration–response curve. ω^2 = Inter-individual variability. σ^2 = Variance for residual random variability. RSE = relative standard error.

Supplementary Figure S2. Prediction corrected Visual Predictive Check (pcVPC) for BIS, RE and SE, based on 1000 simulations to evaluate the model predictive performance of the final model.

Supplemental Table S2. Absolute Conditional Individual Weighted Residuals |CIWRES| stratified for >2 and < 2 and comparison in different age groups.