Serum Diazepam Levels After Oral Administration in Children

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Abstract

Objective : To determine serum levels of diazepam after oral administration in children.

Patients and Method : Forty six children admitted with febrile seizures were orally administered with 0.25 mg/kg/dose of diazepam six hourly for four doses. Trough (prior to the next dose) and peak (at 1 hour 20 minutes after the dose) serum levels of diazepam were analyzed. The patients were observed for adverse effects of the medication.

Results : The peak levels after 1st, 2nd, 3rd and 4th doses were above 0.15 μg/ml which is considered the therapeutic level in 93.5, 97.8, 97.7, and 100 per cent of the patients, respectively. The trough levels prior to the 2nd, 3rd, and 4th doses were greater than 0.15 μg/ml in 75.0, 84.0, and 91.3 per cent, respectively. Neither recurrent seizure nor serious adverse effects occurred in any of the patients.

Conclusion : Serum concentrations above the therapeutic level were achieved after orally administered diazepam at 0.25 mg/kg/dose six hourly for four doses. Oral diazepam may be used as another method in the prevention of recurrent febrile seizures.

Key word : Diazepam, Serum Level, Oral Administration

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Intermittent oral administration of diazepam has been recommended to prevent the occurrence of seizures in children who have had febrile seizures for years[1-3]. There is clinical evidence suggesting that diazepam if given rectally or orally at the time of fever, may prevent recurrences of febrile seizures, provided that the doses are optimal and compliance problems are minimized[4-6].

In 1993, a single dose of diazepam was given orally to each patient with febrile seizures at the Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital. The peak serum diazepam level was determined at one hour and 20 minutes (1.38 ± 0.5 hour) after the dose. The calculated optimal dose of diazepam to maintain serum diazepam levels above the accepted therapeutic level (150 ng/ml) obtained from that study was 0.25 mg/kg body weight/dose every 6 hours[7]. However, there have been no studies concerning the correlation of the above mentioned doses of diazepam to the actual serum diazepam levels and side effects of this drug in Thai children.

This study was conducted to determine the serum level of diazepam after giving an oral dosage of 0.25 mg/kg to the children presenting with febrile seizure every 6 hours for 4 doses and to observe any adverse effects of the drug at the above dosage.

PATIENTS AND METHOD

This was a prospective study carried out at the Department of Pediatrics, Maharaj Hospital, Nakhon Ratchasima, Thailand from February 1st 1994 to October 31st 1995.

Children, who were recruited into this study, were those who had a febrile seizure during this period and were admitted to the hospital for investigations of the cause of infection and for observation of recurrent seizures.

The exclusion criteria were seizures associated with fever caused by infection of the central nervous system, children with diarrhea or vomiting, unstable vital signs, age under 8 months old, or body weight under 7 kg. All patients must not have a history of diazepam, antihistamine, or other sedative drugs taken at least 2 weeks prior to the study. Informed consents were obtained from parents or caretakers of all children enrolled in this study.

Type, cause, duration of seizure and treatment received were recorded. Complete general and neurological examinations were performed in all patients. Diazepam 0.25 mg/kg in the form of a 2 mg tablet (Lot No. T609483 and T705888) were orally administered to the patients at the time of admission and every 6 hours after the first dose for a total of four doses. For small infants, the tablets were crushed and mixed with a small amount of water before administration.

Blood samples were obtained through a heparin locked venous catheter at 1 hour and 20 minutes after each dose of diazepam (peak) and immediately before the next dose (trough) in each patient. The serum was immediately separated and kept in a refrigerator before transferring to the laboratory. Determination of the serum diazepam concentrations were performed by the high performance liquid chromatography (HPLC) method at the Division of Toxicology, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok[8]. The standard diazepam solution of 5 μg/ml was used for comparison.

During the study period, the patients had their blood pressure, pulse rate, and respiratory rate regularly recorded and were observed for recurrence of seizures. The patients were also regularly examined for abnormal neurological signs including the levels of consciousness. The sedative effects of diazepam were determined by the patient's duration of sleep and the ease of being awakened from sleep.

RESULTS

Forty six children (31 males and 15 females), aged 9 to 43 months (average 17.3 months) were enrolled in this study. The majority of children (41/46) had ages ranging from 10 to 24 months.

It was assumed that the serum diazepam was zero prior to the first dose of diazepam. After the first dose, 43 of 46 patients (93.5%) had the peak diazepam levels higher than the acceptable therapeutic level (0.15 μg/ml).

The trough levels before the second dose were above the therapeutic level in 33 patients (75%). However, the peak serum diazepam concentrations after the second dose were over the therapeutic level in almost all patients (44/45).

Before the third and fourth doses, serum diazepam levels were above the therapeutic level in 80 per cent and 91.3 per cent, respectively. The peak serum levels after the doses were above the therapeutic levels in 91.3 per cent and 100 per cent, respectively (Table 1).

The average peak serum diazepam levels after each consecutive dosage were 0.48, 0.61, 0.64 and 0.62 μg/ml, respectively (Fig. 1).

Table 1. Number of patients according to serum diazepam (DZP) levels.

Levels of diazepam	Number of patients													
	1st dose of DZP			2nd dose of DZP			3rd dose of DZP			4th dose of DZP				
	Trough	%	Peak n = 46	%	Trough n = 44	%	Peak n = 45	%	Trough n = 44	%	Peak n = 44	%	Trough n = 46	%	Peak n = 45	%
>0.15 µg/ml	-	-	43	93.5	33	75.0	44	97.8	37	84.0	43	97.7	42	91.3	45	100
<0.15 µg/ml	-	-	3	6.5	11	25.0	1	2.2	7	16.0	1	2.3	4	8.7	0	0

All patients had no alteration of blood pressure, heart rate or respiratory rate throughout the study period. There were seven children whose 3rd peak serum diazepam levels were above toxic concentrations. However, no significant adverse effects of diazepam were observed. Their sleep and wake patterns were not altered. Moreover, there was no recurrent seizure in any children during the 24-hour study period.

DISCUSSION

Diazepam is one of the anticonvulsive drugs which has been used for treatment of convulsions for years. It has been used as the first line treatment of status epilepticus owing to its ability in cessation of convulsions[9,10]. It is readily absorbed, peak serum level is achieved quickly and it rapidly enters the brain[11,12]. It distributes rapidly throughout lipoid tissues and quickly crosses the blood-brain barrier [13]. In the past decade, orally administered diazepam has been used for prophylactic treatment of recurrent febrile seizures[3,6,14]. One milligram of diazepam per kilogram of body weight per day administered orally in three equal doses given every eight hours was well tolerated and produced an adequate serum diazepam level within an hour or less[6]. It was found that oral diazepam given only when fever was present was another mean of reducing the risk of recurrent febrile seizures[3,6]. However, concern has been expressed that diazepam may induce severe respiratory depression. The twenty years of experience has documented that severe adverse effects are extremely rare when normal children are treated with standard recommended doses[3].

In the present study, oral administration of diazepam at a dose of 0.25 mg/kg every 6 hours for a 24-hour period was given to previously healthy children presenting with febrile seizures. It demonstrated the adequacy of the doses and fairly constant serum concentrations above the therapeutic level. The peak serum diazepam levels were higher than the acceptable therapeutic levels in over 93 per cent of these patients at 1 hour and 20 minutes after the first dose. The trough concentrations after the first dose were also above the therapeutic level in 75 per cent of the patients. Serum concentration above the therapeutic level could be maintained almost constantly throughout 24 hours of the study period in most patients. The study also confirmed that orally administered diazepam is readily absorbed.

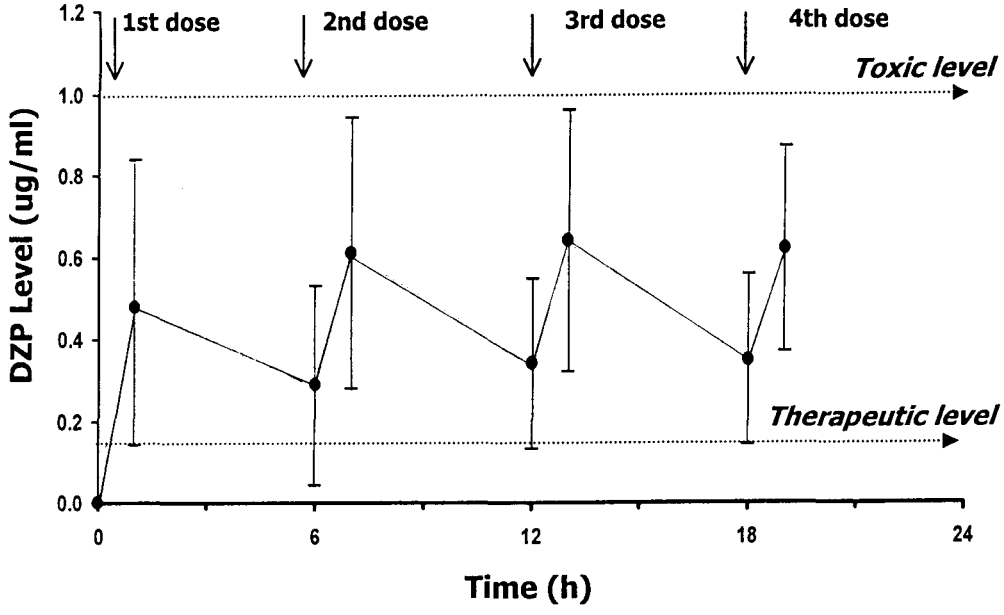

Fig. 1. Diazepam (DZP) level (mean ± SD) *vs* time after oral administration (0.25 mg/kg/dose).

None of the children in the study had any serious adverse effects. However, the level seemed to increase after the consecutive dose was administered. After the fourth dose, some children had serum levels above the toxic level without clinical symptoms. However, this implies that the toxic effect would occur if more doses of diazepam had been given. Because the serum levels obtained by orally administered diazepam were above the therapeutic level in most of the patients, intermittent orally administered diazepam may be another option in the prophylactic treatment of febrile seizures. However, a simple febrile seizure normally occurs in the first 24 hours of the onset of fever[15] and it will not be beneficial to administer diazepam beyond this period of time if intermittent prophylactic treatment of febrile seizures is deployed. Therefore, not more than 4 doses of diazepam should be administered at 6-hourly intervals. According to practice parameters suggested by the Subcommittee on Febrile Seizure, American Academy of Pediatrics, neither continuous nor intermittent anticonvulsant therapy is recommended for children with one or more simple febrile seizures [16,17]. Yet the Academy still has an open statement that in the situation in which parental anxiety associated with febrile seizures is severe, intermittent oral diazepam at the onset of febrile illness may be effective the in prevention of recurrence[16]. In cases with recurrence of seizures, other causes of seizure including infection of the nervous system and pre-existing epilepsy must be considered. Appropriate investigation and treatment according to the etiology must be exercised.

In conclusion, orally administered diazepam of 0.25 mg/kg every 6 hours for 4 doses was able to achieve therapeutic range in most children without any demonstrable adverse effects. Intermittent diazepam prophylaxis in cases of multiple or prolonged recurrent febrile seizures may be useful in reducing the recurrence, provided sufficient doses are given and compliance problems are minimized.

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ระดับยาไดอะซีแพมในเลือดของผู้ป่วยเด็ก

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ผู้รายงานได้ทำการศึกษาระดับยาไดอะซีแพมในเลือดของผู้ป่วยเด็กที่ชักจากไข้ จำนวน 46 ราย หลังจากให้ยาในขนาด 0.25 มก/กก/ครั้ง ทุก 6 ชั่วโมง รวม 4 ครั้ง พร้อมทั้งประเมินผลในการป้องกันชักและเฝ้าดูผลข้างเคียงที่เกิดขึ้นในระยะเวลา 24 ชั่วโมงที่เด็กได้รับยา พบว่าระดับยาหลังให้ยา 1 ชั่วโมง 20 นาที ซึ่งจะเป็นเวลาที่ระดับยาสูงที่สุด มีผู้ป่วยร้อยละ 93.5, 97.8, 97.7 และ 100 หลังให้ยาครั้งที่ 1, 2, 3, 4 ตามลำดับ มีระดับยาสูงกว่า 0.15 ไมโครกรัม/มล ซึ่งเป็นระดับยาที่ถือว่าเป็น therapeutic level และที่เวลาก่อนให้ยาครั้งที่ 2, 3, 4 ตามลำดับ ซึ่งเป็นเวลาที่ผู้ป่วยมีระดับยาต่ำที่สุด มีผู้ป่วยร้อยละ 75.0, 84.0, และ 91.3 มีระดับยาสูงเกิน 0.15 ไมโครกรัม/มล ในระหว่างการศึกษาไม่มีผู้ป่วยรายใดมีอาการชักและไม่มีผลข้างเคียงรุนแรงจากยา ซึ่งสรุปได้ว่าการให้ยาไดอะซีแพมโดยการกินในขนาด 0.25 มก/กก/ครั้ง ทุก 6 ชั่วโมง จะสามารถทำให้ระดับยาในเลือดเพียงพอที่จะป้องกันการชักได้ในผู้ป่วยส่วนใหญ่ และมีความปลอดภัยในการนำมาใช้ป้องกันการชักในเด็กมีอาการชักจากไข้ในช่วงที่มีไข้ร่วมกับการให้คำแนะนำการปฐมพยาบาลที่ถูกต้อง

คำสำคัญ : ไดอะซีแพม, ระดับยาในเลือด, การให้ยาทางปาก

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