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Children on phenobarbital monotherapy requires more sedatives during MRI

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Summary

Background: Phenobarbital induces specific hepatic cytochrome P-450 enzyme pathways causing increased clearance of hepatically metabolized drugs. In this study, we investigated the duration and additional anesthetic requirement during Magnetic resonance imaging (MRI) in epileptic children with or without phenobarbital monotherapy.
Methods: In ASA I–II, 128 children, aged 1–10 years, were included. Group I: epileptic children without anti-epileptic therapy and Group II: children with phenobarbital monotherapy. The initial sedative drugs were 0.1 $mg{\cdot}kg^{-1}$ midazolam with 2 $mg{\cdot}kg^{-1}$ ketamine. An additional 1 $mg{\cdot}kg^{-1}$ ketamine was administrated if required. Rescue propofol (0.5 $mg{\cdot}kg^{-1}$) was provided and repeated to maintain sedation. The duration and consumption of additional sedative requirements was recorded.
Results: The duration of initial and two consequent additional sedative requirements was shorter in Group II ($P = 0.0001$, $P = 0.001$ and $P = 0.27$, respectively). Additional ketamine doses required for adequate sedation were lower in Group I ($P = 0.016$).
Conclusion: We suggest that the variability in response to the initial sedative agents during MRI requires titration of additive sedation with ketamine in epileptic children on phenobarbital monotherapy.

Introduction

Epilepsy is the most common neurologic disorder in children with an incidence of approximately 4%. Up to 70% of patients diagnosed with epilepsy can be rendered seizure-free by currently available anti-epileptic drugs (AEDs) when administered as monotherapy (1,2). Among old generation AEDs, phenobarbital is the most commonly used AED in pediatric population and is a prototypic P-450 enzyme inducer. It stimulates the activity of a variety of cytochrome P-450 (CYP-450) enzymes, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4, as well as glucuronyl transferases and UDP-glucuronosyltransferase (UGT) (2–4). These isoenzymes are also involved in the metabolism of more than 50% of all drugs including anesthetics (5,6). Thereby, the clinical efficacy of concomitantly administered anesthetics that use the common metabolic pathway with phenobarbital might be reduced by an increase in distribution and clearance (7).

Magnetic resonance imaging (MRI) is the preferred radiologic imaging technique for diagnosis and follow-up of epilepsy. The important concern is the selection of sedative anesthetic agents for successful sedation during MRI procedures because of the potential drug interactions with AEDs. The selection would be arranged among the anesthetics that have anticonvulsant effects like thiopental, benzodiazepines, etomidate, ketamine, propofol, and inhalation anesthetics (8,9). All of these anesthetic agents are also metabolized with cytochrome P-450 izoenzymes (10). Thereby, the effective duration of sedation and the required amount of sedatives might increase when either of the anesthetic agents is co-administered with an AED.

The aim of this study was to investigate whether there is any significant difference in the duration of adequate sedation levels to continue a noisy but painless procedure without awakening, consumption of additive sedative anesthetic agents, and the requirement for rescue sedatives in epileptic children with or without phenobarbital monotherapy undergoing MRI.

Methods

This study was approved by Baskent University Institutional Review Board and Ethics Committee (Project no: KA09/210) and supported by Baskent University Research Fund. The informed consent for sedation and imaging was obtained from parents. In ASA physical status I–II, 128 children diagnosed with epilepsy, aged 1–10 years scheduled to undergo MRI with sedation were recruited in this double-blinded prospective clinical study. All of the patients were admitted to the hospital on the day before the procedure. Prior to sedation, a brief physical examination, history of present illness and medical history, and review of systems were conducted.

Exclusion criteria for the study included age <1 year, the presence of congenital heart disease, any condition including upper respiratory infection, pneumonia or episode of acute asthma that result in airway compromise or interfere with intubation, recent use of any medication except phenobarbital, abnormality in liver and kidney function tests, the history of difficulty in previous sedation procedures for MRI, any known allergy to the study drugs, sleep apnea, and a scan expected to last more than 90 min.

The epileptic children without any AED therapy were allocated in Group I ($n = 64$), and the children with phenobarbital monotherapy attributed to epilepsy were allocated in Group II ($n = 64$). The patient characteristics including age, sex, weight, cause and duration of epilepsy, and phenobarbital monotherapy were recorded prior to sedation by an anesthesiologist who was blind to the study protocol. The primary anesthesiologist described the patient's physical status, ASA scores, and the results of systemic evaluation and relevant medication except phenobarbital to another blind anesthesiologist. The second anesthesiologist carried out the sedation procedure and patient assessment in the MRI room. This anesthesiologist was present with the patient inside the MRI room, evaluated the sedation levels, and administered the sedative agents when required according to the protocol and recorded all relevant data.

Eutectic mixture of local anesthetic cream (5%, AstraZeneca) was applied to the skin of all patients 1 h before the insertion of an intravenous catheter. The initial sedative drugs to achieve a sedative state so as to facilitate MRI consisted of IV bolus 0.1 $mg{\cdot}kg^{-1}$ midazolam and 2 $mg{\cdot}kg^{-1}$ ketamine. All patients also received 10 $\mu g{\cdot}kg^{-1}$ atropine after the administration of initial sedatives to prevent secretions. Sedation levels were evaluated by the Children's Hospital of Wisconsin Sedation Scale (CHWSS) (11). The assessed sedation levels were recorded at 5-min intervals. The imaging sequence was started if the sedation level fell below <4 on the Wisconsin Sedation Scale. If adequate sedation and immobilization were not achieved after initial sedative administration with midazolam and ketamine, an additional 1 $mg{\cdot}kg^{-1}$ dose of ketamine was repeated. After additional ketamine administration for deep sedation, rescue sedation with 0.5 $mg{\cdot}kg^{-1}$ propofol IV bolus was provided to maintain sedation and repeated to keep Wisconsin Sedation Scale <4 during scanning. After each administration of additional sedatives, the patient was observed for a 1-min duration to approve the adequate sedation level. If CHWSS was not achieved to the targeted point, an additional bolus administration was performed according to the protocol.

Supplemental oxygen was delivered at 2 $ml{\cdot}min^{-1}$ to spontaneously breathing children via a facemask. The child was positioned with a soft roll under the shoulder and the neck extended. Technical monitoring was performed using a compatible MRI monitoring device (NONIN 8600FO, China) including heart rate and oxygen saturation. The monitoring equipment was placed outside the imaging room and connected to the patient via extension sets. All children were noise-protected during MRI and were positioned inside the magnetic bore after a reliable SpO_2 signal was obtained. Heart rate and oxygen saturation were monitored continuously and recorded at 5-min intervals throughout the anesthesia. Each anesthesia record included the effective duration of initial and con sequent additional sedative requirements and the total amount of additional ketamine and rescue propofol administration. The duration of initial and consequent additional sedative requirements was described as the time the sedation level fell below <4 on the Wisconsin Sedation Scale; the moment that unacceptable motion artifacts on either sequence of images occurred as a result of patient movement. Anesthesia was considered satisfactory when the imaging quality was not disturbed by motion artifacts. Inadequate sedation was defined as difficulty in completing the procedure attributed to the child's anxiety or inability to remain motionless despite rescue sedation with propofol, which failed to produce a sufficient depth of sedation.

The occurrence of procedural and delayed adverse events as vomiting, agitation, hiccup, hypoxia, occurrence of failed sedation and the total time in the MRI scan suite were also recorded. If evidence of airway obstruction was present, supplemental airway maneuvering including tactile stimulus, chin lift, airway placement, and assist ventilation with a bag and mask system or intubation of the trachea was established.

After the imaging sequence was completed, the child was transferred to a recovery room located close to the MRI suite where they were observed by a recovery nurse and their parents. Recovery time was defined as the time from completion of the scan until achievement of a recovery score assessed with Modified Aldrete Scoring of 8 (12). Children were discharged to home when their vital signs returned to baseline, their level of consciousness was close to baseline and when they could maintain a patent airway.

MRI procedure

Unenhanced head examination included parasagittal and axial T1-weighted sequences and axial and coronal proton density and T2-weighted sequences. Contrast-enhanced head examinations included parasagittal and axial T1-weighted sequences, axial proton density and T2-weighted sequences prior to IV injection of contrast material. Following contrast injection with gadopentetate dimeglumine (0.2 $ml \cdot kg^{-1}$), T1-weighted sequences were performed in parasagittal, coronal, and axial planes.

Statistics

Data analysis was performed using SPSS (version 11.0; SPSS Inc., Chicago, IL, USA). The primary outcome parameter of this study was the time period until the first additional sedative requirement according to predetermined sedation level (Wisconsin sedation scale < 4). A power analysis indicated that 59 patients per group were required to detect a true difference of 5 min between groups where the anticipated standard deviation was 8.3. The standard deviation was based on a pilot group of epileptic patients undergoing MRI. The α error was set at 0.05, and the type II error was set at 0.20. A P-value < 0.05 was considered significant for all comparisons. Categorical data were analyzed by chi-squared test. Statistical tests included independent sample t-tests for between group comparisons and the Mann–Whitney U test where the number and distribution of data required nonparametric tests. Logarithmic conversion was used to normalize the data for additional ketamine consumption. Linear regression analysis using stepwise method was applied for correlation analysis. Data were presented as means with standard deviation, numbers and percentages, median with range and geometric mean where appropriate.

Results

The adequate number of patients according to the calculated power of the study was 118; however, a total of 128 patients were studied to compensate for possible exclusions from the study. The patient characteristics were similar between groups (Table 1). The patients in Group I were not receiving anti-epileptic therapy because they were in initial diagnostic or remission period for seizure control, avoiding anti-epileptics by families caused by resistance to epilepsy medications, or MRI control for febrile convulsion. In Group II, the causes of receiving anti-epileptic therapy were generalized or for focal seizure and febrile convulsions. The mean duration of epilepsy was longer in Group II (5.42 ± 20.15 months in Group I and 19.29 ± 24.14 months in Group II) ($P = 0.001$). The mean duration of phenobarbital therapy was 17.71 ± 24.01 months in Group II.

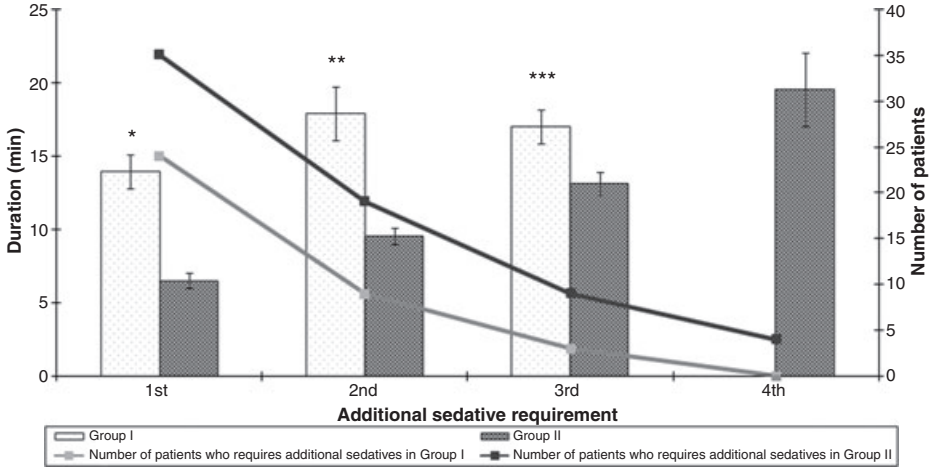
The initial dose protocol with midazolam and ketamine was sufficient for the entire procedure in 64% of patients ($n = 41$) in Group I and in 45% of patients ($n = 29$) in Group II ($P = 0.02$). The rest of the patients in both groups required one to four maintenance doses. The duration of initial and two consequent additional sedative requirements was shorter in Group II ($P = 0.0001$, $P = 0.001$ and $P = 0.27$, respectively). The duration of additional sedative requirements and the variance according to the patient number was demonstrated in Figure 1.

The mean additional ketamine doses required for adequate sedation were different between groups (8.6 ± 0.13 mg in Group I and 10.21 ± 0.09 mg in Group II, $P = 0.016$). The mean rescue propofol doses were similar between groups (2.76 ± 7.54 mg in

Table 1 Patient characteristics

	Group I ($n = 64$)	Group II ($n = 64$)
Age (month)	24 (12–116)	39 (13–118)
Weight (kg)	13.3 ± 5.9	15.2 ± 5.6
Sex (M/F)	37/27	37/27
ASA physical status (I/II)	29/35	34/30

Data expressed as median (min-max) for age and mean and standard deviation for weight. F, female; M, male; ASA, American society of anesthesiologist.



(*,**,***The comparison for the duration of first, second and third additional sedative requirement between groups ($P = 0.0001$, $P = 0.001$ and $P = 0.027$, respectively)

Figure 1 The duration of initial and consequent additional sedative requirements and the number of patients who requires additional sedative agents for each administration.

Group I and 6.25 ± 14.77 mg in Group II). The mean procedure time was comparable between groups (21.87 ± 5.66 min in Group I and 22.65 ± 4.95 min in Group II).

Additional sedative administration was required more commonly in children under anti-epileptic therapy. However, a logistic regression model failed to find any correlation with anti-epileptic therapy duration. All children recovered within a similar period of time (15.26 ± 10.98 min in Group I and 16.28 ± 8.65 min in Group II) and were awake at discharge from the investigation room. Spontaneous respiration was maintained in all patients in both groups, and no ventilation support was required. Transient oxygen desaturation (<95%) occurred in three patients in Group I and in two patients in Group II immediately after initial sedation doses and responded to tactile stimulation. Heart rate and peripheral oxygen saturation during sedation did not differ between groups. Nausea and vomiting were not observed in either of the groups.

Discussion

The study demonstrated that the duration of initial and two consequent additional ketamine requirements was shorter and that the additive ketamine consumption was greater in epileptic children with phenobarbital monotherapy. The reduction in the duration of ketamine after-effects in children given phenobarbital therapy might be postulated to be attributed to hepatic enzyme induction of specific common pathways leading to increased clearance. However, the reduction in duration of ketamine sedation was not correlated with the duration of phenobarbital monotherapy.

These clinical results obtained from our study appear to correlate well with a vast body of literature, which demonstrates that phenobarbital is an effective inducer of CYP3A4 and the induction ratio changes in a concentration-dependent manner, but does not correlate with the duration of phenobarbital therapy (13). Also, the enzyme induction data obtained from *in-vitro* studies demonstrate that phenobarbital induces the gene expression of CYP2C and CYP3A and has an inductive effect on CYP3A4 activity with an average of 3.3-fold in human primary hepatocytes (14,15).

Theoretically, the reflection of this inductive effect in clinical practice might shorten the effective duration of sedatives co-administered with phenobarbital monotherapy, and this might result in prolonged sedation procedures as a result of frequent interpretations. In our study, the effective duration of ketamine sedation in children with phenobarbital monotherapy was 0.46-fold shorter during the initial administration. The shortening was also preceded with an average of 0.53- and 0.77-fold in two consequent administrations. The length of the procedure was comparable between groups, which might depend on the rapid interference of the anesthesiologist who was observing the children nearby in the MRI.

In this study, although the demographic characteristics of patients were similar, we included a wide range of epileptic children in age and epilepsy etiology. This is important because allometric scaling of drug doses

raises and the amount of required sedative agent per kilogram might be misleading. Thereby, the limited range of the children's age with a single specific etiology might enhance the study results. The preferred sedation technique with multidrug administration was also another study limitation. The difference may be the result of both pharmacodynamic and pharmacokinetic effects of drugs with allometric scaling influences.

In conclusion, CYP-450 induction following adequate term of phenobarbital treatment alters the ketamine metabolism and decreases the anesthetic effect by shortening the sleeping time, requiring additional doses. Therefore, the variability in response to the initial sedative agents required titration of additive sedation agents. In clinical practice, anesthesiologists should keep in mind that additional sedative consumption for the sedation management of epileptic children might be required and the possibilities of short sleeping time should be considered for the children under antiepileptic therapy.

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