REVIEW ARTICLE

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# Safety of Diastat®, a Rectal Gel Formulation of Diazepam for Acute Seizure Treatment

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## Contents



## Abstract

Diazepam rectal gel (Diastat®) is the only medication approved by the US FDA for the management of selected, refractory patients with epilepsy, on stable regimens of antiepilepsy drugs, who require intermittent use of diazepam to control bouts of increased seizure activity. An analysis of the safety of diazepam rectal gel reveals that this formulation has certain advantages over intravenous diazepam administration: most notably a very low incidence of respiratory depression, low potential for abuse and the opportunity for out-of-hospital use by non-professional caregivers. Sedation is the most common adverse effect of rectal diazepam treatment, occurring in approximately one-quarter of patients, although

drug-induced somnolence is difficult to distinguish from normal post-ictal sedation. Overdosage of diazepam rectal gel is rarely associated with serious clinical consequences, and overdoses of up to 330% of the maximum recommended dosage have been reported without any respiratory or cardiac depression. Under-administration may be a serious safety issue because of morbidity that may result if seizures are not terminated. Chronic administration may cause tachyphylaxis and should be avoided.

## 1. Introduction

### 1.1 Data Retrieval and Selection

Sources for this review include articles found on PubMed using the search keywords: 'diazepam', 'diazepam + rectal', 'diazepam + rectal + gel', and 'Diastat'. Safety data were gleaned from all articles reporting clinical trials or experience with diazepam rectal gel as well as articles primarily addressing safety issues. In addition, Xcel Pharmaceuticals provided MedWatch reports and information about numbers of prescriptions for the product.

### 1.2 Currently Available Routes of Diazepam Delivery

Diazepam is currently available as a solution, tablet, parenteral injection kit and rectal gel formulation. The intravenous and rectal routes of administration are most appropriate for terminating prolonged seizures, acute repetitive seizures (i.e. clusters) or status epilepticus because these routes allow rapid achievement of therapeutic plasma drug concentrations. Diazepam oral solution is supplied generically by Roxane Laboratories (Columbus, OH, USA) in concentrations of 1 and 5 mg/mL. Roche Laboratories, Inc. supplies diazepam as Valium® tablets (2mg, 5mg, 10mg) or as a parenteral injection kit containing a diazepam solution of 5 mg/mL. Diastat® [1] is the only rectal gel formulation currently on the market. Diazepam rectal gel is supplied in twin-packs of prefilled, single-dose syringes in strengths of 2.5mg, 5mg, 10mg, 15mg and 20mg.[1] These premeasured doses are an improvement over diazepam rectal solution because they are easier to administer and ensure administration of the correct dosage.

### 1.3 Diazepam Rectal Gel: Indications and Uses

The overall management of seizures necessitates emergency treatment for prolonged seizures. Indeed, such seizures, especially if repetitive or evolving to status epilepticus, pose a serious risk of permanent neuronal damage.[2] Paramedics and emergency departments commonly use intravenous benzodiazepines to abort prolonged seizures. However, optimal seizure control may require emergency intervention, made possible by an at-home, emergency treatment option, before hospitalisation or even paramedic arrival.

Diastat® (Xcel Pharmaceuticals, San Diego, CA, USA) is a gel formulation of diazepam intended for rectal administration in the management of selected, refractory patients with epilepsy, on stable regimens of antiepilepsy drugs, who require intermittent diazepam to control bouts of increased seizure activity.[1] Diazepam rectal gel is easier to use than intravenous diazepam, comes in pre-measured doses (unlike rectal diazepam solution), and can be administered by non-medical personnel (such as family members or caregivers) who are properly trained by healthcare providers. Diastat® is the only US FDA-approved medication for the at-home treatment of acute repetitive or prolonged seizures.[1] It is also

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

utilised for the at-home prevention or termination of complex febrile seizures in children.[3]

Several controlled and open-label studies have shown diazepam rectal gel to be effective for terminating seizures of various types. Events studied were usually defined by duration or recurrence rather than specific seizure type (i.e. partial or generalised). Data about freedom from seizures in four double-blind studies[4-7] are summarised in figure 1. Between 55 and 71% of patients in these studies remained seizure-free 12 hours after the administration of diazepam rectal gel. In an open-label study, 77% of 1578 administrations in 149 patients resulted in seizure freedom for at least 12 hours after treatment. No significant differences in the probability of seizure freedom were observed between the first and last seizures treated with diazepam rectal gel, indicating that the subjects had not developed tolerance to diazepam during the study.[8]

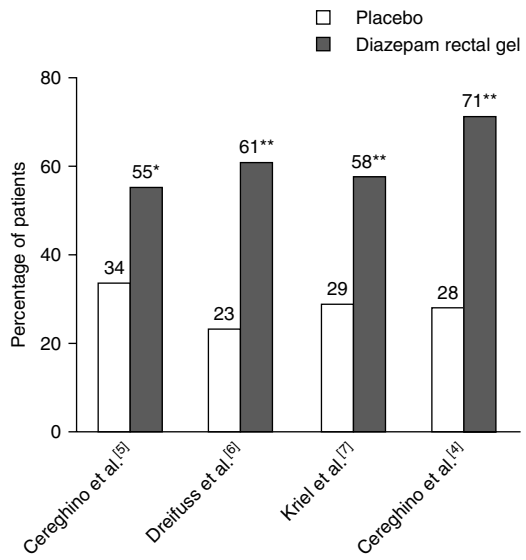


**Fig. 1.** Percentage of patients seizure free 12 hours after administration of diazepam rectal gel in controlled clinical trials.[4-7] * $p < 0.05$; ** $p \geq 0.001$.

### 1.4 Pharmacology, Pharmacokinetics and Dosage

Diazepam is believed to enhance inhibitory neurotransmission by increasing the affinity of γ-aminobutyric acid (GABA) for the $GABA_A$ receptor.[1] This positive allosteric modulation is achieved by inducing a conformational change in the M3 transmembrane region of the $\alpha_1$ subunit of the receptor.[9,10] Enhancement of GABAergic neurotransmission is thought to compensate for the excessive CNS excitation or loss of inhibitory control that underlies seizure development.[9,10]

The pharmacokinetics of diazepam rectal gel are characterised by rapid absorption, followed by slow elimination over several hours. The small surface area and high vascularisation of the rectum favour the absorption of lipid-soluble drugs such as diazepam. Administration of diazepam rectal gel 15mg to healthy adults results in plasma drug concentrations exceeding the target value of 200 μg/L within 15 minutes.[11] The rate of absorption in children has not been determined. Plasma concentrations in adults peak at approximately 400 μg/L at about 1.5 hours and remain above the target value for up to 12 hours. In contrast, intravenous diazepam results in higher and more rapidly achieved peak plasma drug concentrations, although plasma diazepam concentrations fall more quickly. A 7.5mg dose of intravenous diazepam results in plasma concentrations approaching 600 μg/L within a minute, but 2 hours after administration, plasma concentrations are below the target value, and 4 hours after administration, they are below 150 μg/L, which is the estimated lower limit of therapeutic diazepam concentrations (figure 2).[11]

Diazepam is metabolised in the liver via oxidation catalysed by cytochrome P450 (CYP) isoenzymes 3A4 and 2C19.[12] Diazepam has one major active metabolite, desmethyldiazepam, and two minor active metabolites, temazepam (3-hydroxydiazepam) and oxazepam (3-hydroxy-*N*-diazepam).[1] Desmethyldiazepam is oxidised to oxazepam, which is glucuronidated and renally excreted.[12] Diazepam and desmethyldiazepam in plasma are predominantly bound to protein (95–98% bound).[1]

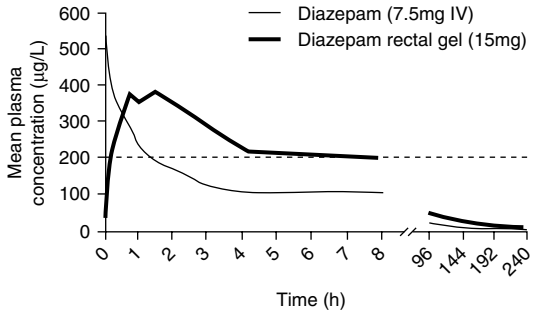


**Fig. 2.** Plasma concentrations of diazepam administered as intravenous (IV) solution or rectal gel (reproduced from Cloyd et al.,[11] with permission from Epilepsia).

The recommended dose of diazepam rectal gel varies by age between 0.2 and 0.5 mg/kg: 0.5 mg/kg for patients aged 2–5 years, 0.3 mg/kg for patients aged 6–11 years and 0.2 mg/kg for patients aged ≥12 years. The manufacturer recommends that the dose be lowered for elderly or debilitated patients. As recommended for patients of all ages, a second dose may be given 4–12 hours after the initial dose, if required, but anecdotal reports suggest that for persistent seizures, doses can be safely administered after ≤1 hour. If the patient has a bowel movement or expels the dose within 10–15 minutes of administration, re-administration may be required. No more than five episodes per month, or one episode every 5 days, should be treated with diazepam rectal gel.[1] Long-term intermittent use can result in tolerance to the drug and exacerbation of tonic-clonic seizures, and abrupt discontinuation after chronic overuse can precipitate rebound seizures.[1]

## 2. Safety Issues with Diazepam

### 2.1 Sedation

Sedation is the most commonly reported dose-dependent adverse event associated with diazepam by any route of administration. The reported incidence of sedation/somnolence with diazepam rectal gel varies widely, ranging from 13–51%.[4-8,13] The prescribing information lists the incidence of somnolence in clinical trials as 23% for diazepam rectal gel, compared with 8% for placebo.[1] Diazepam solution administered rectally has a reported 21% incidence of associated somnolence.[14] Mitchell et al.[8] noted the difficulty in distinguishing between drug-related and normal post-ictal sedation after the administration of diazepam rectal gel: although they reported a 17% incidence of somnolence, they judged that only 9% of patients experienced diazepam-related sedation. In another study, Cereghino and colleagues[5] noted that all occurrences of somnolence, including those in the placebo group, were judged by a blinded investigator to be diazepam related. These results illustrate that normal post-ictal and diazepam-associated sedation appear very similar. Therefore, the actual incidence of diazepam-associated sedation is likely to be somewhat lower than the incidence reported in clinical trials and from other clinical experience. Overall, sedation is a common effect of benzodiazepines, but is a minor concern when compared with the dangers of untreated prolonged seizures. The relatively small risk associated with sedation is outweighed by the need to prevent neuronal damage.

### 2.2 Neurocognitive Effects

Besides sedation, benzodiazepines can cause transient neurocognitive impairment.[1] The adverse neurocognitive effects of diazepam rectal gel are similar to those seen after intravenous diazepam administration, but with slightly delayed onset and somewhat longer persistence, as would be expected from the pharmacokinetics of rectal diazepam administration. Patients given a battery of neuro- psychological tests after administration of diazepam rectal gel demonstrated modest cognitive impairment in parallel with plasma drug concentrations.[11] Test scores returned to baseline values within 4 hours. Neuropsychological test scores after intravenous administration were not significantly different from those after rectal gel administration, except for a sharp dip in alertness and Wechsler Adult Intelligence Scale (WAIS) digit span scores just after intravenous administration.[11]

Behavioural disturbances, especially hyperactivity in children, can occur with diazepam.[7] However, hyperactivity is rarely associated with diazepam rectal gel. Hyperkinesia was reported in <1% of 573 patients in several clinical trials,[1] and a few adult patients reported agitation, euphoria, nervousness and hyperkinesia.[4,6] Among children from two controlled studies, 2 of 68 (2.9%) diazepam and 2 of 65 (3.1%) placebo recipients experienced nervousness; hyperkinesia was not reported.[7]

### 2.3 Respiratory Depression

Some physicians are wary of prescribing diazepam rectal gel because intravenous and oral formulations of diazepam have been associated with respiratory depression. However, a review of available data shows that the incidence of respiratory depression and apnoea associated with rectal administration of diazepam (either gel or solution) is much lower than with intravenous administration. This observation is explained by the differences in pharmacokinetic properties of diazepam between intravenous and rectal routes. Unlike rectally administered diazepam, intravenous diazepam produces a rapid spike in plasma diazepam concentrations well above target values (see section 1.4). This rapid spike often results in respiratory depression. Indeed, one study found a 10.6% incidence of respiratory or circulatory complications (i.e. hypotension, cardiac dysrhythmia or respiratory depression) after an intravenous injection of diazepam 5mg,[15] while another study reported a 15% incidence of respiratory depression.[16] The rate of respiratory depression in children treated with intravenous diazepam for status epilepticus has been reported as 21%.[17]

Rates of respiratory depression associated with rectal administration of diazepam solution vary but tend to be lower than those associated with intravenous administration. Whereas Camfield et al.[18] reported no respiratory complications in a study of 30 children treated with rectal diazepam solution, a previous study[19] reported that 2 of 17 children receiving a total of 65 doses of rectal diazepam solution experienced respiratory difficulties. Elterman[20] reported two cases of respiratory arrest after administration of a rectal diazepam solution (0.5 mg/kg); both patients responded immediately to mouth-to-mouth resuscitation. Kriel et al.[14] reported five cases of respiratory difficulty, including one case of respiratory arrest, in a study of 41 paediatric patients who received a total of 428 doses of rectal diazepam solution given at home; all patients recovered uneventfully.

Norris et al.[21] reported an 8.8% rate of respiratory depression after 91 episodes of treatment with rectal diazepam solution in children, compared with a 16.7% incidence after intravenous administration. Two of the eight patients who experienced respiratory depression after administration of the rectal solution had also been given paraldehyde rectal solution. The authors concluded that the incidence of respiratory depression after rectal diazepam administration is high.[21] However, Kriel et al.[22] challenged this conclusion, emphasising that the Norris study[21] did not include a placebo control and was therefore unable to determine the incidence of respiratory depression resulting from seizures in the study population. Mackereth[23] noted that study participants were drawn from the emergency department, which might impart selection bias in favour of finding cases of respiratory depression. Moreover, in a retrospective review of 50 children with epilepsy who had rectal diazepam available at their schools, Mackereth[23] found only two episodes of respiratory difficulties: one child had not been given diazepam and the other developed respiratory difficulties because of an uncontrolled seizure.

In contrast to the high risk of apnoea associated with intravenous diazepam, no respiratory depression occurred in four controlled clinical studies of diazepam rectal gel in a total of 200 patients with epilepsy.[4-7] In a long-term, 'roll-over' study, in which 31 children and 40 adults with acute repetitive seizures received a total of 246 doses of diazepam rectal gel, two children (one of whom had bronchitis) experienced respiratory adverse

events.[24] Furthermore, in a study of 149 patients who received a total of 1578 doses of diazepam rectal gel,[8] only two instances of transient hypoventilation (neither of which required treatment) occurred. Whether these instances were due to diazepam use or were seizure related is unknown. Interestingly, in a controlled trial in 70 patients receiving diazepam rectal gel, respiratory rates 15–240 minutes after treatment were similar to those in the placebo group and at no timepoint did the minimum respiratory rate in the diazepam group fall below that in the placebo group.[4]

Despite the high level of concern regarding the respiratory adverse effects of benzodiazepines, a study comparing intravenous diazepam, lorazepam and placebo in patients with status epilepticus found that out-of-hospital complications (hypotension, cardiac dysrhythmia, or respiratory depression) were more than twice as common among placebo recipients (22.5%) than among diazepam- or lorazepam-treated patients (10.6% and 10.3%, respectively).[15] Overall, the respiratory complications of some prolonged seizures are significant, and it appears that the very small risk of respiratory depression with diazepam rectal gel is outweighed by the much greater risk of delaying treatment.

### 2.4 Pregnancy and Teratogenicity

Diazepam rectal gel is a pregnancy category D drug, meaning that data from human studies suggest risks that may be outweighed by the benefits of therapy. While no data are available specifically about the use of diazepam rectal gel in pregnant women, prudence dictates that the decision about whether to administer diazepam rectal gel during pregnancy must be made with extreme care. In particular, chronic benzodiazepine use may increase the risk of valproate teratogenicity in pregnant women taking valproate.[25]

## 3. Safety Issues with the Rectal Route of Administration

### 3.1 Caregiver Education

Diazepam rectal gel is approved by the FDA for caregivers to administer at home. Therefore, caregiver education is important. The patient's seizure history and presentation should be reviewed with caregivers, who are typically familiar with a patient's normal seizure pattern, and a treatment plan for prolonged seizures should be implemented. Video material is available to aid in education about administration techniques.

### 3.2 Success of Administration

Diazepam rectal solution has been avoided by some because it tends to leak out of the rectum, preventing delivery of accurate doses.[26] The gel formulation greatly reduces this problem. Ease of administration and dosage accuracy with diazepam rectal gel often provide an advantage when intravenous access is restricted. Fitzgerald and colleagues[26] addressed the issue of successful administration in a study at a residential-care facility for developmentally disabled adults. In their experience, all 36 attempts to administer diazepam rectal gel resulted in successful dose delivery, whereas intravenous lorazepam was successfully administered in only 21 of 71 attempts (30%).

### 3.3 Local Skin Reactions

Rarely, pruritus or rash has been associated with the use of diazepam rectal gel. Dreifuss et al.[6] reported two instances (3.1%) of pruritus in diazepam-treated patients and no instances in placebo recipients. Kriel et al.[7] reported a similar incidence of what was termed 'skin reaction' (4.4% diazepam versus 0% placebo) in paediatric patients from two controlled trials (n = 68). Moreover, in a study by Mitchell and colleagues,[8] one patient discontinued the study because of rash and vomiting, which were judged by the investigators to be poss-

ibly related to the administration of diazepam rectal gel.

### 3.4 Rectal Irritation

Burning or stinging of the rectum can occur with rectal administration of diazepam solution. In 24 healthy volunteers given diazepam in a propylene glycol-alcohol-water solution via rectal tubes, subjects were each given diazepam 35mg in 10mL, diazepam 10mg in 2.5mL and a placebo solution of 2.5mL, in random order 35 days apart.[27] No subjects reported burning or stinging after placebo, but 12.5% experienced burning or stinging after the lower diazepam dose and 60% after the higher dose. Endoscopic assessments 24 hours after administration revealed that three subjects had mechanical irritation of the rectal mucosa from the rectal tubes, and four subjects (two from the higher-dose and one from the lower-dose diazepam group, and one from the placebo group) had reversible local irritation of the rectal mucosa judged to be from the drug, vehicle or both.[27]

The prefilled rectal syringes and rectal gel formulation of diazepam alleviate some of the problems experienced with administration of the rectal solution. The flexible tips of the syringes are designed to prevent mechanical irritation and come in different sizes for adults and children. Rectal pain/burning was rarely reported in clinical trials of diazepam rectal gel: the incidence was 3.6% (3.4% in the placebo group) in a study of children and adults,[5] and 4.4% (3.1% in the placebo group) in an analysis of paediatric patients only.[7] In a trial involving 70 adult patients given diazepam or placebo, the only anorectal event was brief (1 minute) rectal burning in a placebo recipient with a history of prostate hypertrophy.[4] In other controlled and open-label evaluations, anorectal events were not reported.[6,8]

## 4. Overdose, Overuse and Abuse

### 4.1 Overdose

Brown and colleagues[28] analysed data from two clinical trials and one open-label extension study for instances of overdose, defined as doses in excess of 180% of doses recommended in the study protocols (2–5 years of age, 0.5 mg/kg; 6–11 years of age, 0.3 mg/kg; ≥12 years of age, 0.2 mg/kg). From a population of 149 subjects (1578 treatments), ten subjects received 51 overdoses. The mean overdose (±SD) was 214 ± 25% of the recommended dose, whereas the maximal overdose was 256% of the recommended dose. Three of the ten subjects received a single accidental overdose and the remainder received intentional overdoses on several occasions because of initial under-administration. No adverse events were reported in 40 of the 51 instances of overdose (78%). However, for 11 instances of overdose in three patients, adverse events included vomiting (3 cases), otitis media (3), bronchitis (1), convulsion (1), cough (1), fever (1) and somnolence (1); all events resolved without incident. No respiratory or cardiac depression was observed in any patient receiving an overdose. In later clinical trials,[4,7,8] there were five reported accidental overdoses as high as 330% of the recommended dose; all resolved without incident or recognisable clinical consequences. In contrast, under-administration may pose a serious risk if the dose of diazepam rectal gel given is insufficient to prevent recurrent or prolonged seizures, including status epilepticus.

### 4.2 Overuse

Diazepam rectal gel is not intended for frequent or long-term use because of the risks of tolerance and rebound seizures. The prescribing guidelines limit administration to five or fewer episodes per month; i.e. only one episode every 5 days.[1] Frequent administration may exacerbate seizures and create a cyclic pattern of prolonged seizures occurring every few days with the fluctuation of plasma

diazepam and desmethyldiazepam concentrations, similar to that seen with frequent oral diazepam use. Brodtkorb and colleagues[29] reported six cases in which patients frequently received rectal diazepam for prolonged seizures or clusters. Three of these patients had a clear pattern of seizure periods aborted with rectal diazepam, followed by a period of sedation, awakening and more seizures. The other patients had more complex cycles, but in all six cases, the patients improved when rectal diazepam was restricted or eliminated.[29] In some cases, excessive intermittent treatment with rectal diazepam can be successfully replaced by low-dosage long-term oral benzodiazepine therapy.[29] However, this practice may cause tachyphylaxis and reduce the effectiveness of diazepam, given by any route or formulation, in subsequent seizure emergencies.[1]

### 4.3 Abuse

Diazepam is a schedule IV intravenous controlled substance because of the abuse liability of oral and injectable forms of the drug.[1] Diazepam rectal gel presents little potential for abuse, and there have been no reports of intentional misuse. Nevertheless, healthcare providers and pharmacists should monitor the prescription dosage and number of refills given to individuals.

## 5. Information from Spontaneous Reporting

As of February 2003, 1 327 000 diazepam rectal gel syringes had been prescribed in the US. A total of 40 reports (35 original and five follow-up reports) describing 63 adverse events coincident with the use of diazepam rectal gel were spontaneously filed with the manufacturer, who then relayed the reports to the FDA's MedWatch programme. The types of events encountered are summarised in table I. Detailed case histories are available for some events and provide insight into the potential involvement of diazepam rectal gel. In other cases, patients experienced established adverse effects of diazepam (or common effects of seizures), such as somnolence and temporary confusion.

**Table I.** Summary of adverse events involving diazepam rectal gel (Diastat®)

| Adverse event | Number of patients |
|---|---|
| Convulsion/drug ineffective | 8 |
| Gastrointestinal[a] | 7 |
| Emotional/cognitive[b] | 6 |
| Respiratory[c] | 6 |
| Somnolence | 4 |
| Death[d] | 3 |
| Hypotension/vasodilation | 2 |
| Pain | 2 |
| Rash or anaphylactic reaction | 2 |
| Infection | 1 |
| Positive drug screen | 1 |
| Reaction unevaluable | 1 |
| Rectal haemorrhage | 1 |
| Abnormal vision | 1 |
| Total syringes prescribed | 1 327 000 |

a Includes vomiting as well as constipation, diarrhoea and abnormal stools.

b Includes disorientation, confusion, memory impairment, stupor, nervousness and emotional lability.

c Includes hypoventilation/dyspnoea/respiratory depression and apnoea.

d Relationship to drug unknown; causes of death not conclusively determined.

Eight patients experienced convulsion or lack of effectiveness (table I). It is unknown whether diazepam rectal gel was administered correctly or in a timely manner in these cases, or whether the seizures terminated spontaneously or with the aid of other therapeutic interventions. Seven patients reported gastrointestinal events, including vomiting in one patient who had a comorbid lung infection. Notably, only seven instances of respiratory depression in six patients have been reported to the manufacturer. In one of these cases, dyspnoea was reported as secondary to an anaphylactoid reaction: the mother of a 13-month-old patient reported using a discoloured syringe and the patient had a positive test for opiates and a history of anaphylactic reactions.

Three patients have died after the administration of diazepam rectal gel, although whether diazepam was involved remains unknown, since the causes of death were not conclusively determined.

One patient, a 22-month-old girl, developed a whole-body rash after the concurrent administration of diazepam rectal gel and phenobarbital (phenobarbitone). The rash subsided without treatment 3 days later. Although diazepam was not given again, the patient had a recurrence of rash 2 weeks later. For this reason, the reporting physician did not suspect diazepam as the cause of rash.

To conclude much about the incidence of any particular adverse event from spontaneous reports is difficult because such reports are not collected in a systematic way. In addition, some reports describe known complications of seizures, or are for events whose relationship to diazepam is doubtful. Overall, the scarcity of spontaneous adverse-event reports, relative to the large number of doses of diazepam rectal gel prescribed, suggests that serious adverse reactions to this formulation are very rare.

## 6. Conclusions

Diazepam rectal gel provides numerous advantages over intravenous diazepam for the termination of prolonged seizures. Not only does the rectal formulation allow for administration when venous access is restricted, but the safety and ease of use of diazepam rectal gel in prefilled syringes allows patients to be treated at home by trained caregivers. Overuse of diazepam rectal gel should be avoided to prevent tachyphylaxis. The risk of respiratory depression, the most serious adverse event associated with benzodiazepine use, is much lower with rectal rather than intravenous administration of diazepam. Other adverse events are relatively minor and insignificant compared with the risk of uncontrolled prolonged seizures. The opportunity for patient empowerment and the need to prevent neuronal damage dominate the risk-benefit equation in the management of patients with a history of prolonged or clustered seizures. Therefore, diazepam rectal gel has been strongly recommended for the treatment of acute repetitive seizures[30] and complex febrile seizures.[3]

## Acknowledgements

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## References

1. Diastat® [package insert]. San Diego (CA): Xcel Pharmaceuticals, 2001
2. Sutula TP, Hagen J, Pitkänen A. Do epileptic seizures damage the brain? Curr Opin Neurol 2003; 16: 189-95
3. Shinnar S, Glauser TA. Febrile seizures. J Child Neurol 2002; 17 Suppl. 1: S44-52
4. Cereghino JJ, Cloyd JC, Kuzniecky RI. Rectal diazepam gel for treatment of acute repetitive seizures in adults. Arch Neurol 2002; 59: 1915-20
5. Cereghino JJ, Mitchell WG, Murphy J, et al. Treating repetitive seizures with a rectal diazepam formulation: a randomized study. The North American Diastat Study Group. Neurology 1998; 51: 1274-82
6. 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
7. Kriel RL, Cloyd JC, Pellock JM, et al. Rectal diazepam gel for treatment of acute repetitive seizures. The North American Diastat Study Group. Pediatr Neurol 1999; 20: 282-8
8. Mitchell WG, Conry JA, Crumrine PK, et al. An open-label study of repeated use of diazepam rectal gel (Diastat) for episodes of acute breakthrough seizures and clusters: safety, efficacy, and tolerance. North American Diastat Group. Epilepsia 1999; 40: 1610-7
9. Williams DB, Akabas MH. Benzodiazepines induce a conformational change in the region of the gamma-aminobutyric acid type A receptor alpha(1)-subunit M3 membrane-spanning segment. Mol Pharmacol 2000; 58: 1129-36
10. Williams DB, Akabas MH. Evidence for distinct conformations of the two alpha 1 subunits in diazepam-bound GABA(A) receptors. Neuropharmacology 2001; 41: 539-45
11. Cloyd JC, Lalonde RL, Beniak TE, et al. 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
12. Kirkwood CK, Melton ST. Anxiety disorders. In: DiPiro JT, Talbert RL, Yee GC, et al., editors. Pharmacotherapy: a pathophysiologic approach. 5th ed. New York (NY): McGraw-Hill, 2002: 1289-310
13. Groves L, Shellenberger K, Franklin J, et al. Safety and tolerability of a single dose administration of Diastat® (diazepam rectal gel) to patients with epilepsy on antiepileptic drugs (AEDs) [abstract]. Epilepsia 1996; 37 Suppl. 5: 154

14. Kriel RL, Cloyd JC, Hadsall RS, et al. 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
15. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001; 345: 631-7
16. Appleton R, Sweeney A, Choonara I, et al. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. Dev Med Child Neurol 1995; 37: 682-8
17. Appleton R, Martland T, Phillips B. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children (Cochrane review). Cochrane Database Syst Rev 2002; (4): CD001905
18. Camfield CS, Camfield PR, Smith E, et al. Home use of rectal diazepam to prevent status epilepticus in children with convulsive disorders. J Child Neurol 1989; 4: 125-6
19. Hoppu K, Santavuori P. Diazepam rectal solution for home treatment of acute seizures in children. Acta Paediatr Scand 1981; 70: 369-72
20. Elterman RD. Rectal administration of diazepam. J Child Neurol 1994; 9: 340-1
21. Norris E, Marzouk O, Nunn A, et al. Respiratory depression in children receiving diazepam for acute seizures: a prospective study. Dev Med Child Neurol 1999; 41: 340-3
22. Kriel RL, Cloyd JC, Pellock JM. Respiratory depression in children receiving diazepam for acute seizures: a prospective study. Dev Med Child Neurol 2000; 42: 429-30
23. Mackereth S. Use of rectal diazepam in the community [letter]. Dev Med Child Neurol 2000; 42: 785
24. Conry JA, Mitchell WG, Crumrine PK. Diastat® (diazepam rectal gel) treatment of acute repetitive seizures (ARS): a study of long-term, intermittent use [abstract]. Epilepsia 1996; 37 Suppl. 5: 154
25. Laegreid L, Kyllerman M, Hedner T, et al. Benzodiazepine amplification of valproate teratogenic effects in children of mothers with absence epilepsy. Neuropediatrics 1993; 24: 88-92
26. Fitzgerald BJ, Okos AJ, Miller JW. Treatment of out-of-hospital status epilepticus with diazepam rectal gel. Seizure 2003; 12: 52-5
27. Hansen HC, Harboe H, Drenck NE. Local irritation after administration of diazepam in a rectal solution. Br J Anaesth 1989; 63: 287-9
28. Brown L, Bergen DC, Kotagal P, et al. Safety of Diastat when given at larger-than-recommended doses for acute repetitive seizures. Neurology 2001; 56: 1112
29. Brodtkorb E, Aamo T, Henriksen O, et al. Rectal diazepam: pitfalls of excessive use in refractory epilepsy. Epilepsy Res 1999; 35: 123-33
30. Wheless JW, Venkataraman V. New formulations of drugs in epilepsy. Expert Opin Pharmacother 1999; 1: 49-60

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