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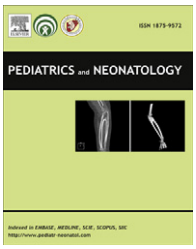

ORIGINAL ARTICLE

Rectal Diazepam Solution Is as Good as Rectal Administration of Intravenous Diazepam in the First-aid Cessation of Seizures in Children With Intractable Epilepsy

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Background: Acute seizures are readily recognizable episodes requiring urgent treatment. This study was conducted to compare the efficacy and safety of suppository use of rectal diazepam solution [Stesolid rectal tube (SRT), Alpharma, Inc., Lierskogen, Norway] with those of intravenous diazepam (IVD), Li Ta Pharma Co, Ltd., Taichung, Taiwan for control of acute seizures in children with intractable epilepsy.
Methods: Subjects were patients, aged 1—18 years, with intractable epilepsy under at least three kinds of antiepileptic treatments. Caregivers were trained to rectally administer SRT or IVD (dosage varying from 0.2 to 0.5 mg per kilogram of body weight) and to monitor respiration condition, seizure severity, and adverse drug effects.
Results: Among the 24 subjects, 9 males and 15 females, treated for a period of 3 months, the ages ranged from 2 to 18 years, with a mean of 9.1 years. Seizure types were generalized tonic and/or clonic. Seizure frequency varied from once per week to 20 times per day. Twenty-one (87.5%) of them had mental retardation and/or developmental delay, and 103 of the 127

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(81.1%) IVD administrations and 90 of the 103 (87.3%) SRT administrations resulted in rapid cessation of seizures within 10 minutes. Each first dose failed to control seizures in 24 and 13 episodes, respectively. A second dose of IVD achieved cessation of seizure in 21 of the 24 episodes and a second dose of SRT in 12 of the 13 episodes within another 10 minutes. Four episodes (3 with rectal IVD and 1 with SRT) of prolonged seizure beyond 20 minutes needed IVD injection at our emergency room. Sedation occurred in 17% of patients, which was attributed to IVD in 8% and SRT in 9% of patients. No respiratory depression was attributable to IVD or SRT. There was no significant statistical difference in efficacy and safety between these two forms of diazepam.

Conclusion: Rectal diazepam solution, administered by capable caregivers, is as effective and safe as rectal administration of IVD for children with intractable epilepsy.

1. Introduction

The management of acute seizures usually demands immediate administration of appropriate antiepileptics for avoiding status epilepticus.[1–4] Although intravenous administration is usually preferred, it is not always accessible, even when patients are staying in the hospital with no available intravenous route, not to mention seizures happening outside the hospital. The rectal route is another choice for administration of antiepileptics. Rectal administration of intravenous diazepam (IVD) has been proved to be effective by a previous report.[3] However, the procedure to prepare for rectal administration of diazepam from intravenous glass ampoule is inconvenient and time consuming. Rectal diazepam gel has been well evaluated and reported before.[5,6] The purpose of this study was to compare the efficacy and safety of a different form of diazepam—rectal diazepam solution carried in a soft plastic tube—with those of a previously used rectal administration of IVD for terminating seizures in children with intractable epilepsy.

2. Materials and Methods

This study was permitted by our Institutional Research Committee. The criteria for eligibility were children aged from 1 to 18 years, with intractable epilepsy under at least three kinds of rational antiepileptics, and absence of liver, pulmonary, and cardiovascular diseases.

One of our five pediatric neurologists evaluated each potentially eligible child, confirmed his or her eligibility, reviewed a questionnaire on the child's history previously completed by a caregiver, and obtained the caregiver's consent. The pediatric neurologists conducted baseline physical, developmental, and neurological assessments. Caregivers were provided with information booklets and charts to record seizure occurrence, number of emergency room (ER) visits for prolonged seizures in the first 3 months of rectal administration of IVD and then another 3 months of rectal diazepam solution, and any adverse effects. The caregivers were asked to telephone the study staff at any situation in which they needed assistance.

IVD (10 mg/2 mL/Amp) was manufactured by Li Ta Pharma Co, Ltd., Taichung, Taiwan Rectal diazepam solution was manufactured by Alpharma, Inc., Lierskogen, Norway [Stesolid rectal tube (SRT)] as a soft, plastic yellow tube for rectal administration, containing 2.5 mL of active ingredient of diazepam in a solution of 4-mg/mL (10 mg/rectal tube) strength. Caregivers were trained to administer IVD and SRT (dosage varying from 0.2 to 0.5 mg/kg of body weight) appropriately and to monitor respiration condition, seizure severity, and adverse effects of drugs. If a seizure did not cease within 10 minutes after administration of the first dose, another one would be administered subsequently. If it did not stop within another 10 minutes, the patient was required to be brought to our ER to receive further management.

Our nursing specialist telephoned caregivers weekly throughout the whole period of 6 months to provide support; assess compliance with medication; confirm and bring up-to-date information on the child's seizure charts; and assess the child's clinical progress, including possible adverse effects of medication. Our pediatric neurologists also telephoned each caregiver, every 8 weeks, to reinforce the study procedures, inquire about any unreported seizures, and confirm medication use. There were three specified reasons for terminating a child's participation in the study: significant increase of seizure frequency; development of possible side effects of medication that caused concern (such as a rash or lethargy); or any kind of worry expressed by caregivers.

2.1. Statistical analysis

Clinical factors obtained from family were analyzed as the difference between rectal administrations of IVD and SRT to stop seizures. These factors included seizure control with one dose, seizure control with two doses, patient numbers with adverse effects, and number of ER visits for seizure control. The association between each of these variables and seizure control was examined. Statistical analysis was performed with χ^2 test for categorical variables using SPSS (12.0) statistical software (SPSS Inc., Chicago, IL, USA). A p value less than 0.05 was accepted as statistically significant.

3. Results

There were 9 male and 15 female patients enrolled in the study without any patient withdrawal from the study. Their ages ranged from 2 to 18 years, with a mean of 9.1 years. Seizure type was generalized tonic and/or clonic with or

without cyanosis. Twenty-one (87.5%) of them had mental retardation and/or developmental delay.

In the 24 subjects enrolled in the study (Table 1), 103 of the 127 (81.1%) IVD administrations and 90 of the 103 (87.3%) SRT administrations resulted in cessation of seizure within 10 minutes, and 24 IVD and 13 SRT administrations that failed to stop seizure within 10 minutes needed a subsequent dose. The second IVD dose achieved cessation of seizure in 21 of the remaining 24 episodes of seizures within another 10 minutes, and the second SRT dose achieved cessation of seizure in 12 of the remaining 13 episodes within another 10 minutes. Four episodes (3 with rectal IVD and 1 with SRT) of prolonged seizure beyond 20 minutes received IVD injection at our ER. Sedation occurred in 17% of patients, attributed to IVD in 8% and SRT in 9%. No respiratory depression was attributable to IVD or SRT. No other serious adverse events occurred in the 6 months of study period. No significant statistical difference could be found between these two treatments.

4. Discussion

Because rectal absorption occurs by passive diffusion through the lipoidal membrane, the optimal medication should be both lipid soluble and nonionized.[7] Factors that influence absorption include particle size, surface properties, solubility, and fluid content in the rectum. In general, suppositories are characterized by delayed and more variable absorption than rectal solutions, which get into contact with a greater surface area of the colon and rectal mucosa. Because the lower portion of the rectum is drained by the middle and inferior rectal veins, which bypass the portal circulation, absorbed medications avoid first-pass elimination in the liver and enter directly into the systemic circulation.[8] In children, the usual dose of rectal diazepam has been 0.5 mg/kg. A clinical response was obtained in 72% of adults treated with 30 mg of rectal diazepam, with a mean time to cessation of seizure being 11.2 minutes.[9] Because the diazepam is highly lipophilic, it readily crosses the blood—brain barrier. Electroencephalographic changes are induced as early as 1—10 minutes after either intravenous or rectal administration.[10,11] The antiepileptic effect may be related more to rapid brain penetration by diazepam than to its serum concentration.[12,13]

The management of acute seizure demands administration of appropriate medications, especially when the seizure is prolonged and status epilepticus is impending. Characteristics of the ideal medication include, (1) rapid onset of action, (2) wide spectrum of activity, (3) minimal redistribution, (4) short elimination half-life, (5) wide therapeutic margin of safety, and (6) easy administration. In general, diazepam has been considered to be the antiepileptic of choice for treating status epilepticus and cluster seizures. However, intramuscular diazepam may cause necrosis at the site of injection, and absorption after oral and intramuscular administration is slow and variable. Conversely, rectal diazepam is rapidly absorbed. Peak serum concentrations may be obtained within 6 minutes.[14] Absorption varies with the formulation used and is slower with suppositories than with solutions.[15]

Since its first use in 1975,[16] rectally administered parenteral diazepam solution has been an excellent alternative when emergency therapy is needed and intravenous access is not available. However, it is inconvenient and time consuming to cut the ampoule, draw the diazepam solution into the gauge, insert a lubricated rectal tube, and push it into the rectum. In the United States, a diazepam rectal gel has been shown to be effective and less time consuming.[6,17—19] The diazepam in solution form is better for rectal absorption than that in gel form.[20]

Rectal diazepam is effective both in aborting seizures and in preventing febrile seizures. Knudsen[21] reported that rectal diazepam stopped seizures in 96% of patients if given within 15 minutes after seizure onset. If given later in the course of the seizure, it was effective in only 57% of patients. When given prophylactically at the time of fever, rectal diazepam was as effective as daily phenobarbital in preventing febrile seizures.[22,23]

Caregivers can be taught to use rectal diazepam at home.[24—27] Kriel et al[25] reported that 85% of 67 families reported the effectiveness of rectal diazepam in controlling their children's seizures. Adverse effects were reported by 45% and usually consisted of drowsiness or behavioral changes.[27] Respiratory difficulties were experienced by five patients, although it was impossible to determine whether they were caused by the medication or the seizures.[27] When used as recommended, diazepam rectal gel has a low rate of serious morbidity or mortality.[27] Our patients did not have serious adverse effects. Local irritation after rectal administration of diazepam has been reported before,[28] but it did not occur in our study.

Rectal emergency medication may elicit social fear, and it may elicit increased expectations of bullying if recurring.[29] We did not face similar situations because most of our enrollees had mental retardation and/or developmental delay. SRT could decrease the care burden for those special kids with epilepsy no matter whether they stayed at home or

Table 1 Difference between rectal administration of IVD and SRT to stop seizures in 24 children with intractable epilepsy

	PRN administration of		
	IVD	SRT	p^*
Total seizure episodes in 3 mo	127	103	
Seizure control with 1 dose	103 (81.1%)	90 (87.3%)	0.197
Seizure control with 2 doses	21/24	12/13	1.0
Patient numbers with adverse effects	2	1	1.0
No. of ER visits for seizure control	3	1	0.629

* No significant difference (χ^2 test, $p > 0.05$).
IVD = intravenous diazepam; SRT = Stesolid rectal tube; PRN = as necessary; ER = emergency room.

special-care institutes. In another study, most children who were prescribed diazepam rectal gel did not encounter resistance to its use in school and day care settings.[30,31] It could be applied in children for dental or other procedures too.[32]

In conclusion, rectal diazepam solution, administered at home by trained caregivers, is as effective and safe as rectal administration of the parenteral form of diazepam for children with intractable epilepsy.

References

1. Camfield CS, Camfield PR, Smith E, Dooley JM. Home use of rectal diazepam to prevent status epilepticus in children with convulsive disorders. *J Child Neurol* 1989;**4**:125—6.
2. Seigler RS. The administration of rectal diazepam for acute management of seizures. *J Emerg Med* 1990;**8**:155—9.
3. Dieckmann RA. Rectal diazepam for prehospital pediatric status epilepticus. *Ann Emerg Med* 1994;**23**:216—24.
4. Alldredge BK, Wall DB, Ferriero DM. Effect of prehospital treatment on the outcome of status epilepticus in children. *Pediatr Neurol* 1995;**12**:213—6.
5. Dreifuss FE, Rosman NP, Cloyd JC, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med* 1998;**338**:1869—75.
6. O'Dell C, Shinnar S, Ballaban-Gil KR, et al. Rectal diazepam gel in the home management of seizures in children. *Pediatr Neurol* 2005;**33**:16—72.
7. Giovannitti JA, Trapp LD. Adult sedation: oral, rectal, IM, IV. *Anesth Prog* 1991;**38**:154—71.
8. Graves NM, Kriel RL, Jones-Saete C, Cloyd JC. Relative bioavailability of rectally administered carbamazepine in humans. *Epilepsia* 1985;**26**:429—33.
9. Remy C, Jourdil N, Villemain D, Favel P, Genton P. Intrarectal diazepam in epileptic adults. *Epilepsia* 1992;**33**:353—8.
10. Milligan N, Dhillon S, Oxley J, Richens A. Absorption of diazepam from the rectum and its effect on interictal spikes in the EEG. *Epilepsia* 1982;**23**:323—31.
11. Franzoni E, Carboni C, Lambertini A. Rectal diazepam: a clinical and EEG study after a single dose in children. *Epilepsia* 1983;**24**:35—41.
12. Milligan N, Dhillon S, Richens A, Oxley J. Rectal diazepam in the treatment of absence status: a pharmacodynamic study. *J Neurol Neurosurg Psychiatry* 1981;**44**:914—7.
13. Elterman RD. Rectal administration of diazepam. *J Child Neurol* 1994;**9**:340—1.
14. Dulac O, Aicardi J, Rey E, Olive G. Blood levels of diazepam after single rectal administration in infants and children. *J Pediatr* 1978;**93**:1039—41.
15. Dhillon S, Oxley J, Richens A. Bioavailability of diazepam after intravenous, oral and rectal administration in adult epileptic patients. *Br J Clin Pharmacol* 1982;**13**:427—32.
16. Agurell S, Berlin A, Ferngren JE, Hellstrom B. Plasma levels of diazepam after parenteral and rectal administration in children. *Epilepsia* 1975;**16**:277—83.
17. Mitchell WG, Shellenberger K, Groves L, et al. Rectal diazepam gel (Diastat) for acute repetitive seizures: results of a double-blind, placebo-controlled study in children and adults with epilepsy. *Epilepsia* 1996;**37**(Suppl 5):S154.
18. Cloyd JC, Lalonde RL, Beniak TE, Novack GD. A single-blind, crossover comparison of the pharmacokinetics and cognitive effects of a new diazepam rectal gel with intravenous diazepam. *Epilepsia* 1998;**39**:520—6.
19. Sharp GB, Conry JA, Bergen DC, Bell WE. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med* 1998;**338**:1869—75.
20. Sznitowska M, Gajewska M, Janicki S, Radwanska A, Lukowski G. Bioavailability of diazepam from aqueous-organic solution, submicron emulsion and solid lipid nanoparticles after rectal administration in rabbits. *Eur J Pharm Biopharm* 2001;**52**:159—63.
21. Knudsen FU. Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children. *Arch Dis Child* 1979;**54**:855—7.
22. Knudsen FU. Effective short-term diazepam prophylaxis in febrile convulsions. *J Pediatr* 1985;**106**:487—90.
23. McKinlay I, Newton R. Intention to treat febrile convulsions with rectal diazepam, valproate or phenobarbitone. *Dev Med Child Neurol* 1989;**31**:617—25.
24. Hoppu K, Santavouri P. Diazepam rectal solution for home treatment of acute seizures in childhood. *Acta Paediatr Scand* 1981;**70**:369—72.
25. Kriel RL, Cloyd JC, Hadsall RS, Carlson AM, Floren KL, Jones-Saete CM. Home use of rectal diazepam for cluster and prolonged seizures: efficacy, adverse reactions, quality of life and cost analysis. *Pediatr Neurol* 1991;**7**:13—7.
26. Lombroso CT. Intermittent home treatment of status and clusters of seizures. *Epilepsia* 1989;**30**(Suppl 2):S11—4.
27. Pellock JM, Shinnar S. Respiratory adverse events associated with diazepam rectal gel. *Neurology* 2005;**64**:1768—70.
28. Hansen HC, Harboe H, Drenck NE. Local irritation after administration of diazepam in a rectal solution. *Br J Anaesth* 1989;**63**:287—9.
29. Timmerman A, Jennekens-Schinkel A, Oostrom KJ, van Nieuwenhuizen O. Stesolid emergency treatment: cave social fear! *Seizure* 2008;**17**:333—8.
30. Terry D, Paolicchi J, Karn M. Acceptance of the use of diazepam rectal gel in school and day care settings. *J Child Neurol* 2007;**22**:1135—8.
31. O'Dell C, O'Hara K. School nurses' experience with administration of rectal diazepam gel for seizures. *J Sch Nurs* 2007;**23**:166—9.
32. Diner MH, Fortin RC, Marcoux P, Legault V. Behavioral influences of rectal diazepam in solution on dental patients with mentally and physically handicapping conditions. *Spec Care Dentist* 1988;**8**:19—22.