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Objective : *The pharmacokinetics of diazepam administered via the buccal and rectal routes were studied and compared, in order to investigate the feasibility of the route of administration, i.e., whether or not the buccal route can serve as an alternative to the conventional rectal route for the treatment of seizures in children.*

Setting : *The Queen Sirikit National Institute of Child Health, Bangkok.*

Study design : *Opened-label, randomized, 2-way crossover trial.*

Patients : *Twenty epileptic children (12 girls and 8 boys) were recruited into the study. Their age ranged between 3 -13 years and their weight range was between 12 to 79 kg. All of them had normal renal and hepatic functions. The dose they received varied between 0.13-0.5 mg/kg.*

Methods : *The subjects were divided into two groups, and they received diazepam through both routes of administrations (via rectal and buccal routes). Blood samples were collected following the schedule, and they were then analyzed with HPLC and UV detector.*

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Results : *The mean C_{max} was 264.07 ± 149.53 ng/mL after buccal administration, and was 314.84 ± 180.33 ng/mL after rectal administration. These values were not statistically significantly different (P=0.184). However, 90 % confident interval of ln C_{max} ratio showed that C_{max} after buccal administration was between 65 % to 104 % of rectal administration which means that the absorption via the buccal route was not within ± 20 % (the acceptance criteria for bioequivalence of the rectal route). The result also indicated that there were some correlation between the dose and C_{max} after the buccal administration; therefore, the increase in dose should result in the increase of C_{max}. However, this same correlation was not found after the rectal route administration. The mean time to reach C_{max} (T_{max}) after the buccal administration was significantly longer than after the rectal route (15.75 ± 7.83 and 11.5 ± 5.64 minutes; P=0.031). Absorption rate constant (K_a) was 21.81 ± 35.40 $hour^{-1}$ for the buccal route and 51.64 ± 76.91 $hour^{-1}$ for the rectal route with no statistical difference between the routes of administration (P=0.153).*

Conclusions : *It seems feasible for the buccal route to be used as an alternative to the rectal route for diazepam administration in active seizure children especially after a better buccal formulation has been developed.*

Keywords : *Diazepam, buccal route, rectal route, seizures in children.*

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ดวงจิต พนมวัน ณ อยุธยา, เด่นพงศ์ พัฒนเศรษฐานนท์, สุรภี เรืองสุวรรณ. เภสัชจลนศาสตร์ของการให้ไดอะซีแพมทางกระพุ้งแก้มเปรียบเทียบกับการเหน็บทวารในผู้ป่วยโรคลมชักเด็ก. จุฬาลงกรณ์เวชสาร 2550 มี.ค; 51(3): 153 - 66

วัตถุประสงค์ : *ศึกษาเภสัชจลนศาสตร์ของยาไดอาซีแพมให้ทางกระพุ้งแก้มเปรียบเทียบกับให้ทางทวารหนัก เพื่อที่จะใช้เป็นวิถีใหม่ในการให้ยาระงับอาการชักในเด็ก*

สถานที่ทำการศึกษา : *สถาบันสุขภาพเด็กแห่งชาติมหาราชินี กรุงเทพมหานคร*

รูปแบบการวิจัย : *ทำการศึกษาไปข้างหน้า แบบเปิด และ สุ่มแบบข้ามกลุ่ม*

ผู้ป่วยที่ได้ทำการศึกษา : *ผู้ป่วยเด็กโรคลมชัก 20 ราย (ชาย 8 รายและหญิง 12 ราย) อายุ 3 -13 ปี น้ำหนัก 12-79 กิโลกรัม ขนาดยาที่ได้รับ0.13-0.5 มิลลิกรัมต่อกิโลกรัม ผู้ป่วยทุกรายมีการทำงานของตับและไตปกติ*

วิธีทำการศึกษา : *ผู้ป่วยถูกแบ่งออกเป็น 2 กลุ่มเท่า ๆ กัน ทั้งสองกลุ่มจะได้รับยาทั้งสองวิถี สลับกันโดยเว้นช่วงห่างของการให้ยา 1 เดือน หลังจากรับยาผู้ป่วยในแต่ละวิถีจะถูกเจาะเลือดเพื่อเก็บพลาสมาตามเวลาที่กำหนด โดยระดับยาในพลาสมาจะถูกนำไปวิเคราะห์ด้วยเครื่องแยกความดันสูง (HPLC และ UV detector)*

ผลการศึกษา : *พบค่าเฉลี่ยระดับยาสูงสุดในพลาสมาของผู้ป่วย (C_{max}) 264.07 ± 149.53 และ 314.84 ± 180.33 นาโนกรัม/มิลลิลิตร เมื่อได้รับยาทางกระพุ้งแก้มและทางทวารหนักตามลำดับ เมื่อพิจารณาสัดส่วน ln C_{max} ที่ได้จากวิถีทั้งสองที่ช่วงความเชื่อมั่น 90 % พบว่า C_{max} ของการให้ยาทางกระพุ้งแก้มอยู่ในช่วง 65 % ถึง 104 % ของการให้ยาทางทวารหนัก แสดงว่าการดูดซึมของยาผ่านทางกระพุ้งแก้มไม่ได้อยู่ในระหว่าง ± 20% ของการดูดซึมผ่านทางทวารหนัก (ซึ่งเป็นเกณฑ์ที่ยอมรับว่าการดูดซึมผ่านทั้งสองเส้นทางมีชีวสมมูลกัน) เมื่อให้ยาผ่านทางกระพุ้งแก้ม ขนาดยาที่ให้มีความสัมพันธ์กับค่า C_{max} ที่ได้ ดังนั้นถ้าเพิ่มขนาดยาที่ให้ C_{max} ก็น่าจะเพิ่มขึ้นด้วย ในทางตรงกันข้ามไม่พบความสัมพันธ์ระหว่างขนาดยาและ C_{max} เมื่อให้ยาผ่านทางทวารหนัก เวลาที่ระดับยาขึ้นสูงสุด (T_{max}) หลังจากให้ยาทางกระพุ้งแก้มช้ากว่าการให้ยาทางทวารหนักอย่างมีนัยสำคัญทางสถิติ (15.75 ± 7.83 และ 11.5 ± 5.64 นาที; P=0.031) ค่าคงที่ของการดูดซึมยาทางกระพุ้งแก้มเท่ากับ 21.81 ± 35.40 ต่อชั่วโมง ขณะที่ทางทวารหนักเท่ากับ 51.64 ± 76.91 ต่อชั่วโมง (P=0.153)*

วิจารณ์และสรุป : *มีความเป็นไปได้สูงที่การให้ยาไดอาซีแพมทางวิถีกระพุ้งแก้มจะสามารถทดแทนการให้ยาทางวิถีทวารหนักได้โดยเฉพาะอย่างยิ่งถ้ามีการปรับปรุงสูตรตำรับให้เหมาะสมยิ่งขึ้น*

คำสำคัญ : *ไดอะซีแพม, วิถีกระพุ้งแก้ม, วิถีเหน็บทวาร, ลมชักในเด็ก*

Convulsive *status epilepticus* is the most common neurological medical emergency which continues to be associated with significant morbidity and mortality[1-4], if prompt pre-hospital treatment is given, fewer antiepileptic drugs (AEDs) are required in the emergency department and seizures tend to be shorter, thus results in decreasing morbidity and mortality.[5-7] So, early treatment before admission to hospital is best with an effective medication that can be safely administered. Recently, there have been attempts to abort *status epilepticus* by treating prolonged or repetitive seizures with benzodiazepines. Rectal diazepam has been used successfully in the treatment of acute episodes[8-12] and it is widely accepted for its safety, particularly in children. The rectal cavity provides an excellent absorptive surface for the absorption of lipophilic drugs and high blood concentrations of diazepam can be achieved within minutes. The drug has been shown quite effective in aborting prolonged seizure or eliminating cluster of seizures.[9] However, rectal administration of the drug in an emergency situation is very difficult and it is not always acceptable or convenience. Since the oral and rectal cavities share similar surface areas and pH. Both are also rich in blood supplies, and the absorption is direct into the systemic circulation, which also avoids high first-pass metabolism.[13] Buccal diazepam may offer a suitable alternative to the rectal diazepam in the treatment of acute seizures. This study was therefore designed to compare the pharmacokinetics of diazepam after administration through the rectal and buccal routes in order to determine whether or not the buccal route can be used as an alternative to the conventional rectal route for the treatment of acute seizure with diazepam in epileptic children.

Patients and Method

Patients

This study was designed as an opened-label, randomized, 2-way crossover trial in order to compare the pharmacokinetics of diazepam between the buccal and rectal administrations in epileptic children. The study protocol was reviewed and approved by the independent review board of the Queen Sirikit National Institute of Child Health as well as the ethics committee of the Ministry of Public Health. The subjects in this study were selected from a group of epileptic patients at the Queen Sirikit National Institute of Child Health. Written informed consent was given by the parents or their legal guardians. The epileptic patients were recruited based on the following criteria:

Inclusion Criteria

Patients who had all of these characteristics were enrolled in this study. In-patient children with active epilepsy. Those who are between 3 -15 years whose parents or legal guardian consented to enroll in the study.

Exclusion Criteria

Patients who had either one of these characteristics were excluded from this study:

The patient was on concomitant therapy with benzodiazepines.

The patient had received benzodiazepines and stopped for less than 3 weeks prior to the start of the study.

The patient had changed or unstable vital sign.

The patient had impaired liver and/or renal function.
The patient had known allergy to diazepam.
The patient with otherwise health condition inappropriate for the study as diagnosed by physicians.

Number of Subjects

The consideration was primarily based on the report of Moolenaar et al.[14] that peak plasma concentration (C_{max}) of diazepam after rectal administration was 369 ± 58 ng/mL. In order to compare the absorption of diazepam between the two routes, we made the assumption that if the C_{max} obtained after the buccal route administration is 20 % higher or lower than those obtain from the rectal route, it will be concluded that there is a significant difference in the absorption ability between the two routes. The lowest number of subjects needed in each group was seven. However, several others studies[15-17] reported larger variations among their subjects which resulted in larger standard deviations, which means that a larger number of subjects is required. Therefore, this study was decided to recruit at least double the number of subjects to cover for fluctuations. With this regard, twenty subjects were recruited in the study.

Method

Twenty epileptic children who met the aforementioned criteria participated in this study. They were divided in two groups: ten of them received diazepam via buccal route and the other ten received diazepam via rectal route for the treatment of acute seizure. The dosages used were 0.5 mg/kg. The total maximum dose, however, was kept not to be over 10 mg. After a washed-out period of at least one month, the route of administration was then switched in each group. Series of plasma samples were collected from the patients after diazepam administration via both routes. Two to two point five milliliters of blood samples were collected at time 0 minute (before taking diazepam), 5, 10, 15, 30, 60, 240, and 480 minutes after administering diazepam. The plasma portions were separated and kept at $-70^{\circ}C$ until analyzed. Clinical data of heart rate, pulse rate, blood pressure and consciousness were monitored and recorded at the time that the blood samples were drawn. The time of seizure stopped after diazepam administration was defined for patients who had acute seizure. If the seizure continued for longer than 5 minutes after the drug administration, the treatment was deemed ineffective and the standard treatment was then administered according to the attending physician.

Diazepam intravenous solution, 10 mg/2 mL produced by the Government Pharmaceutical Organization (GPO), was used in both routes of administration.The concentrations of diazepam in plasma samples were quantified using the High Performance Liquid Chromatography (HPLC). The method of extraction of the plasma samples was modified from the methods of Raisys VA et al.[18] and Brodie LR et al.[19] The average percentage of recovery was 99.63 %. The coefficient of variations (% CV) of diazepam concentrations at 25, 500, 1000 ng/ml were less than 10 % both within run (5.10 %, 1.02 %, 1.81 %) and between run (8.38 %, 2.05%, 3.96 %) respectively.

The pharmacokinetic parameters of diazepam via the buccal and rectal administrations were derived, i.e., the maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), the area under the concentration-

time curve (AUC_{0-8hr}), absorption rate constant (K_a), elimination rate constant (K_e) and the half-life ($T_{1/2}$), using RSTRIP version 2.0 program which is the program for compartmental modeling and kinetic analysis for PC.

Comparisons of C_{max}, areas under the curves (AUC), time to reach the maximum concentration (T_{max}) and absorption rate constants (K_a) between the routes of administrations were performed by repeated measures ANOVA.

Table1. Summarizes the descriptive characteristics of the epileptic children who were enrolled in the study.

No.	Sex	Age (yrs)	Wt (kg)	Dose (mg/kg)	Epilepsy Diagnosis	Type of Seizure	AEDs
1.	F	10.92	30.5	0.33	Post encephalitis	CPS, tonic, partial → 2° generalized	PHT, PB
2.	F	13.00	25	0.4	Lennox-Gastaut syndrome	Partial → 2° generalized	PHT, VPA
3.	M	5.00	15	0.46	Unclassifiable	Partial → 2° generalized	PHT, PB
4.	M	11.00	30	0.33	Unclassifiable	Tonic	PHT, VPA
5.	M	11.00	32	0.31	Complex partial seizure	CPS	PHT
6.	M	11.00	18	0.5	Lennox-Gastaut syndrome	CPS, atonic, partial → 2° generalized	VPA, PB
7.	M	6.50	27.5	0.36	Unclassifiable	Tonic, myoclonic	VPA
8.	F	3.58	12	0.5	Lennox-Gastaut syndrome	Partial → 2° generalized, tonic	PHT, VPA,PB
9.	M	13.75	57	0.18	Complex partial seizures	CPS	CBZ
10.	F	13.83	79	0.13	Tuberous sclerosis	CPS, partial → 2° generalized	PHT, VPA
11.	F	3.75	12	0.5	Generalized seizure	GTC	PHT, PB
12.	F	13.66	29	0.34	Unclassifiable	Tonic, atonic	VPA, PB
13.	M	6.08	16	0.5	Myoclonic seizure	Myoclonic	VPA
14.	F	8.00	16	0.5	Unclassifiable	Partial → 2° generalized	VPA
15.	F	8.83	30	0.33	Unclassifiable	CPS, partial → 2° generalized	CBZ, PB
16.	M	13.00	39	0.26	Unclassifiable	Partial → 2° generalized, tonic	CBZ
17.	F	12.00	49	0.2	Unclassifiable	Partial → 2° generalized	PHB
18.	F	5.92	20	0.5	Generalized tonic	Tonic	PHT, PHB
19.	F	5.75	16	0.5	Lennox-Gastaut syndrome	Partial → 2° generalized, tonic, Infantile spasm, myoclonic	PHT, VPA, TPM
20.	F	12.42	49	0.2	Complex partial seizure	CPS	CBZ, PB

AEDs = Antiepileptic Drugs, **Wt** = Weight, **M**= Male, **F**= Female,
CPS = complex partial seizure,
Partial → 2° generalized = Partial seizure evolving to secondary generalized seizure,
PHT = Phenytoin, **VPA** = Sodium Valproate,
PB = Phenobarbital, **CBZ** = Carbamazepine, **TPM** = Topiramate

Results

Of the 30 epileptic children recruited, twenty epileptic children completed the study (main reason for droppings out was due to the inconvenience of the parent to bring the child back for the crossover trial which should not interfere with the results). Twelve of them were female (60 %); their age range was 3 -13 years and the mean age was 9.45 ± 3.56 years (mean SD). The mean weight was 30.08 ± 17.26 kg (mean ± SD) and the range was 12-79 kg. Their dose received varied between 0.13-0.50 mg/kg and 7 of them received 0.5 mg/kg. Epileptic children in this study were diagnosed to be Lennox-Gastuat syndrome, tuberous sclerosis, myoclonic seizure, generalized seizures, complex partial seizures, and post encephalitis; some of them were unclassifiable. Laboratory data of the all patients, i.e., serum albumin, alanine aminotransferase (ALT), blood urea nitrogen (BUN) and serum creatinine indicated their liver and renal functions were within normal ranges. Demographic data and types of seizures are shown in table 1.

Pharmacokinetics of Diazepam after Buccal and Rectal Routes of Administration

The mean diazepam concentration (mean ± SD) at various times after the buccal and rectal administrations are presented in table 2 and figure 1. From the data obtained it was found that the maximum concentration (C_{max}) of diazepam after the buccal administration was 220.47 ± 140.47 ng/mL and was obtained in 15 minutes while for the rectal route, the C_{max} was found to be 268.41 ± 190.81 ng/mL at the time of 10 minutes. Pharmacokinetics parameters of diazepam after buccal and rectal administrations were derived from 2 methods, i.e., non-compartmental analysis (method A) and compartmental analysis derived from RSTRIP program (method B).

Table 2. Mean concentrations of diazepam in plasma at various times after buccal and rectal administration with dosage of 0.5 mg/kg (maximum dose 10 mg)

Time(min)	Mean Diazepam Concentrations Mean ± S.D. (ng/mL)	
	Buccal Route	Rectal Route
0	0	0
5	134.33 ± 136.48	178.82 ± 139.33
10	206.93 ± 142.69	268.41 ± 190.80
15	220.47 ± 140.47	263.47 ± 153.87
30	196.64 ± 115.22	191.86 ± 110.28
60	147.84 ± 85.51	158.00 ± 84.05
240	100.99 ± 52.22	103.53 ± 50.63
480	64.69 ± 45.55	70.19 ± 44.39

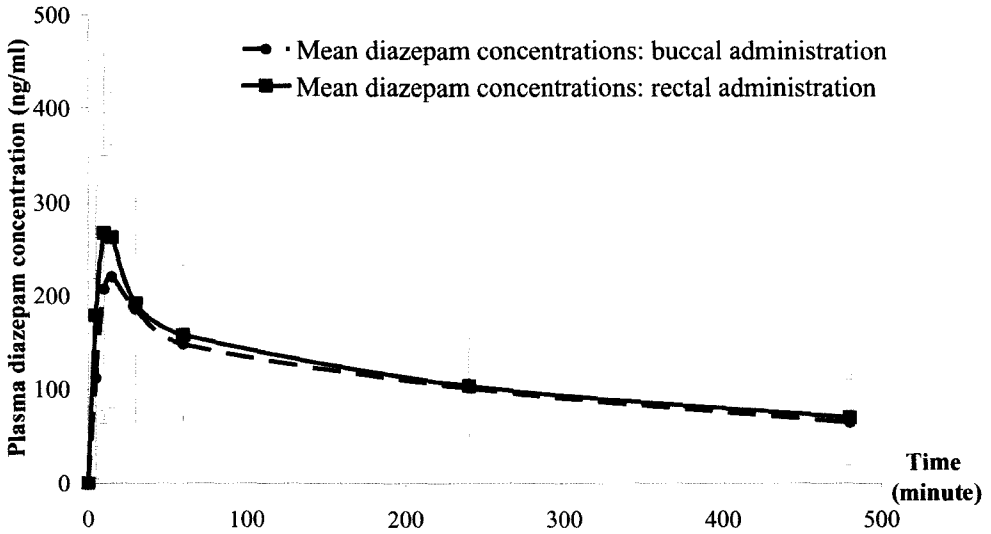

Figure 1. Mean diazepam concentrations in plasma versus time curves after buccal (BD) and rectal (RD) administrations of diazepam in the dosage of 0.5 mg/kg (maximum dose 10 mg).

Method A : Non-Compartmental Analysis

The pharmacokinetic parameters consisted of maximum concentration (C_{max}), time to reach C_{max} (T_{max}) which were directly observed from the data of individual patient, and area under the curve from the time of 0 minutes to 8 hours (AUC_{0-8hr}) which was calculated from trapezoidal integration, as reported in table 3. The mean maximum concentrations (C_{max}) after rectal and buccal administrations were compared by repeated measures ANOVA, the results revealed that there were no statistically significant differences between the two routes of administration (P = 0.184). Data of individual patients show that there were nine patients whose C_{max} was higher after buccal administration than rectal administration, while the other eleven patients were the opposite. There were also high variations of C_{max} after administration by both routes. However, 90 % confident interval (90 % CI) of ln C_{max} ratio showed that C_{max} after buccal diazepam administration was between 65 to 104 % of rectal

Table 3. Comparisons of pharmacokinetic parameters of diazepam between buccal and rectal administration from non-compartmental analysis.

Parameters	Route	Mean ± S.D.	90%CI of ln ratio	Significance
C_{max}(ng/mL)	Buccal	264.07 ± 149.53	0.6573 to 1.0452	P = 0.184
	Rectal	314.84 ± 180.33		
T_{max}(min)	Buccal	15.75 ± 7.83	-	P = 0.031
	Rectal	11.50 ± 5.64		
AUC_{0-8hr}($ngml^{-1}min$)	Buccal	52828.50 ± 28462.40	0.7150 to 1.1540	P =0.678
	Rectal	55942.90 ± 27712.53		

diazepam administration. The data also revealed that 90 % confident interval of ln $AUC_{0\text{-}8\,hr}$ after buccal administration was between 28 % lower and 15 % higher than rectal administration. However, no statistical significance was found in the differences of $AUC_{0\text{-}8hr}$ between the two routes according to the repeated measures ANOVA (P = 0.678). The means of time to reach maximum concentration after administration (T_{max}) were faster after rectal administration than after buccal administration and they are shown to be statistically significantly different (P = 0.031).

Method B : Compartmental Analysis by RSTRIP Program

The results were shown in table 4. C_{max} after buccal administration and after rectal administration showed no statistically significant difference (P = 0.203) whereas 90 % CI of ln C_{max} ratio showed that C_{max} after buccal administration was between 35 % lower and 8 % higher than those obtained after rectal administration. There were no significant differences between $AUC_{0\text{-}8hr}$ (P = 0.893) and $AUC_{0\text{-}\infty}$ (P = 0.915) between the two routes. However, 90 % CI of ln AUC ratios showed that $AUC_{0\text{-}8hr}$ after buccal administration was between 68 to 147 % of rectal administration while $AUC_{0\text{-}\infty}$ after buccal route was between 68 to 170 % of rectal route. When the absorption rate constant (K_a) were compared by repeated measures ANOVA, it was found that there was no statistically significant difference between buccal route and rectal route (P = 0.153). In case of T_{max}, the result shows that buccal administration reached the maximum concentration slower than rectal administration, however, this difference was not statistically significant (P = 0.35). Half-life of diazepam was 4.11 ± 1.94 and 4.29 ± 2.39 hours after buccal and rectal administrations, respectively. These results are consistent with a previous study by Tungnararutchakit K [20] which reported the half-life of diazepam in 1 to 3 year-old Thai children after oral administration to be 4.16 ± 3.59 hours. However,

Table 4. Comparisons of pharmacokinetic parameters of diazepam from compartmental analysis between buccal and rectal administration.

Parameters	Route	Mean ± S.D.	90%CI of ln ratio	Significance
C_{max} (ng/mL)	Buccal	212.05 ± 118.16	0.6556 to 1.0835	P = 0.203
	Rectal	250.85 ± 132.26		
T_{max} (min)	Buccal	19.93 ± 13.29	-	P = 0.350
	Rectal	15.63 ± 14.46		
K_a (hr^{-1})	Buccal	21.81 + 35.40	-	P = 0.153
	Rectal	51.64 ± 76.91		
$AUC_{0\text{-}8hr}$ ($ngml^{-1}min$)	Buccal	50609.82 ± 31913.19	0.6806 to 1.4770	P = 0.893
	Rectal	49288.7 ± 32425.54		
$AUC_{0\text{-}\infty}$ ($ngml^{-1}min$)	Buccal	74504.35 ± 44156.99	0.6816 to 1.7073	P = 0.915
	Rectal	76307.75 ± 63249.07		

the literature review indicated the elimination half-life ($T_{1/2\beta}$) of diazepam in children 2 to 12 years was about 15 -21 hours [21] which was different from the results in this study. The present study calculated the parameter from only 8 points of sampling time with the last sample collected at 8 hours only after drug administration. Therefore, the data were fitted by the pharmacokinetics computer program (RSTRIP) to be a one compartment model. If the blood samples were collected further for a longer period of time, the second compartment might show up and could result in a longer reported half-life. Clearance and volume of distribution could not be calculated from this study, since these parameters were related to the amount of drug entered general circulation, while in this study the drug was sucked out of the buccal cavity after 5 minutes to prevent choking, so the amount of drug that actually reached blood circulation could not be predicted.

Clinical effects of diazepam after buccal and rectal administration

The efficacy of diazepam intrarectal was reported to be 28.6 to 100 % [22] while another study indicated that seizure frequency was significantly reduced. Also, the mean time to their next seizure was significantly longer after rectal gel diazepam compared to the placebo group.[23] In the treatment of acute seizures, little data are available to define the effective drug plasma concentration of diazepam. The minimum plasma concentration required to suppress seizures is thought to range between 200 to 600 ng/mL in most emergency setting. Also, 200 ng/mL is the concentration considered necessary to control *status epilepticus* in human. [2,23-25] The number of patients whose maximum concentrations (C_{max}) after buccal and rectal diazepam could reach the target concentrations, 500 ng/mL to be able to terminate seizure and 200 ng/mL to be able to control seizure data are displayed in table 5. The results revealed that there were only 2 out of 20 patients (10 %) in each group whose C_{max} level reached the level of 500 ng/mL. However, most patients showed their C_{max} levels were above 200 ng/mL

Table 5. The number of patients whose plasma diazepam levels reached target concentrations.

Time (min)	Concentration (ng/mL)	Number of Patients	
		Buccal Administration (n = 20)	Rectal Administration (n = 20)
5	> 500*	2	1
	> 200	2	7
10	> 500*	2	1
	> 200	10	12
15	> 500*	1	1
	> 200	9	11
30	> 500*	0	0
	> 200	10	9

* including patients who have diazepam concentration > 200 ng/ml

[13 (65 %) and 15 (75 %) patients after buccal and rectal administrations, respectively]. Considering the time to reach target concentration, the number of patients whose plasma level reached 500 ng/mL within 5 minutes after administration were only two after buccal administration and only one after rectal administration. Two patients after buccal administration reached the target of 200 ng/mL, while 7 patients after rectal administration reached this level of target concentrations within 5 minutes. Within 10 minutes, the number of patients who reached the target of 500 ng/ml did not change. Nevertheless, as for the 200 ng/mL target concentration, there were 10 patients (50 %) after buccal administration and 12 patients (60 %) after rectal administration respectively reached this target. Plasma diazepam levels were lower than 200 ng/mL in the majority of the patients (95 %) at 4 hours and in all patients at 8 hours after drug administration via either route (table 6). The majority of the patients complained about the bitter taste of diazepam when used via buccal administration. During the period of study, their heart rate, blood pressure and respiratory rate were measured at the time the blood samples were collected. No cardiovascular and respiratory depressions were recorded in any subjects.

Discussion

From all of the data above, the absorption ability of diazepam via the buccal route was not significantly different from the rectal route, moreover, except for the time to reach maximum concentration (T_{max}) which via the buccal route was a little more delayed as compared to the rectal route. High variations were found from both the rectal and buccal diazepam administrations. From this study we found the standard deviation of C_{max} after buccal administration was 149.53 ng/mL which was quite wide. This implies that if the number of subjects were increased, some difference might be able to determine. At the same time, since 90% CI of ln C_{max} ratio after buccal route was between 35 % less to 8 % higher than those obtained after rectal route which means that there were significant differences in the absorption ability between the two routes according to the assumption that we have proposed (C_{max} obtained after buccal route was more than 20 % lower than those obtained after rectal route). C_{max} obtained after each route of administration was slightly lower than the target levels and was highly variable; this might in part be due to the variations of dosage received by each patient since the maximum total dose was kept not to be over 10 mg per administration.

Table 6. The number of patients whose plasma diazepam level was lower than 200 ng/mL at various times after drug administration.

Time (minutes)	Number of Patients	
	Buccal Administration (n = 20)	Rectal Administration (n = 20)
30	10	11
60	14	14
240	19	19
480	20	20

However, since there seemed to be some correlation between the dose and C_{max} after buccal administration which means that if the doses are increased C_{max} will also be increased via buccal route while the correlation between the dose and C_{max} were less obvious after rectal route which means that the increase in doses in this later route might not result in higher C_{max}. In this study, even though the patients had chronic epilepsy, they did not show *status epilepticus* at the time they were given the drug. Their clinical efficacy could not be truly determined. The numbers of patients who reached the target concentration of 200 ng/mL and 500 ng/mL had to be used as the indicator instead and they were not different between the two routes. There were only nine children who had acute seizures during the period of study; the majority of the episodes occurred and ceased in a few minutes, so the real clinical efficacy could not be evaluated. All of these nine patients, however, showed no re-occurrence of any clinical seizures beyond 12 hours after the administration of diazepam via either route.

The dosage formulation used to administer via both buccal and rectal routes was the parenteral solution dosage form. Most patients complained of the bitter taste of the formulation. However, this problem could be solved through a pharmaceutical research to develop a more pleasant flavor formulation. At the same time, due to the problem of aspiration (choking), the volume given to the patients while they were on seizure should keep as low as possible. The concentration of the buccal formulation should therefore be increased from the present parenteral formulation.

Moreover, the development of product preparation to a ready-to-administer preparation for the buccal use might help solve the problem on the difficulty of drawing diazepam from the ampoule. Similar to the rectal diazepam[26], buccal diazepam could be useful in the pre-hospital management of pediatric *status epilepticus* as well as for home use for cluster and prolonged seizures. However, in reality caregivers should be trained in administration techniques to avoid aspiration.

Conclusion

It seems to be quite feasible that the buccal route of diazepam administration can be used as an alternative to the conventional rectal route of administration especially after a better formulation has been developed. Further studies in higher dosage at the time of seizure should be performed to observe the true effects on clinical outcome.

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