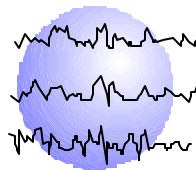


EFFICACY AND RISK OF RESPIRATORY DEPRESSION WITH RECTAL DIAZEPAM USE IN CHILDREN WITH EPILEPSY

Mary C. Gustafson, PharmD
Frank J. Ritter, MD
Michael D. Frost, MD



This paper has been prepared specifically for:

American Epilepsy Society Annual Meeting
Los Angeles, CA
December 1 – 6, 2000

Please consider this information to be preliminary findings.

Minnesota Epilepsy Group, P.A.[®]
225 Smith Avenue N., Suite 201
St. Paul, MN 55102
Phone: (651) 241-5290
Fax: (651) 241-5248

ABSTRACT

Rationale: Rectal diazepam (0.5 mg/kg-maximum single dose 20 mg) is our standard practice for terminating prolonged (seizure > 5 minutes and continuing) or acute repetitive seizures in children, both inpatient and at home. Recently, clinically significant respiratory depression, requiring mechanical support has been reported in 8.8% of children receiving rectal diazepam (Norris et al, Dev. Med. Child Neurol 1999;41:340-343). This is a major concern, especially when prescribed for home use. We analyzed all uses of rectal diazepam on our pediatric epilepsy unit since 1998 for efficacy and risk of respiratory depression.

Methods: We follow a strict hospital protocol. For at least 20 minutes following the administration of rectal diazepam, there is continuous observation and respiratory rate is recorded every five minutes. Charts were reviewed for age, weight, dose, seizure response, respiratory rate.

Results: 532 doses of rectal diazepam were administered to 78 children ages 3 mos. to 20 years (mean age 6.75 years). The average dose was 0.6 mg/kg. Single doses ranged from 0.3 to 1.3 mg/kg. Those receiving less than 0.5 mg/kg weighed over 40 kg with our maximum single dose 20 mg. Seven children had repeat doses within 10 minutes, 8 had 3 or more doses in < 24 hours.

Rectal diazepam terminated prolonged seizures or acute repetitive seizures in 96% (511/532) of administrations. There were no (0/532) episodes of clinical respiratory depression.

Conclusions: We reviewed only inpatients because we had protocol documentation of effectiveness and respiratory status on every use of rectal diazepam. This eliminates the possibility of an unreported case of respiratory depression. Rectal diazepam was 96% effective. No clinically significant respiratory depression was seen in 532 uses. We have prescribed rectal diazepam for over 10 years, giving an estimated 1500-2000 doses to over 300 children without a reported case of respiratory depression. Our experience is quite different from that reported by Norris et al. Possible explanations for these differences will be discussed.

Epilepsia, 41(S7):85, 2000

INTRODUCTION

Prolonged and acute repetitive seizures require prompt treatment to prevent possible status epilepticus, subsequent neuronal injury and hospitalization. Benzodiazepines are the treatment of choice. Following rectal administration, diazepam is readily absorbed and rapidly distributed into the CNS, providing a fast and effective treatment. The safety of rectal diazepam has been debated. Recently, clinically significant respiratory depression requiring mechanical support has been reported in 8.8% of children receiving rectal diazepam (Norris et al., *Dev Med Child Neurol*, 1999;41:340-343). This frequency is much greater than reported from previous series, and raises concerns about the out of hospital use of rectal diazepam. Out of hospital rectal diazepam (DZP) has been an integral part of seizure management for many of our patients with intractable epilepsy.

Our standard rectal diazepam dose for terminating prolonged (seizure > 5 minutes and continuing) or acute repetitive seizures in children is 0.5 mg/kg (maximum dose 20 mg). We analyzed all uses of rectal DZP on our pediatric epilepsy unit since January 1998 for efficacy and risk of respiratory depression.

METHODS

A strict protocol for administering rectal diazepam and monitoring patients is followed on our pediatric epilepsy unit. 0.5 mg/kg to a maximum dose of 20 mg of diazepam for children 40 kg or more is administered rectally. The buttocks are held shut to prevent seepage. For at least 20 minutes following the administration of rectal diazepam, there is continuous observation and clinical monitoring of respiratory rate by nurses.

Hospital charts of all patients admitted to the pediatric epilepsy unit from January 1998 to April 2000 who received rectal diazepam for interruption of acute repetitive or prolonged seizures were reviewed for age, weight, dose, seizure and respiratory response.

RESULTS

532 doses of rectal diazepam were administered to 78 children for prolonged or acute repetitive seizures. Age range was three months to 20 years (mean age 6.75 years). Single doses ranged from 0.3 to 1.3 mg/kg (average dose 0.6 mg/kg). All patients receiving less than 0.5 mg/kg weighted over 40 kg with our maximum single dose 20 mg. Seven children were given repeat doses within ten minutes; eight children had three or more doses in less than 24 hours.

Rectal diazepam terminated prolonged or acute repetitive seizures in 96% (511/532) of administrations. There were no (0/532) episodes of clinical respiratory depression.

DISCUSSION

Rectal diazepam use was reported initially in 1975 with subsequent reports documenting rapid absorption and peak serum concentrations occurring 4-30 minutes after administration¹. Effectiveness in interrupting prolonged and acute repetitive seizures has been well documented throughout the past two and one-half decades. In a study by Knudsen et al, children receiving rectal diazepam within 15 minutes of onset of ongoing seizures had a 96% efficacy rate for aborting seizures. Our results support this efficacy. Administration beyond 15 minutes reduced the efficacy rate to 57%². This suggests effectiveness of therapy correlates with timing of drug administration.

Initial studies suggested rectal diazepam resulted in few adverse effects. In Knudsen's study, 317 children receiving rectal diazepam for prophylaxis against febrile seizures were analyzed. None had any clinically significant respiratory depression³. In a study by Appleton et al., children presenting with convulsions to the emergency room were assigned to receive either lorazepam or diazepam intravenously, unless intravenous access was not possible, then rectally. Nineteen children received rectal diazepam 0.3-0.4 mg/kg with one reported respiratory depression (5%)³. It is unclear from this study if the one patient with respiratory depression received other additional antiepileptic drug therapy prior to the respiratory depression. Dieckmann et al., compared the feasibility, effectiveness and safety of rectal diazepam and intravenous diazepam in the treatment of pediatric status epilepticus prior to ER arrival. Of the sixteen patients receiving rectal diazepam, no patient required intubation after rectal diazepam administration. Five patients required intubation (31%) following the additional administration of intravenous diazepam and phenobarbital. Single rectal diazepam dose ranged 0.16 mg/kg to 0.57 mg/kg⁴. A review by Seigler of 843 administrations of rectal diazepam revealed three cases of respiratory depression.

In Norris' prospective study analyzing the incidence of respiratory depression following the use of diazepam in children presenting with seizures, 91 patient episodes of rectal diazepam were studied. Eight children had respiratory depression (8.8%). Seven patients required ventilation (7.7%)⁵.

This high risk of respiratory depression following rectal diazepam is not supported by our study. Our study population, however, differs from those of previous studies. In our group, all patients with prolonged seizures received treatment at 5 minutes. Our strict protocol for administering rectal diazepam and monitoring patients has been followed since its institution in 1990 on our pediatric epilepsy unit. Approximately 1,500 doses of rectal diazepam have been administered over 10 years without a reported case of respiratory depression. This is despite our average single dose of 0.6 mg/kg which is higher than single doses reported in previous studies. Duration of seizure in both Dieckmann's and Norris' studies were not documented. However, due to the nature of these studies with treatment initiated by emergency responders or after arrival to the

emergency room the duration of seizures prior to initial treatment in those groups would have been longer than 5 minutes. The duration of seizure activity in Appleton and colleagues study is not documented for the patient experiencing respiratory depression. Longer seizure duration does appear to be associated with higher morbidity.

It would be difficult to design an ethical, prospective study evaluating the adverse effects of various duration of seizures prior to treatment to assess the effect of seizure duration alone on morbidity. Clinical experience is therefore necessary to provide the best therapy. Our study, which limits the duration of prolonged seizures to ≤ 5 minutes, controls one variable potentially responsible for respiratory depression. Limiting our population to patients on our pediatric epilepsy unit controls variability in monitoring seizures and respiratory depression. No cases of respiratory depression resulted and seizure activity was aborted in 96% of cases.

CONCLUSIONS

In our study, no clinically significant respiratory depression occurred in 532 administrations of rectal diazepam. Rectal diazepam was 96% effective in stopping prolonged (> 5 minutes and continuing) seizures and acute repetitive seizures. Rectal diazepam appears to be both safer and more effective with early administration.

References

1. Graves NM, Kriel RL. Rectal administration of antiepileptic drugs in children. *Ped Neurol*, 3:321-6, 1987.
2. Knudsen FU: Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children. *Arch Dis Child*, 54:855-7, 1979.
3. Appleton R, et al. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. *Dev Med Child Neurol*, 37:682-8, 1995.
4. Dieckmann RA, et al. Rectal diazepam for prehospital pediatric status epilepticus. *Ann Emerg Med*, 23(2):216-24, 1994.
5. Seigler RS: The administration of rectal diazepam for acute management of seizures. *J Emerg Med*, 8:155-9, 1990.
6. Norris E, et al. Respiratory depression in children receiving diazepam for acute seizures – a prospective study. *Dev Med Child Neurol*, 41:340-3, 1999.