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SCIENTIFIC ARTICLE

The impact of different antiepileptic drugs on the sedation of children during magnetic resonance imaging

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Abstract

Background and objectives: The induction and inhibition of cytochrome P450 isoenzymes by antiepileptic drugs lead to changes in the clearance of anesthetic drugs eliminated via hepatic metabolism. We investigated the duration of the sedation and additional anesthetic needs during magnetic resonance imaging in epileptic children receiving antiepileptic drugs that cause either enzyme induction or inhibition.

Methods: In American Society of Anesthesiology I–II, 120 children aged 3–10 years were included. Group 1: children using antiepileptic drugs that cause cytochrome P450 enzyme induction; Group 2: those using antiepileptic drugs that cause inhibition; and Group 3: those that did not use antiepileptic drugs. Sedation was induced with the use of 0.05 mg kg⁻¹ midazolam and 1 mg kg⁻¹ propofol. An additional 0.05 mg kg⁻¹ of midazolam and rescue propofol (0.5 mg kg⁻¹) were administered and repeated to maintain sedation. The duration of sedation and the additional sedation needed were compared.

Results: The duration of the initial dose was significantly shorter in Group I compared with groups II and III ($p=0.001$, $p=0.003$, respectively). It was significantly longer in Group II compared with groups I and III ($p=0.001$, $p=0.029$, respectively). The additional midazolam needed for adequate sedation was increased in Group I when compared with groups II and III ($p=0.010$, $p=0.001$, respectively). In addition, the rescue propofol dose was significantly higher only in Group I when compared with Group III ($p=0.002$).

Conclusion: In epileptic children, the response variability to the initial sedative agents during the magnetic resonance imaging procedure resulting from the inhibition or induction of the cytochrome P450 isoenzymes by the antiepileptic drugs mandated the titration of anesthetic agents.

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PALAVRAS-CHAVE

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Impacto de diferentes medicamentos antiepilépticos na sedação de crianças durante a ressonância magnética**Resumo**

Justificativa e objetivos: A indução e a inibição das isoenzimas do citocromo P450 pelos medicamentos antiepilépticos levam a alterações na depuração de medicamentos anestésicos eliminados pelo metabolismo hepático. Investigamos a duração da sedação e a necessidade adicional de anestésicos durante a ressonância magnética em crianças epiléticas que receberam antiepilépticos que causam a indução ou a inibição de enzimas.

Métodos: Foram incluídas no estudo 120 crianças, estado físico ASA I-II, entre 3-10 anos. Grupo 1: em uso de antiepilépticos que causam a indução de enzimas do citocromo P450; Grupo 2: em uso de antiepilépticos que causam a inibição de enzimas do citocromo P450; e Grupo 3: que não usavam antiepilépticos. A sedação foi induzida com midazolam (0,05 mg kg⁻¹) e propofol (1 mg kg⁻¹). Um adicional de 0,05 mg kg⁻¹ de midazolam e resgate com 0,5 mg kg⁻¹ de propofol foram administrados e repetidos para manter a sedação. A duração da sedação e a sedação adicional necessária foram comparadas.

Resultados: A duração da dose inicial foi significativamente menor no Grupo I em comparação com os grupos II e III (p=0,001, p=0,003, respectivamente) e significativamente maior no Grupo II em comparação com os grupos I e III (p=0,001, p=0,029, respectivamente). A necessidade de midazolam adicional para sedação adequada foi maior no Grupo I em comparação com os grupos II e III (p=0,010, p=0,001, respectivamente). Além disso, a dose de resgate de propofol foi significativamente maior apenas no Grupo I em comparação com o Grupo III (p=0,002).

Conclusão: Em crianças epiléticas, a variabilidade da resposta aos agentes sedativos iniciais durante a ressonância magnética, resultante da inibição ou indução das isoenzimas do citocromo P450 pelos medicamentos antiepilépticos, exigiu a titulação dos agentes anestésicos.

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Introduction

Epilepsy is the most common chronic neurological disorder among children and is characterized by paroxysmal attacks.¹ Magnetic resonance imaging (MRI) is a generally preferred imaging modality in the management of epileptic children.² In MRI procedures, the selection of anesthetic agents with anticonvulsant activity as well as drug interactions between antiepileptic drugs (AEDs) and anesthetics are integral components of the anesthetic plan for patients with epilepsy.^{3,4}

The induction and inhibition of cytochrome P450 (CYP-450) in liver metabolism comprise the most important mechanism in pharmacokinetic drug interactions regarding AEDs.⁴ Commonly used AEDs, such as phenytoin, carbamazepine, primidone and phenobarbital induce several CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19 and CYP3A4) as well as UDP-glucuronyl transferase (UGT) and epoxide hydrolases; on the contrary, valproic acid is the most important inhibitor of the enzymes (CYP2A6, CYP2B6 and CYP2C9) in drug metabolism.^{3,5}

It has been demonstrated that these isoenzymes are involved in the metabolism in over 50% of anesthetic agents. Midazolam, one of the most widely used anesthetic agents with anticonvulsant activity in MRI procedures, is metabolized by CYP3A4/CYP3A5, whereas propofol is metabolized by CYP2C9, CYP2B6 and UGTs. Thus, the alterations in the distribution and clearance resulting from the simultaneous use of anesthetics that share the same metabolic pathways with AEDs will change the duration of sedation and the sedation level needed.⁶⁻⁸

In the present study, we aimed to investigate whether there was a difference in terms of the adequate duration of sedation, the additional sedative agent used or needed to rescue sedative agents among epileptic children using AEDs that cause either enzyme induction or inhibition, or those that did not use AEDs under midazolam-propofol anesthesia during MRI.

Materials and methods

This study was approved by the Ethics Committee of the Institutional Human Research Board of Mustafa Kemal University. Overall, 120 children with epilepsy (American Society of Anesthesiology (ASA) I, II; aged 3–10 years) undergoing cranial MRI with sedation were included in this prospective clinical trial.

Epileptic children were classified into three groups as follows: Group 1, children using agents that cause CYP-450 induction (n=30); Group 2, children using agents that cause CYP-450 inhibition (n=30); and Group 3, those not receiving AEDs (n=60).

The day before the MRI, all patients were assessed by an anesthesiologist, including history of current disease, medical history and physical examination. All parents were informed of the fasting periods allowed under the American Society of Anesthesiologists Preprocedure Fasting Guidelines.^{9,10}

The children with a risk status \geq ASA III, those younger than 3 years, those with severe pulmonary or cardiac disorders, congenital head-neck or face anomaly and excessive

tonsil hypertrophy, those with gastroesophageal reflux or full stomach, obese children, those with sleep-apnea, and those with abnormal renal function tests or a history of allergy against agents used in the study or a history of difficulty in previous MRI procedures were excluded. Children with accompanying diseases such as cerebral palsy or mental-motor retardation were not excluded from the study.

Before the procedure, written informed consent was obtained from parents. Demographic data such as weight, age and gender, ASA status, history of epilepsy, antiepileptic medication and accompanying diseases were recorded. In all patients, 0.5 mg kg⁻¹ midazolam was given orally by mixing it into a particle-free fruit juice for premedication 30 min before the intravenous catheter placement, and patients were taken into the MRI room when the Parental Separation Anxiety Scale reached 1–2.^{11,12} The time from premedication with oral midazolam to arrival in the MRI room was referred to as the time of readiness for the procedure (sedation ready). In both groups, 0.05 mg kg⁻¹ midazolam (i.v.) was given as the primary sedative, followed by 1 mg kg⁻¹ propofol for 30 s. The sedation level was assessed throughout the imaging procedure with the University of Michigan Sedation Scale (UMSS)¹³ and it was considered adequate when patients could be awakened only by significant physical stimulus. The time to arrive at a sufficient sedation level (UMSS = 3) was referred to as the induction time. To prevent the pain of the propofol injection, 0.25 mg mL⁻¹ lidocaine was added to the same syringe.¹⁴

When sedation and immobilization could not be achieved during the imaging procedure, a midazolam dose was titrated by 0.05 mg kg⁻¹ increments (maximum increment: 1 mg and maximum total dose: 0.1 mg kg⁻¹), and a propofol bolus of 0.25–0.5 mg kg⁻¹ was given as a rescue dose when midazolam titration failed. The duration between the initial dose and the additional sedation needed was defined as UMSS < 3 and movement of patient causing to repeated imaging procedure. Discomfort or inevitable movement of the children resulted in the cancellation of the imaging despite the fact that sedation was considered as inadequate sedation.

The heart rate and peripheral oxygen saturation were monitored during the procedure (MILLENNIA 3155MVS, USA) and recorded at 5-min intervals. Non-invasive blood pressure measurements were only performed before and at the end of the procedure as it could cause awakening due to muff.⁹ Clinically, hypotension was defined as a 20% or more reduction in systolic artery pressure compared with the baseline value.¹⁴

All children were protected from noise during the procedure and supplemented with 2 mL min⁻¹ O₂ via a face mask in order to maintain spontaneous respiration. Intervention decisions were made in cases of SpO₂ < 94%, apnea lasting 20 s (apnea), a decrease in the heart rate by more than 20% compared to the baseline value (bradycardia) and arrhythmias. Airway support maneuvers were performed in cases of airway obstruction and hypoxia, including tactile stimulus, chin lifting, airway placement and bag-mask ventilation after the discontinuation of the MRI.¹⁴ In addition, adverse events occurring during induction, MRI and before discharge were recorded, including nausea, vomiting, apnea, cough, hiccup, irritability, agitation, allergic reaction and aspiration.

Data regarding procedure time, termination or repetition of the MRI procedure, and additional midazolam or propofol applications were recorded for all patients. The duration of the procedure was defined as the time from the initiation of the MRI procedure to its completion, including interruptions.

When the imaging procedure was completed, children were transferred to the recovery room within the magnetic resonance (MR) unit and observed by parents and a nurse anesthesiologist. Recovery time was defined as the time from completion of the MRI procedure to the discharge from the recovery room (Modified Aldrete score ≥ 8 and Comfort Scale score ≥ 3).^{14,15} The children were then transferred to the department of pediatrics and were discharged after vital signs and levels of consciousness returned to baseline values.

Parents' level of satisfaction with the sedation experience was assessed on the basis of a 4-point Likert scale (very dissatisfied, somewhat dissatisfied, somewhat satisfied and very satisfied). The quality of MR sequences was assessed according to the presence/absence of artifacts resulting from movement of the patient by a radiologist blinded to patients and sedation technique via a 3-point scale: (1) excellent, no artifact due to movement; (2) procedure was completed with minor movement; and (3) major movement and aborted procedure.¹⁶

In addition, a phone interview was conducted 24 h after discharge by a blinded anesthesiology resident regarding delayed adverse events, nocturnal enuresis, insomnia, and nightmares.

Statistical analysis

SPSS for Windows version 13.0 (Statistical Package for Social Sciences) was used for all statistical analyses. Sample size estimates were based on the duration of the initial dose (in minutes). It was estimated that a sample size of 21 per group would provide 80% power to detect a clinically meaningful difference of 1.5 min when the accepted standard deviation was 8.3 and the α error was 0.05. Standard deviation was determined based on a pilot study on epileptic children undergoing MRI.

The normal distribution of continuous variables was tested with the Kolmogorov–Smirnov test. Chi-square tests were used for comparisons between categorical variables. Kruskal–Wallis and Mann–Whitney *U* tests were used in the comparisons of continuous variables between groups. $p < 0.05$ was considered significant for all statistical data.

Results

The data were obtained from 120 epileptic children, using antiepileptic agents for focal or generalized convulsions, who had no MRI scan and received sedation for MRI that was performed for initial diagnosis or for evaluating the remission course as well as the management of accompanying diseases during a period of 19 months between September, 2012 and April, 2013.

Table 1 presents the demographic data and the proportion of patients with the rate of accompanying diseases in both groups. Procedural data are presented in Table 2.

The mean duration of epilepsy was significantly shorter in Group III (30.78 ± 23.80) compared with groups I and II (58.83 ± 32.33 and 59.93 ± 33.85, respectively; $p = 0.001$).

Table 1 Patients characteristic data.

	Group I (n = 30)	Group II (n = 30)	Group III (n = 60)	p
Sex				
Male (%)	12 (40%)	14 (46.7%)	22 (36.7%)	0.659
Female (%)	18 (60%)	16 (53.3%)	38 (36.3%)	
Age (month)	7.0 (3.0–10.0)	8.0 (3.0–10.0)	5.0 (3.0–10.0) ^a	0.003 ^a
Weight (kg)	22.0 (10.0–36.0)	22.5 (10.0–35.0)	16.0 (10.0–30.0) ^a	0.001 ^a
ASA I/II	17/13	14/16	27/33	0.567
Rate of accompanying (%)	11 (36.7%)	13 (43.3%)	25 (41.7%)	0.856

n, number of cases.

Results are presented as median (min–max) except for gender, rate of accompanying and ASA physical status (count).

^a $p < 0.05$.

Table 2 Procedural data in three groups.

Variable	Group I (n = 30)	Group II (n = 30)	Group III (n = 60)
Sedation-ready	30.00 (30.00–35.00)	30.00 (20.00–35.00)	30.00 (20.00–40.00)
Induction time	55.00 (50.00–60.00)	12.00 (10.00–15.00)	55.00 (45.00–60.00)
Duration of initial dose	10.00 (5.00–13.00) ^{a,b}	12.00 (10.00–15.00) ^c	10.00 (8.00–15.00)
Additional midazolam dose	0.82 (0.00–1.80) ^{a,b}	0.00 (0.00–1.30)	0.00 (0.00–1.25)
Rescue propofol dose	0.00 (0.00–20.00) ^{a,b}	0.00 (0.00–12.00)	0.00 (0.00–12.50)
Duration of procedure (min)	13.00 (7.00–25.00) ^{a,b}	10.00 (7.00–15.00)	10.00 (7.00–20.00)
Recovery time (min)	12.00 (10.00–18.00)	13.00 (10.00–30.00)	10.00 (7.00–20.00)

n, number of cases.

Statistically significant differences ($p < 0.05$) were noted as follows:

^a Group I vs Group II.

^b Group I vs Group III.

^c Group II vs Group III.

The duration of antiepileptic medication was similar in groups I and II (58.06 ± 32.00 mg, 59.60 ± 33.50 , respectively; $p > 0.05$).

The duration of the initial dose was significantly shorter in Group I when compared with groups II and III ($p = 0.001$ and $p = 0.003$, respectively). It was significantly longer in Group II when compared with groups I and III ($p = 0.001$ and $p = 0.29$, respectively). The initial dose protocol with midazolam and propofol was adequate to complete the MRI procedure in 11 patients (36.7%) in Group I; in 21 patients (70%) in Group II; and in 43 patients (71.7%) in Group III ($p = 0.03$). For the remaining patients, the need for additional midazolam for adequate sedation, an additional midazolam dose was increased in Group I when compared with groups II and III ($p = 0.010$, $p = 0.001$ and $p = 0.003$, $p = 0.001$, respectively). Also it was not changed in Group II compared with Group III. In addition, the rescue propofol dose was significantly higher only in Group I when compared with Group III ($p = 0.002$).

No significant correlation was detected between the duration of the antiepileptic medication and the duration of the initial dose or the dose needed for additional sedation in groups I and II.

The duration of the procedure was similar in groups II and III, while it was significantly higher in Group I when compared with groups II and III ($p = 0.034$ and $p = 0.004$, respectively).

Spontaneous respiration was achieved without the need for ventilation support in all patients. Temporary oxygen

desaturation (<95%) was observed in three patients in Group I (10%) and each two patients (6.6%) in Group II and Group III immediately after the initial sedation dose, which rapidly responded to tactile stimulus, including slight neck extension and chin support.

Although systolic arterial pressure was decreased to a level of 10% below the baseline value after sedation, hypotension was not observed in any patient. In addition, none of the patients experienced cardiovascular adverse events, such as bradycardia or arrhythmia during or after sedation. The recovery times after MRI were similar among the groups.

Paradoxical reaction, early or delayed adverse effects were not observed in any patient and there was no case in which the MRI procedure could not be completed due to failure of sedation or a major movement, and no patient was excluded from the study on these grounds. All parents were very satisfied with the sedation experience. No significant difference was observed in the quality of MR sequences among the groups ($p > 0.05$).

Discussion

Although unfavorable effects of AEDs on CYP-450 enzyme systems are well known, to the best of our knowledge, this is the first study to compare the interactions of anesthetics in MRI. The results of our study demonstrated that the duration

of the initial dose of midazolam-propofol was shorter in children using AEDs that cause enzyme induction, while it was prolonged in children using AEDs that cause enzyme inhibition and in those not using antiepileptic agents. Moreover, the results showed that additional sedation need increased in children using AEDs that cause enzyme induction, while it decreased in cases using AEDs that cause enzyme inhibition.

We suggested that the variation in the duration of initial doses resulted from alterations in the metabolism of anesthetic agents caused by antiepileptic agents that uses common metabolic pathways with midazolam and propofol.

As such, clinical reflections on the inducer or inhibitory effects of AEDs are also different in sedation procedures. The usage of AEDs that inhibit enzyme induction can shorten the sedation period of sedatives, thereby resulting in prolonged procedural times due to frequent repetitions. Conversely, AEDs with inhibitory effects may prolong sedation as well as the recovery time. Both situations can cause dissatisfaction in children and their parents, resulting in a waste of time and money.^{2,14,17}

In our study, there was a need for additional doses; thus, the duration of the procedure was markedly increased because of significantly shortened durations under the initial midazolam-propofol dose in children using AEDs that cause enzyme induction. In a study on epileptic children receiving phenobarbital monotherapy, Eker et al.² reported that results on the need for additional sedation and the duration of sedation were in agreement with our study. Similar results have been demonstrated in animal models regarding enzyme induction.^{18,19}

Although the duration of the initial doses of midazolam-propofol was significantly prolonged in children using AEDs that cause enzyme inhibition, this did not result in problems or adverse effects. Also, it did not result in a prolonged duration of the procedure since there was no repetition of the MRI.

No correlation was detected between the duration of the initial midazolam-propofol dose and the need for additional doses with the duration of the medication, including enzyme inducing or inhibiting agents. The induction or inhibition caused by AEDs was concentration-dependent and was not related to the duration of the medication.^{20–23} Thus, our results are in agreement with the literature in this area.

Although the demographic characteristics of the groups were largely similar, Group III consisted of younger ages and lower mean weights. This difference was attributed to the lower mean age in children who underwent evaluations for new diagnosis in Group III.

While metabolic interactions on specific CYP isoenzymes may vary depending on genetic and environmental factors, pharmacokinetic and pharmacodynamic variations can also be observed in relation to age. CYP and UGT isoenzymes are markedly differentiated during the maturation of children, and reach adult levels at 2–3 years of age.²¹ We think that our results were not affected by this change in isoenzymes, despite the wide age range in our study, since three years of age was selected as the lower limit of eligibility.

A combination of phenobarbital or carbamazepine with anesthetic agents with a similar profile of activity may also enhance anesthetic effects.¹ In our study, midazolam and propofol were preferred because of the shorter time of action and their association with comfortable recovery.²⁴ In

addition, the major advantage of propofol was the lack of paradoxical reactions.²⁵ In agreement with the literature, no significant adverse effect or complication, including paradoxical reactions (sedation, agitation, and irritability) was observed in our patients.

In conclusion, AEDs have many physiological and pharmacological effects on anesthetic agents and are the most important constituent of the practice of anesthesia. Anesthesiologists should be aware of important drug interactions and underlying mechanisms in the sedation of children using antiepileptic agents and required dose titrations should be made by meticulously observing clinical responses.

Conflicts of interest

The authors declare no conflicts of interest.

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