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PAEDIATRICS

Impact of propofol on mid-latency auditory-evoked potentials in children†

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Editor's key points

- Propofol-induced changes in mid-latency auditory-evoked potentials (MLAEPs) have not been well described in children.
- The authors recorded MLAEPs during the awake state and at three different propofol target concentrations.
- Dose-dependent changes in MLAEP latencies and amplitudes were found.
- MLAEP-based analyses may be suitable for depth of anaesthesia monitoring during propofol anaesthesia in children.

Background. Propofol is increasingly used in paediatric anaesthesia, but can be challenging to titrate accurately in this group. Mid-latency auditory-evoked potentials (MLAEPs) can be used to help titrate propofol. However, the effects of propofol on MLAEP in children are unclear. Therefore, we investigated the relationship between propofol and MLAEP in children undergoing anaesthesia.

Methods. Fourteen healthy children aged 4–16 yr received anaesthesia for elective surgery. Before surgery, propofol was administered in three concentrations (3, 6, 9 μg ml^{-1}) through a target-controlled infusion pump using Kataria and colleagues' model. MLAEPs were recorded 5 min after having reached each target propofol concentration at each respective concentration. Additionally, venous propofol blood concentrations were assayed at each measuring time point.

Results. Propofol increased all four MLAEP peak latencies (peaks Na, Pa, Nb, P1) in a dose-dependent manner. In addition, the differences in amplitudes were significantly smaller with increasing propofol target concentrations. The measured propofol plasma concentrations correlated positively with the latencies of the peaks Na, Pa, and Nb.

Conclusions. Propofol affects MLAEP latencies and amplitudes in children in a dose-dependent manner. MLAEP measurement might therefore be a useful tool for monitoring depth of propofol anaesthesia in children.

Keywords: monitoring, auditory-evoked potentials; paediatric anaesthesia; propofol

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Although volatile anaesthetics are the most frequently used hypnotic medication in paediatric anaesthesia, the i.v. drug propofol is becoming increasingly popular. The advantages and disadvantages associated with the use of propofol in paediatric anaesthesia were recently highlighted by Lerman and Jöhr.[1] Although volatile anaesthetics are simple to administer, they are associated with a high rate of emergence agitation in children.[2–4] In contrast, recovery of paediatric patients after propofol anaesthesia is seldom associated with emergence agitation.[5] A further advantage of propofol is the reduced frequency of postoperative nausea and vomiting.[6] However, one of the major challenges associated with the use of propofol is the limited ability to continuously measure propofol concentrations in patients,[7] in contrast to the simple and effective end-tidal measurement of volatile anaesthetics. EEG-based monitors can be used to estimate the effect of propofol on brain cortical activity. Measurement of mid-latency auditory-evoked potentials (MLAEPs) is another method used to assess the effect of propofol on the brain activity.[8] In contrast with adults, the influence of

† This study was performed during November 2006 and August 2007 and was therefore not registered at a public trial platform.
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propofol on MLAEP in children is not well described. Therefore, the aim of this study was to investigate the alterations in raw MLAEPs during anaesthesia with propofol and to examine potential dose–response relationships between three propofol target concentrations, measured propofol concentrations, and MLAEP parameters.

Methods

Patients and study design

Study approval was obtained by our institutional review board (Project-Nr. 148/00, University of Munich, Munich, Germany) and written informed consent was signed either by the child and their parents or by the parents alone.

In total, 14 patients aged 4–16 yr were enrolled in the study (Table 1). All patients were undergoing elective lower limb orthopaedic surgery. Patients classified ASA I or II were selected for this study. Exclusion criteria were a history of neurological or hearing disorders, the intake of centrally acting substances, or neurological diseases.

MLAEP acquisition

MLAEP measurement was performed as follows (see also Daunderer and colleagues).[8] For the measurement of auditory-evoked potentials (AEPs), the skin was cleaned with acetone before the attachment of Ag/AgCl adhesive electrodes (Neuroline 7200 00-S, Ambu/Medicotest, Denmark) on A1, A2, Fp1, Fp2, Fpz, and Cz according to the international 10/20 system. Adjustable headphones were then applied and the correct placement was visually controlled. For accurate data acquisition, inter-electrode impedances were kept below 5 kOhm. The electrodes were connected to a preamplifier (POD, Siemens Medical, Erlangen, Germany) wired to feed four recording channels (A1/Fp1, A2/Fp2, A1/Cz, and A2/Cz with Fpz as the common ground). Amplification and digitalization of the signals occurred within the preamplifier (sensitivity 0.017 mV, sampling rate 4 kHz). Signals were transmitted to the recording system via broadband fibreglass cables. Measured data were analysed in an offline analysis with specially designed software (NaMo v. 8.0, Toennies/Viasys, Hoechberg, Germany). Extraction of 1000 successive EEG epochs of 100 ms duration after each stimulus was done. Out of the 1000 EEG epochs, one single high-quality AEP for each channel was averaged. The time taken to obtain one AEP measurement was ~108 s. EEG epochs with amplitudes above the cutting point of 250 μV were rejected and not added to the AEP. No other additional data filtering was done. As a consequence of the online rejection, when values were above the cutting point, only an approximate time for one AEP collection can be given—in this study, it was an average time of 108 s. AEP signals were manually inspected and the channel with the best recordings was selected. For quality control, two independent investigators (M.F., G.F.) performed the visual data analysis. These investigators were aware of the recordings but blinded to individual patient data (age, body weight) and clinical data (propofol target concentrations, state of consciousness). Signal quality was classified as excellent, acceptable, or insufficient for interpretation. Distorted or insufficient AEP signals were excluded from further analysis. MLAEP peaks were identified according to the nomenclature of Picton and colleagues.[9] Negative peaks were manually marked by the two investigators with Na and Nb, whereas positive peaks of the MLAEP were marked as Pa and P1. In addition, the differences of interpeak amplitudes Na/Pa, Pa/Nb, and Nb/P1 were measured and calculated. Adequate AEP detection was validated by identification of the brainstem AEP peak V (data not shown).

Table 1 Patient characteristic data; data are presented as mean (SD) (range)

Patient characteristic data	Mean (SD) (range)
Patient characteristics	
Number of patients (*n*)	14
Age (yr)	8.6 (4.3) (4.0–16.5)
Weight (kg)	29.2 (14.6) (15.0–60.0)
Height (cm)	125.9 (26.2) (67.0–160.0)
Gender: male/female (*n*)	6/8
Details of anaesthetic procedure	
Duration of anaesthesia (min)	171.4 (52.0) (78.0–253.0)
Premedication	
Dosage midazolam (mg kg^{-1}) p.o.	0.42 (0.14)

Anaesthetic regime

After the patients' arrival at the operating theatre, standard clinical monitoring (including ECG, pulse oximetry, oscillometric arterial pressure monitoring) was applied. An i.v. line was inserted into a forearm vein. After placement of the above-described MLAEP unit, a first AEP recording was taken in the premedicated awake state. Patients were advised to keep their eyes open and fixate on one point. Anaesthesia was induced by the application of propofol using a target-controlled infusion (TCI) pump (Alaris, Höchberg, Germany). This TCI pump was based on the pharmacokinetic model of Kataria and colleagues,[10] consisting of a weight-proportional model in which age is an additional covariate for the rapid distribution compartment (V_2).

Anaesthesia was induced using a target concentration (C_t) of propofol of 6 μg ml^{-1}. Before tracheal intubation, a single i.v. dose of 0.4 mg kg^{-1} atracurium was administered. After intubation, the C_t was raised to 9 μg ml^{-1}. A second i.v. line was inserted in an extremity different from the one into which the propofol was being infused. After reaching the target concentration, steady state was kept for an extra 5 min. Thereafter, the MLAEP of the respective target concentration was recorded and documented into the study computer. Subsequently, the second concentration (C_t of 3 μg ml^{-1}) was programmed into the TCI pump. After achieving this target propofol concentration, 5 min was left to pass until taking the MLAEP reading. The same

procedure was done for the third target concentration of 6 μg ml^{-1}. After the propofol titration and MLAEP recording, and before surgical manipulation, all patients received 0.3 μg kg^{-1} sufentanil. Further anaesthetic management was based on the anaesthetic standard for surgical procedures. The anaesthetist was blinded to the AEP monitoring and recording.

Modified AEP index

Reviewing the literature, MLAEPs are often indexed to simplify their applicability. We applied therefore a modified index according to the work of Mantzaridis and Kenny[11 12] to our data. For calculation of this index, all amplitude readings were multiplied by 100. We then summed the square roots of the absolute difference in the amplitude of every two consecutive peaks observed between 10 and 100 ms. This results in a single index number.

Determination of plasma propofol concentration

At the end of every MLAEP observation, a venous blood sample was drawn from the second i.v. line. Venous whole blood samples were stored at −60°C until further analysis. Propofol measurement was done by liquid chromatography ion spray tandem mass spectrometry according to the method described by Beaudry and colleagues.[13]

Statistical analysis

Comparisons were performed for the modified AEP index, peak latencies, and differences in peak amplitudes between the awake state and the three propofol concentrations ('consciousness states') using the Page test for comparison of four and three samples (out of four propofol levels, i.e. three propofol concentrations and baseline without propofol) ordered by concentration followed by pairwise comparisons with the Wilcoxon signed-rank test. Exploring potential endpoints for monitoring different states in anaesthesia, closed testing accounts for multiple comparisons of groups at a two-sided 0.05 level of significance. However, the 0.05 level was not further adjusted for testing of the multiple endpoints.

Propofol whole blood concentrations and selected peak MLAEP were calculated in a non-linear regression and applied to a dose–response curve. The data were fitted to the commonly used E_{max} model: Effect$=E_0+(E_{max}-E_0)\times C_{pl}^{\gamma}/(C_{pl50}^{\gamma}+C_{pl}^{\gamma})$, where 'Effect' reflects the drug response, C_{pl} the measured propofol plasma concentration, C_{pl50} the propofol concentration associated with 50% of the maximal drug effect, E_0 the baseline effect, corresponding to the response, when the dose of the drug is zero, E_{max} the maximal effect on MLAEP, which can be achieved by propofol, and γ the Hill coefficient of the dose–response curve.

Data are presented as mean (SD). Statistical calculations were performed using Sigma Plot 11.0, Chicago, IL, USA, StatXact of Cytel Studio 6.2.0, CytelCorporation, Cambridge, MA, USA, and R 2.14, www.r-project.org.

Results

General patient characteristic data and details of anaesthesia are presented in Table 1.

MLAEPs were recorded from 14 individuals at each time point, resulting in 56 MLAEPs in total. The data quality was rated excellent in 39 AEPs and good in 17 AEPs. None of the MLAEPs was excluded.

All four peak latencies of the MLAEPs increased with higher propofol target concentrations (C_t) (Fig. 1). For the peak Pa, all measurements were different from the premedicated awake state, including at the lowest infusion target (3 μg ml^{-1}). Differences were also seen between the different propofol target concentrations in each MLAEP peak. In most of the cases, the increase in peak latencies reached the level of statistical significance (Fig. 1). In the majority of patients, the P1 latency reached the upper measuring limit of 100 ms at propofol target concentrations of 6 and 9 μg ml^{-1}. In these cases, latency values were set at 100 ms. Similar results could be found for the peak latency Nb at the highest target propofol concentration (9 μg ml^{-1}) (Fig. 2).

MLAEP peak latencies were not the only signals to be altered under the influence of propofol. Differences of the corresponding amplitudes decreased with increasing propofol concentrations (Fig. 3). This was statistically significant for differences of amplitudes for Na/Pa and Pa/Nb in comparison with the awake state (Fig. 3). As described above, for the two highest propofol concentrations, the difference Nb and P1 were frequently outside the measuring window of 100 ms. This fact creates border effects for Nb/P1. Therefore, the validity of the difference in amplitudes of Nb/P1 is limited.

In general, the correlation between peak latencies and differences in amplitudes and the propofol target concentrations is variable. For example, Pa shows less change at the 3 μg ml^{-1} level compared with strong alteration at TCI levels of 6 and 9 μg ml^{-1}. In contrast, larger changes can be seen for the peak latency Nb at TCI 3 μg ml^{-1}.

Changes in inter-peak amplitudes also demonstrate differences. Strong changes can be seen for Na/Pa at TCI 3 μg ml^{-1} but hardly any at the same level for Nb/P1. This is also associated with the border effects of the measuring window of 100 ms of latency.

In 10 out of the 14 study persons, a second i.v. line could be established for blood sampling for venous propofol concentration determination. In four patients, no second i.v. line could be inserted or blood could not be aspirated from the i.v. line. A total of 40 venous blood samples for propofol analysis were collected in these patients. Linear regression between TCI target concentration and measured propofol plasma concentration showed $r=0.704$ ($P<0.001$, $n=40$).

When propofol blood concentrations were plotted against peak latencies Na, Pa, Nb, and P1, a non-linear increase in latencies was observed (Fig. 4). Differences in amplitudes showed a non-linear decrease with higher propofol concentrations (Fig. 5). The results of fitting to the E_{max} model are shown in Table 2.

The calculated modified AEP index decreased with increasing propofol concentrations in all individuals. The level of statistical significance was reached between all different 'consciousness states'. The MLAEP index showed a non-linear

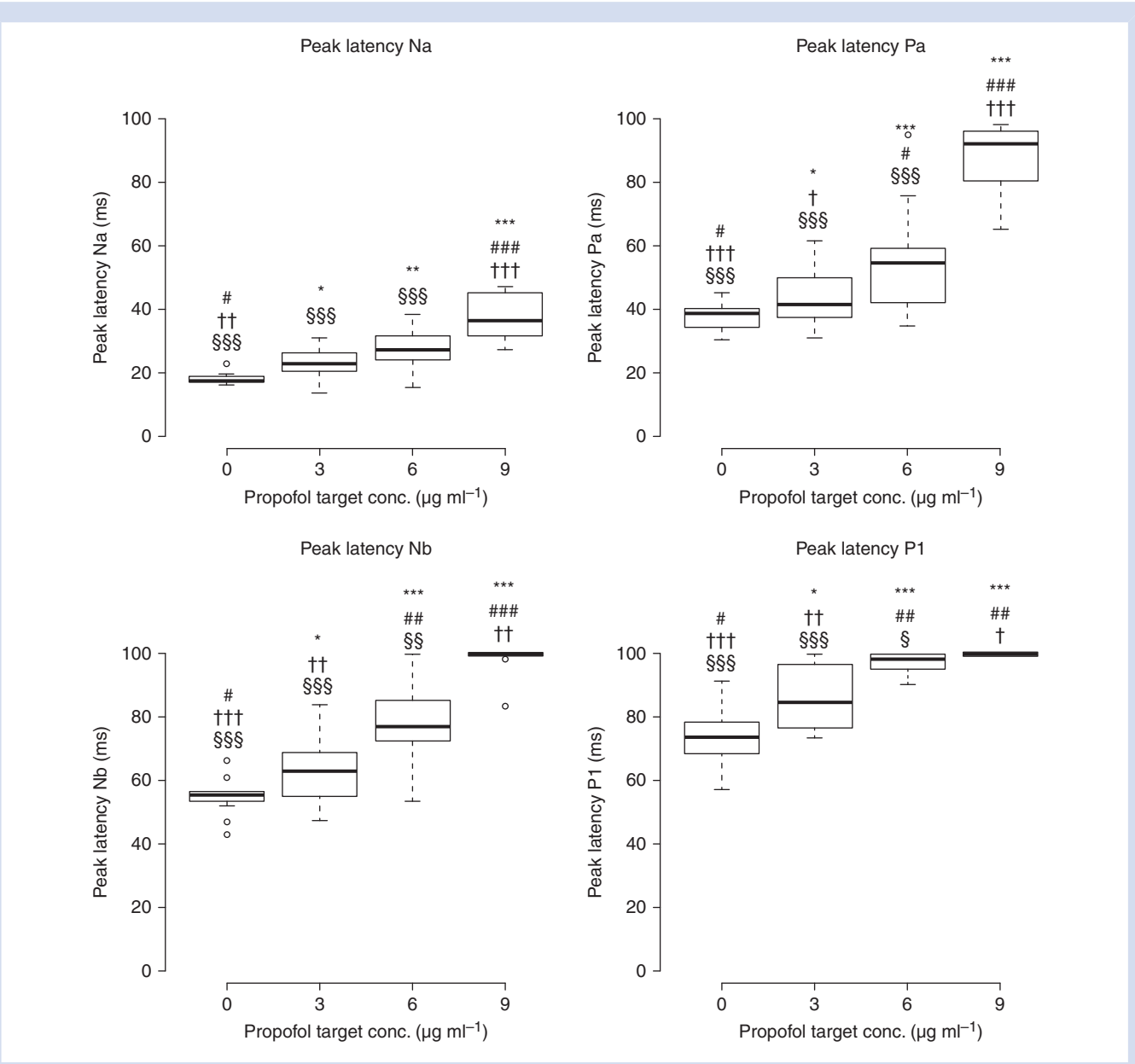

Fig 1 Peak latencies Na, Pa, Nb, and P1 at different conditions; multiple adjusted *P*-values after closed testing using the Page test and the Wilcoxon signed-rank test. Symbols for statistical significance: *indicates comparison with the 0 μg ml^{-1} group, $^{\#}$with the 3 μg ml^{-1} group, †with the 6 μg ml^{-1} group, and §with the 9 μg ml^{-1} group. One symbol reflects a *P*-value of <0.05, two symbols a *P*-value of <0.01, and three symbols a *P*-value of <0.001. Owing to the applied measuring system, the upper limit was set at 100 ms; therefore, peak latencies Nb and P1 experience an artificial ceiling effect at propofol concentrations of 6 and 9 μg ml^{-1}.

decrease with higher measured propofol plasma concentrations (Fig. 6).

Discussion

Our main finding is that propofol infusion alters raw MLAEPs in children, and that these changes occur in a dose-dependent manner. Propofol increases peak latencies Na, Pa, Nb, and P1 and decreases differences of amplitudes for Na/Pa and Pa/Nb in comparison with the awake state.

Reports on changes of MLAEP latencies and amplitudes secondary to propofol administration can be found in adults,[14 15] but to the best of our knowledge, such findings have not been described in children.

Munoz and colleagues[16] reported changes in the AEP index (A-Line ARX, AAI) with propofol in children. However, the data quality was poor and only 12 out of 20 patients had reliable data sets. We were able to measure MLAEP for all our patients at each time-point with a good quality. Furthermore, we observed that MLAEP latencies increased over time under the influence of propofol. This is in good

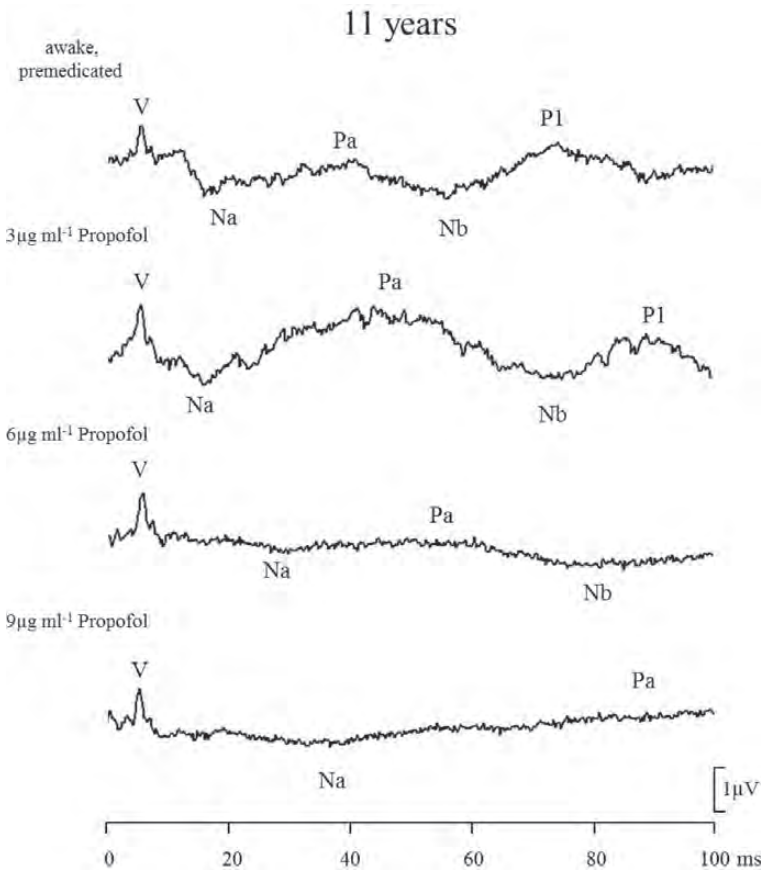

Fig 2 Original MLAEP curves of an 11-yr-old boy.

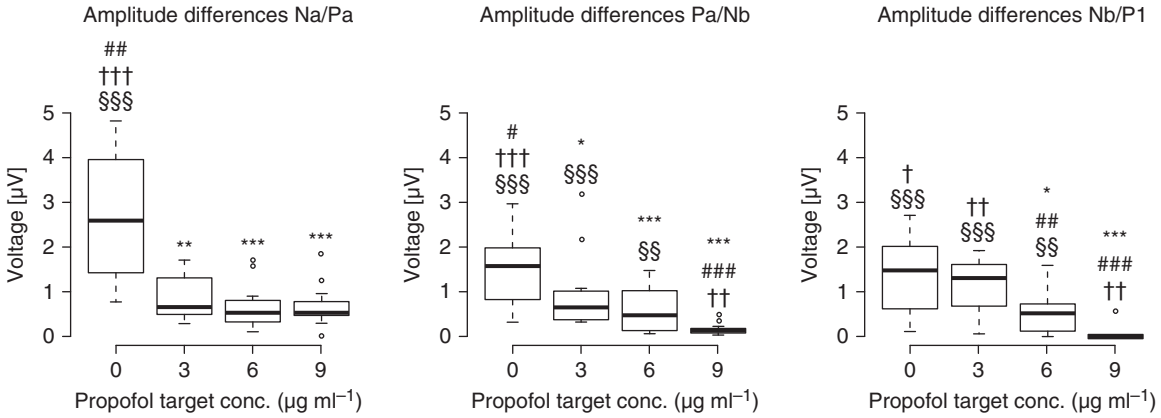

Fig 3 Comparison of the peak latency differences Na/Pa, Pa/Nb, and Nb/P1 at different conditions; multiple adjusted *P*-values after closed testing using the Page test and the Wilcoxon signed-rank test. Symbols for statistical significance: *indicates comparison with the 0 μg ml^{-1} group, #with the 3 μg ml^{-1} group, †with the 6 μg ml^{-1} group, and §with the 9 μg ml^{-1} group. One symbol reflects a *P*-value of <0.05, two symbols a *P*-value of <0.01, and three symbols a *P*-value of <0.001. As the upper measuring limit was set at 100 ms, peak latency difference Nb/P1 experienced for propofol concentrations of 6 and 9 μg ml^{-1} an artificial ceiling effect.

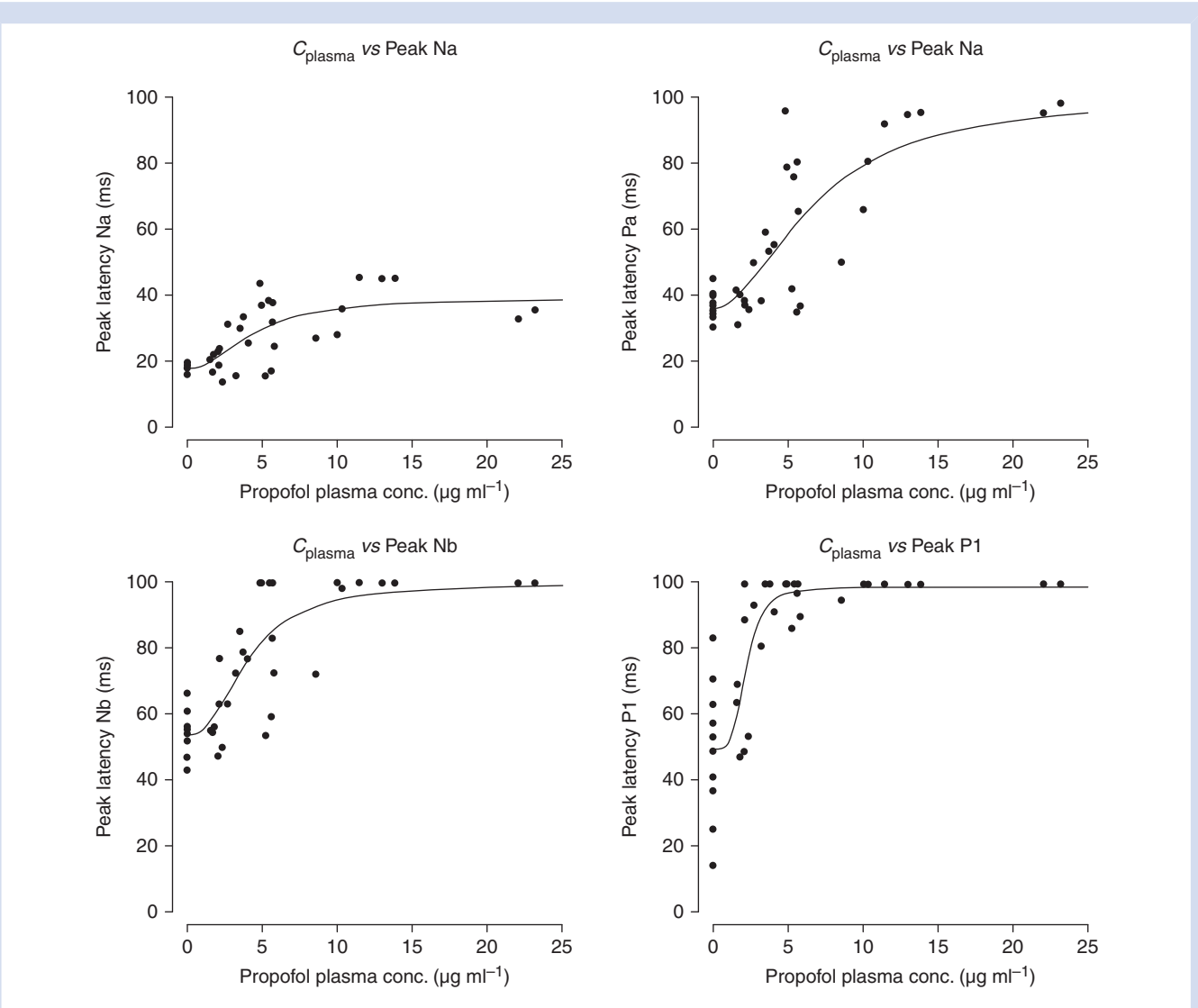

Fig 4 MLAEP peak latencies Na, Pa, and Nb in correlation with propofol plasma concentration; sigmoidal dose–response model, curve fitted. Owing to the applied measuring system, the upper limit was set at 100 ms; therefore, peak latencies Nb and P1 experience an artificial ceiling effect at propofol concentrations of 6 and 9 μg ml^{-1}.

accordance with findings in adult patients[17] and our earlier results with sevoflurane in children.[8 18] We also observed significant changes in the amplitudes of MLAEP. This contrasts with our previous work, where we did not detect changes in the latencies of MLAEP with sevoflurane.[8] The changes in MLAEP amplitudes in this current investigation are consistent with observations in adults in whom a significant decrease in amplitudes has also been seen.[15 17]

Our second major finding is that MLAEPs are altered by propofol in a dose-dependent manner. With increasing target propofol concentrations, MLAEPs show increasing latencies and decreasing amplitudes. This dose-dependency of increasing latencies and decreasing amplitudes has also been reported in several studies in adults.[14 19]

For our study, we decided to administer propofol via a TCI pump based on Kataria and colleagues' model, which is validated in paediatric patients. In contrast to adults, however, there are more confounding factors that can affect a TCI system in paediatric patients. Greater inter-individual pharmacokinetic variability with respect to age and the maturation process exists in children. TCI pumps deliver a dose calculated according to a particular pharmacokinetic model based on specific parameters such as age and weight.[20 21] A major drawback of pharmacokinetic models is that estimated concentrations can differ from actual blood concentrations. Nevertheless, an increase in target concentrations invariably leads to an increase in administration rates. In our study, higher target concentrations, that is, higher administration rates, were associated with increased MLAEP latencies and decreased differences in amplitudes.

Since the dose–effect relationship of propofol on MLAEP cannot be accurately described by using target concentration alone, we measured venous propofol concentrations. This revealed a sigmoidal relationship between blood propofol

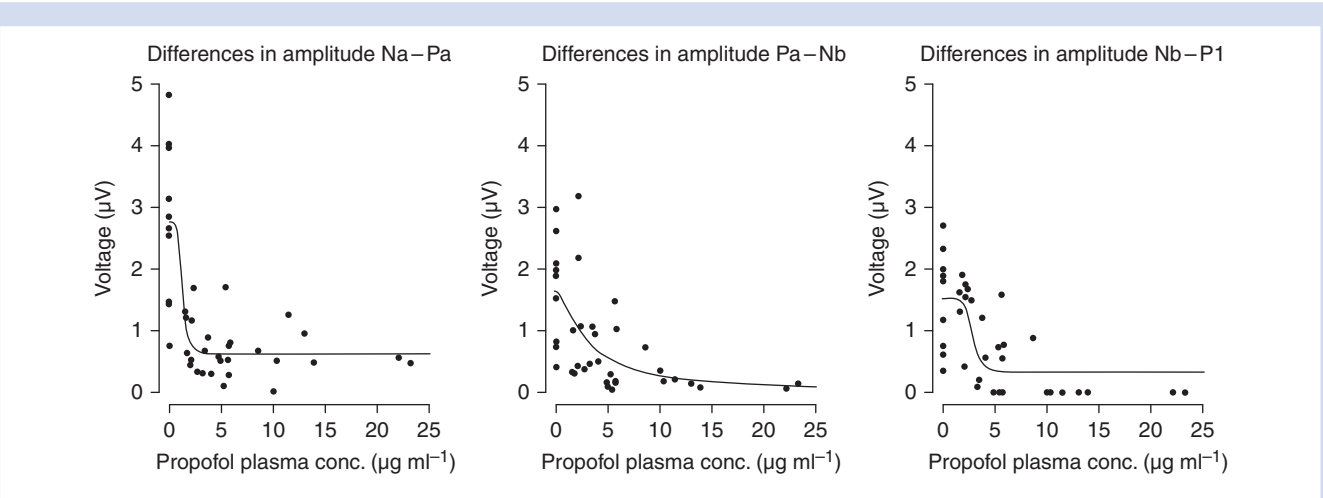

Fig 5 MLAEP differences in amplitudes, Na/Pa, and Pa/Nb in correlation with propofol plasma concentration; sigmoidal dose–response model, curve fitted. As the upper measuring limit was set at 100 ms, peak latency difference Nb/P1 experienced for propofol concentrations of 6 and 9 μg ml^{-1} an artificial ceiling effect.

Table 2 Parameter estimated from the E_{max} model. Measured venous propofol concentrations, peak latencies, and amplitude differences were fitted to the following E_{max} model: Effect$=E_0+(E_{max}-E_0)\times C^{\gamma}_{plasma}/(C^{\gamma}_{plasma50}+C^{\gamma}_{plasma})$. E_0, baseline effect; E_{max}, maximum drug effect; C_{plasma}, propofol plasma concentration; $C_{plasma50}$, propofol concentration associated with 50% of maximum drug effect; γ, Hill coefficient

	Peak Na	Peak Pa	Peak Nb	Peak P1	Na/Pa	Pa/Nb	Nb/P1
E_{max}	38.99	100	99.6	99.24	0.62	0.00001	0.33
C_{50}	4.377	6.828	4.076	2.197	1.267	3.117	2.841
γ	2.108	1.935	2.344	4.082	4.779	1.41	7.06
E_0	17.62	36.06	53.64	74.67	2.76	1.643	1.516

concentrations and peak latencies. A similar relationship was demonstrated for amplitudes.

One of the limitations of our study was that blood samples were not available in all our patients for estimation of venous propofol concentrations. Nevertheless, the data points demonstrate a sigmoidal dose–effect relationship, as seen in other studies using alternative monitoring systems, for example, BIS and A-Line.[16] For the peak Nb and P1 latencies, the limit value of 100 ms was reached when higher propofol plasma concentrations were achieved. While MLAEP measurements still differed significantly between the TCI groups of 6 and 9 μg ml^{-1}, the measured plasma MLAEP effect relationship needs to be interpreted cautiously with these truncated data. To eliminate this artificial ceiling effect due to the limit of 100 ms, we calculated a modified AEP index based on the algorithm of Kenny and Mantzaridis.[11 12] This index takes into account changes in amplitude and latency, but does not rely on identification of the positive and negative peaks of each AEP waveform. The AEP index reduced significantly with increasing calculated and measured plasma propofol concentrations. This AEP index was calculated offline after the actual MLAEP raw measurement. In contrast to our study with good signal quality, Munoz and colleagues[16] described a poor A-line ARX index (AAI) signal quality under the influence of propofol in children. The main difference is—besides the two different methods—the 'collection time' of the MLAEP. The AAI system enables the extraction of the AEP within 1.7 s.[22] The system used in the current study generates one AEP from 1000 sweeps gathered during 108 s. The advantage of the latter is a higher AEP quality but at the price of a long duration of acquisition. This may explain the different findings in these two studies.

Another important fact is that MLAEPs have an age dependency which partially reflects the electrophysiological correlate of the ongoing maturation processes of central auditory pathways.[8 23 24] MLAEP values are thought to be comparable with those measured in adults by the age of 12–15 yr.[24 25] In the current study, MLAEP could be detected in all participants regardless of the age of the participant and the propofol concentrations. Also the MLAEP peak latencies all increased similarly with higher propofol concentrations, which is consistent with the findings of Iselin-Chaves and colleagues[17] who investigated MLAEP under the influence of increasing propofol concentrations.

Additionally, all children were premedicated with midazolam, which could be a confounding factor. Benzodiazepines are known to influence MLAEP when continuously applied but very few when given as a single medication.[26]

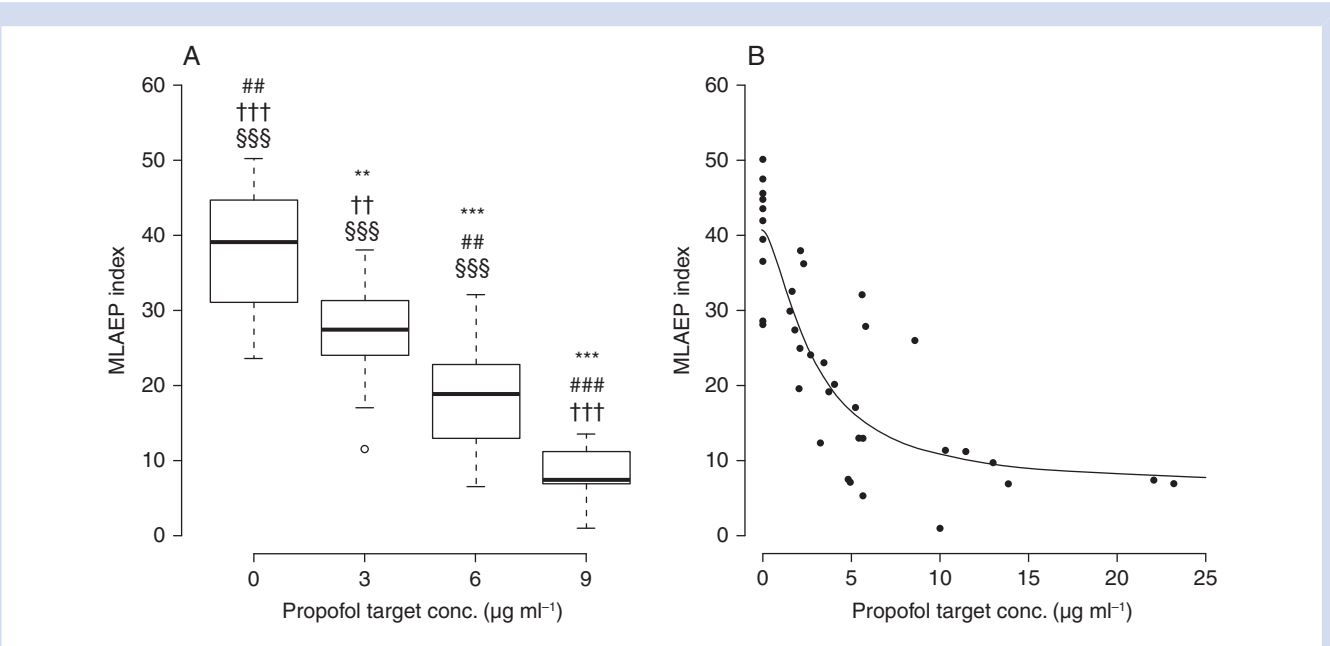

Fig 6 Modified AEP index: (A) box-plots of the modified AEP index at the respective propofol target concentrations; (B) measured plasma concentrations in correlation with the modified AEP index. Symbols for statistical significance: *indicates comparison with the 0 μg ml^{-1} group, #with the 3 μg ml^{-1} group, †with the 6 μg ml^{-1} group, and §with the 9 μg ml^{-1} group. One symbol reflects a *P*-value of <0.05, two symbols a *P*-value of <0.01, and three symbols a *P*-value of <0.001.

In summary, this study showed that propofol anaesthesia in children increases MLAEP peak latencies Na, Pa, Nb, and P1 and decreases differences of amplitudes for Na/Pa and Pa/Nb.

In contrast to adults, the peak Pa seems to be the better readout parameter for alterations in depth of anaesthesia with propofol. In adult patients, Thornton and colleagues[27] evaluated the peak Nb as the best readout parameter. Additionally, our data demonstrated that differences in amplitudes are detectable and show a relationship to increasing propofol concentrations. Na/Pa seems to have more sensitivity at lower propofol levels, whereas Pa/Nb has more discrimination at higher propofol levels.

These findings may be important to further investigations examining MLAEP and indexed MLAEP as a tool for monitoring depth of anaesthesia in children, as we now have a better insight into the raw MLAEP dynamics in children.

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Declaration of interest

None declared.

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