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Estimation of the Plasma Effect Site Equilibration Rate Constant (k_{e0}) of Propofol in Children Using the Time to Peak Effect

Comparison with Adults

Hernán R. Muñoz, M.D., M.Sc., Luis I. Cortínez, M.D.,† Mauricio E. Ibacache, M.D.,‡ Fernando R. Altermatt, M.D.‡*

Background: **Targeting the effect site concentration may offer advantages over the traditional forms of administrating intravenous anesthetics. Because the lack of the plasma effect site equilibration rate constant (k_{e0}) for propofol in children precludes the use of this technique in this population, the authors estimated the value of k_{e0} for propofol in children using the time to peak effect (t_{peak}) method and two pharmacokinetic models of propofol for children.**

Methods: **The t_{peak} after a submaximal bolus dose of propofol was measured by means of the Alaris A-Line auditory evoked potential monitor (Danmeter A/S, Odense, Denmark) in 25 children (aged 3–11 yr) and 25 adults (aged 35–48 yr). Using t_{peak} and two previously validated sets of pharmacokinetic parameters for propofol in children, Kataria's and that used in the Paedfusor (Graseby Medical Ltd., Hertfordshire, United Kingdom), the k_{e0} was estimated according to a method recently published.**

Results: **The mean t_{peak} was 80 ± 20 s in adults and 132 ± 49 s in children ($P < 0.001$). The median k_{e0} in children was 0.41 min^{-1} with the model of Kataria and 0.91 min^{-1} with the Paedfusor model ($P < 0.01$). The corresponding $t_{1/2}$ k_{e0} values, in minutes, were 1.7 and 0.8, respectively ($P < 0.01$).**

Conclusions: **Children have a significantly longer t_{peak} of propofol than adults. The values of k_{e0} of propofol calculated for children depend on the pharmacokinetic model used and also can only be used with the appropriate set of pharmacokinetic parameters to target effect site in this population.**

PHARMACOKINETIC studies and the development of computer-controlled infusion devices have lead to new ways of administering intravenous drugs. Target-controlled infusion allows achieving and maintaining predetermined plasma concentrations of different drugs whose pharmacokinetic parameters have been previously estimated. Although this combination of pharmacokinetics and computer technology is with no doubt a significant advance for delivering intravenous drugs, there are still some problems and limitations regarding target-controlled infusion systems.[1] One of them refers to the fact that it is the effect site or "biophase" concentration, not the plasma concentration, that best correlates with drug effect. Therefore, targeting the plasma concentration results in a delayed effect with respect to plasma concentration in non–steady state conditions,[2,3] and the effect site seems to be a more logical target when rapid variations in the level of effect are needed as occurs in clinical anesthesia.[1] Targeting the effect site, however, requires specific pharmacokinetic parameters of the biophase such as the plasma effect site equilibration rate constant (k_{e0}), which describes the removal of the drugs from the effect site. The k_{e0} can be incorporated into the pharmacokinetic model to calculate the dosing scheme to target effect site instead of plasma; however, this parameter has not been defined for a number of drugs. For example, propofol is the only drug with commercially available target-controlled infusion devices for adults (Diprifusor; Graseby Medical Ltd., Hertfordshire, United Kingdom) and children (Paedfusor; Graseby Medical Ltd.), and although the k_{e0} of propofol has been determined for the adult population,[4–6] we are not aware of any report of this parameter in children. Moreover, and in addition to potential pharmacodynamic differences between these two populations, because the k_{e0} is specific to a particular vector of pharmacokinetic parameters, it is not correct to extrapolate a value derived from an adult model into a pediatric pharmacokinetic model of propofol. These facts preclude the more rational approach of targeting effect site when infusing propofol in this population.

Because measuring effect site concentration is not possible in clinics, a surrogate measurement, such as the drug effect within the central nervous system, is needed. Electroencephalographic-derived indices, such as those of the Bispectral Index and auditory evoked potential (AEP) monitors, display a continuous measurement of the hypnotic effect of drugs such as propofol, and after the administration of a bolus dose that produces a submaximal effect, the peak effect and the time from injection to peak effect (t_{peak}),[7] can be identified. When there is no drug initially in the body, the magnitude of the maximum effect depends on the dose; however, t_{peak} occurs at the same time regardless of dose.[7] Minto *et al.*[8] have shown that t_{peak} is a model-independent pharmacodynamic parameter that can be used with the appropriate pharmacokinetic parameter set to calculate the value of k_{e0} that accurately predicts t_{peak}. Provided that we have an adequate measurement tool for the drug effect, the t_{peak} method may offer advantages over more traditional methods to estimate k_{e0}. These include the

* Associate Professor of Anesthesiology, † Assistant Professor of Anesthesiology, ‡ Instructor of Anesthesiology.

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Address reprint requests to Dr. Muñoz: Departmento de Anestesiología, Hospital Clínico U.C., Marcoleta 367, P.O. Box 114-D, Santiago, Chile. Address electronic mail to: hmunoz@med.puc.cl. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

determination of a single point (the maximum effect) instead of the complete course of drug effect,[4] the fact that no assumptions are needed on the degree of equilibration between plasma and biophase after an infusion[6] or step modifications of plasma concentrations,[5] and the fact that the t_{peak} method requires a reduced number of mathematical iterations that can lead to increasing inaccuracies.[4–6] Schnider *et al.*[6] found that the t_{peak} of propofol tends to increase with age in adults. Although *a priori* it is not possible to extrapolate the t_{peak} of propofol obtained from adults to children, we hypothesize that this value in children may be smaller. Therefore, the objective of this study was to determine the t_{peak} of propofol in children and compare this value with that of adults. A derived and equally important objective is to calculate the k_{e0} of propofol in children with two pharmacokinetic models of propofol for this population using the t_{peak} method.

Materials and Methods

After institutional ethics committee approval (School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile) and obtaining informed consent, 25 adult patients aged 35–48 yr and 25 children aged 3–11 yr were studied. All patients were unpremedicated, had American Society of Anesthesiologists physical status I, and were scheduled to undergo elective surgery during general anesthesia. Exclusion criteria included a weight greater than 120% of ideal, long- or short-term (within the previous 48 h) intake of any sedative and analgesic drug, and any known adverse effect to the study drugs. In the operating room, after routine monitoring, three electrodes (A-Line electrodes; Medicotest A/S, Oelstykke, Denmark) were positioned at the mid forehead (+), the left forehead (reference), and the left mastoid (−) in all patients. A bilateral click stimulus of 70 db and 2 ms duration was applied by means of headphones, and the midlatency AEPs elicited were processed continuously using the Alaris A-Line AEP monitor, version 1.4 (Danmeter A/S, Odense, Denmark). The A-Line AEP monitor uses an Auto Regressive method with exogenous input (ARX) model to process the AEPs and displays the A-Line ARX-index (AAI), a dimensionless number from 100 (fully awake) to 0 (conceivably a flat electroencephalography). The index was obtained as "normal AAI," which displays the on-line measured index at a rate of 1 Hz. Because the monitor initially needs a period of time to process the AEPs and give the first AAI value, the subsequent values are shown with a time delay of approximately 6 s. When the impedance of the electrodes was less than 5 kΩ and there were no warnings of poor quality signal on the screen of the monitor, a bolus dose of propofol (1%; Fresenius Kabi, Hamburg, Germany) producing a submaximal effect (*i.e.*, the minimum AAI value generated by the A-Line AEP monitor was > 0) was injected manually as fast as possible (always in less than 5 s) and followed by a flush of saline. Because initially the "useful" dose of propofol had to be determined, the first patients in both groups received different doses on a weight basis. Patients who did not lose the eyelash reflex were excluded from the study because their recording of AAI values did not always allow the detection of an evident minimum. Besides the confirmation of the presence or absence of the eyelash reflex, no other stimulation was applied (*i.e.*, noninvasive arterial pressure) to patients. When a minimum AAI value was obtained and partial recovery from propofol was evident as suggested by increasing AAI values, the study was finished and anesthesia continued according to the attending anesthesiologist.

The AAI values recorded by the AEP monitor at a frequency of 1 Hz were imported into an Excel (Microsoft Corporation, Redmond, WA) spreadsheet for off-line determination of the time of peak effect (t_{peak}, time from the beginning of injection of propofol until the minimum AAI value). In the few cases where a minimum AAI value remained constant for a few seconds (usually for 5–6 s), the time until the first lowest AAI value was considered the t_{peak}. Because the AAI value is displayed with a 6-s delay, for subsequent analysis, we subtracted 6 s from the t_{peak} determined off-line. Because at t_{peak} the maximum effect site concentration (C_e) of propofol occurs and equals that of plasma (C_p), after a bolus, we can calculate these concentrations (μg/ml) with the dose (mg) and the Unit Disposition Function of the effect site at t_{peak} ($C_e(t_{peak})$) with the formula

$$C_p(t_{peak}) = \text{Dose (mg)} \times \sum_{i=1}^{n} A_i e^{-\lambda_i t_{peak}} = C_e(t_{peak}). \quad (1)$$

where A and λ are pharmacokinetic parameters. Then, using $C_e(t_{peak})$ the value of k_{e0} was calculated with the equation

$$C_e(t_{peak}) = \text{Dose (mg)} \times \sum_{i=1}^{n} \frac{k_{e0} A_i}{k_{e0} - \lambda_i} (\lambda_i e^{-\lambda_i t_{peak}} - k_{e0} e^{-k_{e0} t_{peak}}). \quad (2)$$

This equation was solved for k_{e0} for each patient with the Solver function of Excel using the pharmacokinetic parameters for propofol determined by Schnider *et al.*[9] for adults and those determined by Kataria *et al.*[10] for children. In children, k_{e0} was also calculated with the pharmacokinetic model used in the Paedfusor. The constants of this model are k12 = 0.114, k13 = 0.0419, k21 = 0.055, k31 = 0.0033. Central compartment volume and k10 vary with age and weight, but for children aged 12 yr or younger they are V1 = 458.4 ml/kg and

Table 1. General Data

	Adults (n = 25)	Children (n = 25)
Age, yr	41 ± 4	6.6 ± 2.3*
Weight, kg	68 ± 13	29 ± 12*
Height, cm	165 ± 10	124 ± 16*
Propofol, mg/kg	1.6 ± 0.1	2.7 ± 0.3*
Baseline AAI value	68 ± 16	72 ± 17
Minimum AAI value after propofol	15 ± 6	26 ± 11*

Values are presented as mean ± SD.

* $P < 0.05$ between groups.

AAI = A-Line ARX index.

$k10 = 0.1527 \times \text{weight}^{-0.3}$.[11] Finally, as a simple way to validate the model, in terms that the population k_{e0} determined for each group is capable to predict a t_{peak} similar to the measured t_{peak}, the median k_{e0} determined from all children and all adults was used to calculate, with the corresponding pharmacokinetic parameters, the "predicted" t_{peak} for each patient.

Statistical analysis was with the Kolmogorov–Smirnov test as a test of normality. This was followed by paired and unpaired Student *t* tests, and Wilcoxon and Mann–Whitney tests for variables with and without normal distribution, respectively. A *P* value less than 0.05 was considered significant. Values are presented as mean ± SD or median (range).

Results

Demographic data for both groups, the dose of propofol, and AAI values are shown in table 1. There was a wide variability in the baseline AAI values in both children and adults. Moreover, whereas there was no difference between children and adults in the AAI values measured awake, after propofol, adults reached a lower AAI value compared with children (fig. 1 and table 1).

The t_{peak} was 80 ± 20 s (43–108 s) in adults and 132 ± 49 s (53–209 s) in children ($P < 0.001$; fig. 2). In both groups, there was a non- statistically significant tendency to an increase of t_{peak} with age. In all patients, it was possible to determine with equation 2 the k_{e0} that exactly matched the measured t_{peak} (minus the 6-s delay) (fig. 3). The Kolmogorov–Smirnov test detected that the k_{e0} and $t_{1/2}$ k_{e0} did not have normal distribution; consequently, they were analyzed with Mann–Whitney and Wilcoxon tests. The calculated median k_{e0} was 0.56 min^{-1} (0.30–2.00 min^{-1}) in adults. In children, the median k_{e0} was 0.41 min^{-1} (0.12–1.85 min^{-1}) using the model of Kataria and 0.91 min^{-1} (0.40–3.34 min^{-1}) with the Paedfusor parameters ($P < 0.001$, Wilcoxon test). These k_{e0} values led to a median $t_{1/2}$ k_{e0} value of 1.24 min (0.35–2.33 min) in adults and 1.7 min (0.4–5.9 min) and 0.8 min (0.2–1.7 min) in children with the Kataria and Paedfusor models, respectively ($P < 0.001$, Wilcoxon test). When the k_{e0} and $t_{1/2}$ k_{e0} from adults were compared with those from children, a statistically significant difference was found only with those parameters determined with the Paedfusor model ($P < 0.01$, Mann–Whitney test).

The "predicted" t_{peak} in adults using a k_{e0} of 0.56 min^{-1} was 82 ± 2 s (77–85 s) and was not significantly different from the measured t_{peak} with the paired Student *t* test. (fig. 4). In children, using a k_{e0} of 0.41 min^{-1} and the pharmacokinetic model of Kataria, the "predicted" t_{peak} was 131 ± 25 s (94–184 s). In this same age

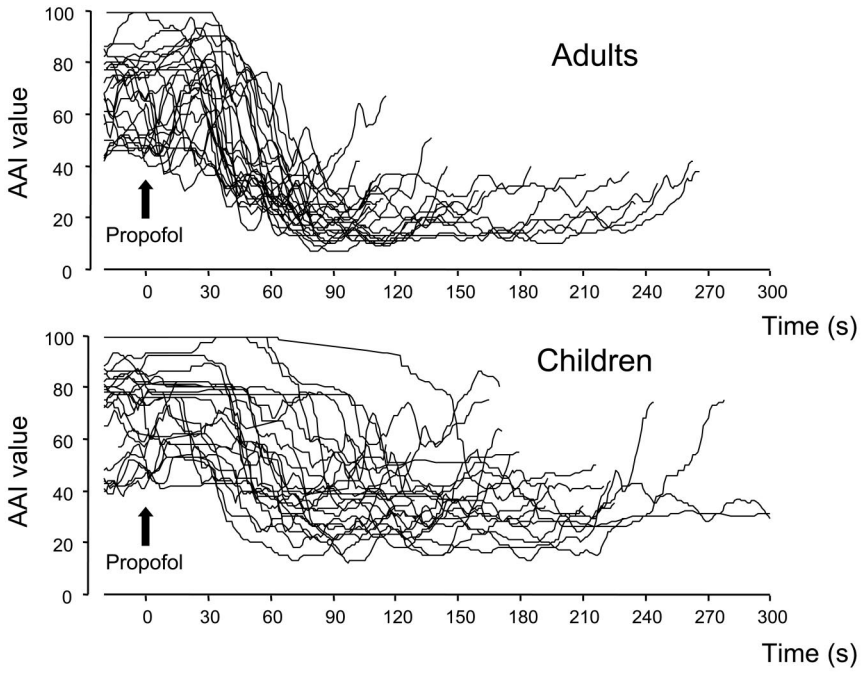

Fig. 1. Evolution of the A-Line monitor index (AAI) values during the study in the 25 adults (*top*) and 25 children (*bottom*). The *arrows* indicate the injection of propofol.

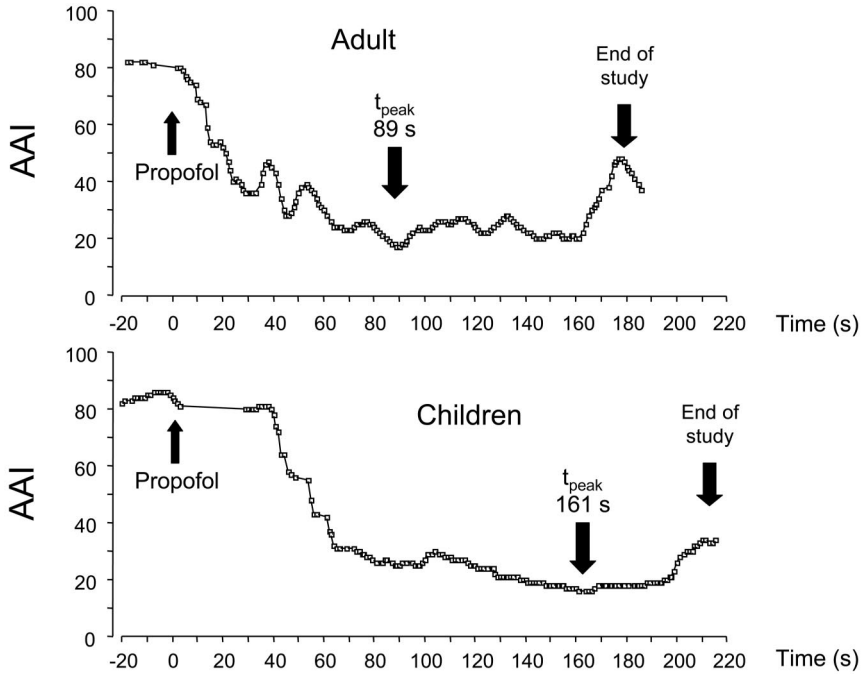

Fig. 2. Evolution of the raw A-Line monitor index (AAI) recording over time from 20 s before propofol administration (time = 0 s) until the end of study in two patients. The *upper graph* corresponds to a 38-yr-old woman (weight, 69 kg; height, 166 cm) who had a time to peak effect (t_{peak}) of 89 s after 100 mg propofol. The *lower graph* corresponds to a 5-yr-old girl (weight, 22 kg; height, 117 cm) who had a t_{peak} of 161 s after 60 mg propofol. For further analysis, 6 s were subtracted from these t_{peak} values because this is the time delay of the A-Line AEP Monitor in showing the AAI values.

group, using a k_{e0} of 0.91 min^{-1} and the Paedfusor pharmacokinetic model, the "predicted" t_{peak} was 128 ± 3 s (125–140 s). These were not significantly different from the measured t_{peak} with the paired Student *t* test (fig. 4).

Discussion

The main finding of this study is that the peak effect of propofol in children occurs significantly later as compared with adults. Expectedly, the calculated values of k_{e0} and $t_{1/2}$ k_{e0} depend on the pharmacokinetic model used to derive these parameters.

Propofol is widely used for intravenous anesthesia; however, we are not aware of any study determining the k_{e0} of propofol in children. An accurate determination of a given drug's k_{e0} is useful for targeting the effect site instead of the plasma concentration during computer-controlled drug administration, for designing and interpreting clinical pharmacologic research, and for simulations of the time course of a drug effect.

To calculate the k_{e0}, the t_{peak} method was used as proposed by Minto *et al.*[8] The t_{peak} is a pharmacokinetic model–independent parameter that can be directly observed after a bolus dose of a drug, provided that the

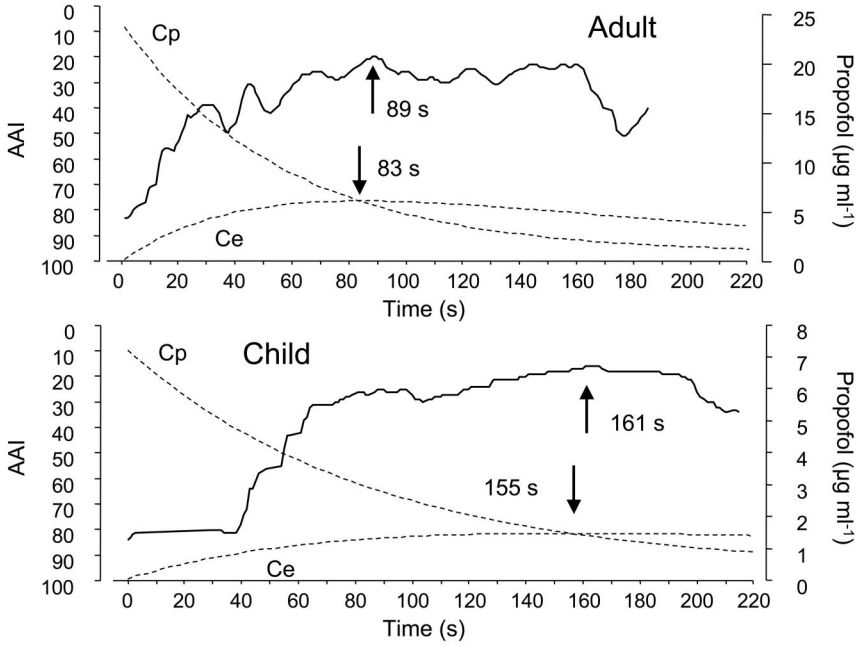

Fig. 3. A-Line ARX index (AAI) values after propofol (*thick line*) of the same adult (*upper graph*) and child (*lower graph*) of figure 2. AAI recordings have been turned upside-down to display graphically the "increase" in the effect. The *thin, dashed lines* represent the plasma (C_p) and effect site (C_e) concentration of propofol after 100-mg and 60-mg bolus doses in the adult and child, respectively. In the adult, C_p and C_e have been estimated with the parameters of Schnider and the individual plasma effect site equilibration rate constant (0.502 min^{-1}). In the child, C_p and C_e have been estimated with the parameters of Kataria and the individual plasma effect site equilibration rate constant (0.229 min^{-1}). C_es peak 6 s earlier than time to peak effect measured from the AAI recording because we subtracted the 6-s delay in the signal of the monitor for calculation of C_e peak.

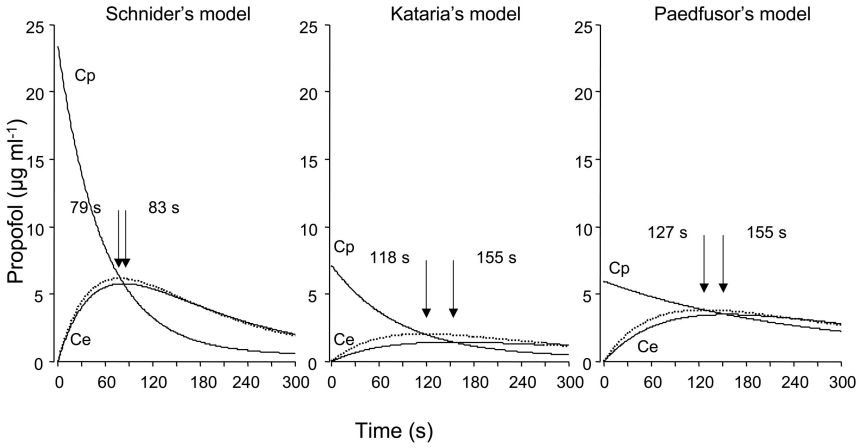

Fig. 4. Time evolution of plasma (C_p) and effect site (C_e) concentration of propofol of the same woman and girl of previous figures. The *left graph* corresponds to the adult and her estimated C_p and C_e with the model of Schnider and her own plasma effect site equilibration rate constant (k_{e0}) (0.502 min^{-1}) (C_e with *continuous line*). The *dotted line* corresponds to C_e calculated with the same model and the median k_{e0} obtained from the adult group (0.56 min^{-1}). The *center* and *right graphs* correspond to the C_p and C_e of the girl calculated with the parameters of Kataria and Paedfusor. C_es with *continuous line* were obtained with the individual k_{e0}s derived from the models (0.23 min^{-1} and 0.66 min^{-1} with the parameters of Kataria and Paedfusor, respectively). C_es with *dashed lines* were calculated using the population k_{e0}s (0.41 min^{-1} and 0.91 min^{-1}, respectively).

drug is given for the first time, that a submaximal response is elicited, and that its time course can be measured accurately.[3,7,8] In turn, this t_{peak} can be mathematically related to any adequate pharmacokinetic model to calculate the corresponding k_{e0} that will result in a maximal effect site concentration at the moment of t_{peak}.[3,6,8] The mean t_{peak} of 80 s found in our study for adults is shorter than the t_{peak} of 96 s observed by Schnider *et al.*[6]; however, we injected propofol in less than 5 s, whereas in the study of Schnider, the injection lasted 18 s (range, 13–24 s), and this might have lead to different t_{peak}s. Using the pharmacokinetic model for propofol of Schnider *et al.*,[9] we found a median value for the k_{e0} of 0.56 min^{-1} and a $t_{1/2}$ k_{e0} of 1.2 min in adults. This $t_{1/2}$ k_{e0} calculated in our study is 20% smaller than the 1.5 min reported by Schnider *et al.*[6] Although this difference (and that in k_{e0}) can be first accounted for by the differences found in t_{peak} values, it might also be secondary to the use of different monitors of drug effect. In addition, anthropometric differences in the populations under study leading to different pharmacokinetic variables and therefore to different k_{e0} values cannot be ruled out. The $t_{1/2}$ k_{e0} of propofol reported in this study and that of Schnider are smaller than $t_{1/2}$ k_{e0}s calculated in other studies and that go up to 4.0 min.[4,5] In this last case, however, these differences could be secondary to the use of different pharmacokinetic models for propofol because the value of k_{e0} is critically dependent on the pharmacokinetic model used.

In the case of children aged 3–11 yr, we found a t_{peak} of 132 s, which is significantly larger than that of adults. Therefore, our initial hypothesis of a shorter or faster t_{peak} in children than adults, which would agree with the tendency to an increase of t_{peak} with age in adults,[6] is not supported by our findings. The t_{peak} or time of maximal effect site concentration of a drug after a bolus depends on two simultaneously occurring processes: One is the decreasing plasma concentration, and the other is the increasing effect site concentration. The faster the decrease of plasma concentration is, the sooner t_{peak} occurs. As shown in figures 4 and 5, the pharmacokinetic models of propofol of both Kataria and the Paedfusor in children predict a slower decrease of plasma concentration compared with the model of Schnider in adults. This

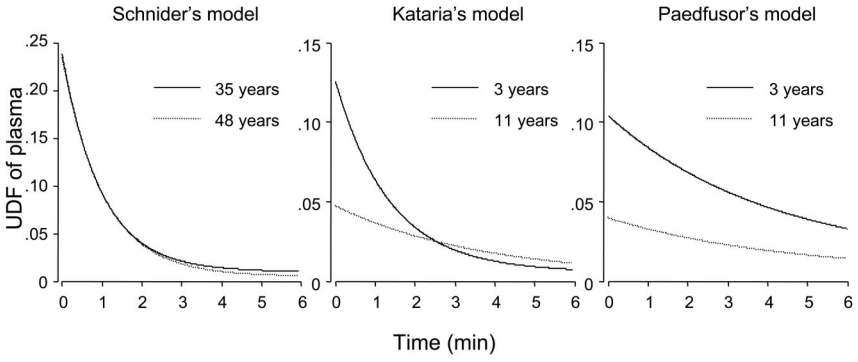

Fig. 5. Unit disposition function (UDF) of the plasma *versus* time determined with the model of Schnider in the youngest and eldest adult of our study (*left*) and in a 3-yr-old child and an 11-yr-old child according to the model of Kataria (*center*) and the Paedfusor (Graseby Medical Ltd., Hertfordshire, United Kingdom) parameters (*right*). The variability is much larger in children, particularly using the Paedfusor model. This variability in the rate of plasma concentration decay may explain part of the variability of time to peak effect in children.

could be an explanation for a slower t_{peak} in this age group. The larger variability of t_{peak} in children could be also secondary to the much larger variability in pharmacokinetic parameters within children aged 3–11 yr compared with adults aged 35–48 yr, as shown in figure 5.

When the t_{peak} found was used to calculate the k_{e0}, the results were significantly different depending on the pharmacokinetic model used. With the model of Kataria *et al.*,[10] the k_{e0} was 0.41 min^{-1}, resulting in a $t_{1/2}$ k_{e0} of 1.7 min that supports a slower t_{peak} in children than in adults, whereas with the Paedfusor parameters, the k_{e0} was 0.91 min^{-1}, and the $t_{1/2}$ k_{e0} was 0.8 min. These results emphasize two facts: One is that the k_{e0} value is critically determined by the particular set of pharmacokinetic parameters used to calculate it; therefore, k_{e0} cannot be used interchangeably with different models. The other is that despite a shorter $t_{1/2}$ k_{e0}, as occurs with the value determined by the Paedfusor, compared with that from adults, t_{peak} can be longer secondary to a much slower decrease of plasma concentration. We are not aware of any other reported value for these variables in children, and these findings must be prospectively confirmed.

To validate the estimates of k_{e0}, we compared the mean measured t_{peak} with the mean predicted t_{peak} in each population using the median k_{e0}. The observed time of peak effect in adults (80 s) agrees almost exactly with the predicted t_{peak} of 82 s using the pharmacokinetics of Schnider *et al.*[9] and a k_{e0} of 0.56 min^{-1}. In children, the predicted t_{peak} of 131 s using the pharmacokinetics reported by Kataria *et al.*[10] and a k_{e0} of 0.41 min^{-1} and the predicted t_{peak} of 128 s with the Paedfusor parameters and a k_{e0} of 0.91 min^{-1} also match almost exactly the observed value of 132 s. This good agreement between mean measured and predicted t_{peak}s suggests that the incorporation of the appropriate k_{e0} calculated in this study to the pharmacokinetics of Kataria and the Paedfusor may result in adequate models for targeting the effect site concentration of propofol in children.[3]

A criticism of our methodology might be related to the specific electroencephalographic monitor used. The Alaris AEP monitor (version 1.4) used in our study delivers a dimensionless number (AAI value) derived from the processing of the midlatency AEPs and might be regarded as very different from the electroencephalographic-derived measures in several aspects. While Alaris AEP monitor must be validated in children, the similarity of the t_{peak} in our study with that obtained by Schnider *et al.*[6] suggests that both monitors are measuring, at least in adults, a similar underlying process that is modified by propofol. The baseline AAI values were similar in children and adults, whereas the minimum value was significantly higher in children. Although figure 5 shows that both pediatric models for propofol predict a lower peak effect site concentration than in adults, thus suggesting that a pharmacokinetic difference may explain different minimum AAI values, pharmacodynamic differences cannot be ruled out.

As previously mentioned, at least theoretically, the effect site is a more logical target than plasma. This reduces the delay to obtain a given drug effect and possibly also its variability, which occurs when the target is plasma concentration.[2,3] Because targeting the effect site is initially accompanied by a high plasma concentration or "overshoot," the possibility that this might lead to more incidence of adverse effects (*e.g.*, hypotension in the case of propofol)[1] is a potential disadvantage of this technique. However, controlled studies with propofol have not shown more adverse effects when targeting an effect site concentration instead of plasma.[2,3]

In conclusion, we have measured the time to peak effect of propofol in children and adults. Although this time is significantly longer in children, the finally calculated k_{e0} is particular to the model used to derive this parameter. The k_{e0}s obtained from the models of Kataria and the Paedfusor for propofol in children can be used with caution with the corresponding models to target effect site concentration of propofol in children. However, these parameters must be further validated before their widespread use in clinical anesthesia.

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