Rectal Administration of Carbamazepine Suspension

John R. Manderville, James R.P. Godin, and Kathryn L. Slayter

INTRODUCTION

Clinicians sometimes face a situation in which a patient requires anticonvulsant medication but is unable to take medication orally. The parenteral route may be a suitable alternative for the delivery of many medications, but may not be appropriate in other cases, for example, because of lack of IV access or patient discomfort. Furthermore, not all anticonvulsant medications are available in parenteral form. The rectal route has been used for interim or long-term administration of anticonvulsants such as diazepam,[1] valproate,[2,3] phenobarbital,[4] carbamazepine,[5-9] and (with less success) phenytoin.[10-12]

The clinical usefulness and bioavailability of rectally administered carbamazepine (in suspension, suppository, or gel form) has been previously described.[5-9] However, very little, if any, information has been published regarding the rectal use of the commercially available Tegretol suspension, which has been available on the Canadian market since 1995. This case report describes the successful use of Tegretol suspension, administered rectally in a patient with an uncontrolled seizure disorder.

CASE REPORT

A 54-year-old man from a local rehabilitation centre was admitted to the general medicine service on October 11, 1998 (day 0), for treatment of recurrent seizures and decreased level of consciousness. The patient was mentally challenged, had a long-standing pre-existing (complex partial) seizure disorder with secondary generalization, and had poor verbal communication skills. Upon admission to hospital he was unable to swallow; therefore, all medications that he had been receiving before admission were withheld. The following drugs were discontinued: primidone 250 mg PO tid and 125 mg PO qhs, levofloxacin 500 mg PO daily, carbamazepine (Tegretol) controlled-release tablets 300 mg PO bid and 400 mg PO qhs, lorazepam 1 mg PO qid, psyllium 10 mL PO bid, and magnesium citrate 150 mL PO 3 times weekly. Aside from the patient's markedly elevated serum level of phenobarbital (215 µmol/L) (Table 1), his chemistry results on admission (including electrolyte, glucose, urea, and creatinine levels, as well as complete blood count) were unremarkable. Culture results for blood and urine were negative. Administration of IV fluids (5% dextrose in normal saline) was initiated, and one IV dose of 2.5 mg diazepam was given to terminate a generalized seizure. For the remainder of the patient's hospital stay, diazepam was given rectally on an as-needed basis to treat further seizure activity (see Table 1).

Shortly after admission, the patient's prognosis was deemed to be guarded, and after discussion with his mother the decision was taken not to attempt alternative feeding methods (i.e., total parenteral nutrition or nasogastric feeding). Since the patient was experiencing recurrent seizures and was still unable to swallow, carbamazepine was restarted on day 5. Each dose of the commercially available oral suspension of carbamazepine (Tegretol; 300 mg [15 mL] bid and 400 mg [20 mL) qhs]) was drawn into a syringe and administered rectally. Treatment with sublingual lorazepam 1 mg qid was also initiated. On the preceding day (day 4) the serum phenobarbital level had been 150 µmol/L, and it was decided to continue withholding phenobarbital and primidone. Mild hypokalemia and hypomagnesemia, which had developed since admission, were treated with parenteral potassium chloride and magnesium sulfate on day 5.

On day 11 the serum phenobarbital concentration had dropped to 45 µmol/L. To prevent further decline in phenobarbital concentrations, rectal phenobarbital

Table 1: Blood Chemistry Results, Seizure Activity, and Diazepam Medication for a Patient with Seizures and Decreased Level of Consciousness

Date	Day of Admission	Time of Day (for Testing)	Serum Drug Level* (µmol/L)			No. of Seizure Episodes Observed	Diazepam Dose
			Phenobarbital	CBZ (by HPLC)	CBZ Epoxide (by HPLC)		
Oct. 11	0	1000	215	17	15	1	2.5 mg IV
Oct. 12	1					2	2.5 mg PR 5 mg PR
Oct. 13	2	0815	190	<8	<4	8	3 x 5 mg PR 5 x 2.5 mg PR
Oct. 14	3					5	5 x 5 mg PR
Oct. 15	4	0740	150	<8	<4	2	2 x 5 mg PR
Oct. 16†	5					1	5 mg PR
Oct. 17	6						
Oct. 18	7					1	2.5 mg PR
Oct. 20	9	0810	70	21	4		
Oct. 22	11	1420	45	<8	<4		
Oct. 27	16	0735	50	31	9		
Oct. 28‡	17					1	5 mg PR

CBZ = carbamazepine, HPLC = high-pressure liquid chromatography.
*The following levels would be considered "therapeutic" at the authors' institution: 65–150 µmol/L for phenobarbital, 17–34 µmol/L for CBZ and CBZ epoxide.
†Rectal CBZ therapy initiated.
‡Rectal CBZ therapy terminated.

therapy was initiated on day 13. Seventy milligrams (approximately 2.3 mL of the 30 mg/mL solution for injection) was administered rectally every 12 h. By day 17, the patient had improved to the point that he could begin tolerating oral medications, so all rectal administration of drugs was discontinued, oral administration of primidone and carbamazepine was restarted, and all IV fluids were discontinued. The patient's status continued to improve, and he was discharged on day 20.

DISCUSSION

Rectal use of carbamazepine has been described previously. Graves and others[5] compared the bioavailability of an oral tablet and a rectal suspension in volunteers and found that the total absorption, maximum serum concentration, and time to achieve maximum serum concentration were comparable. While the slow rate of rectal absorption would appear to preclude use of the suspension in status epilepticus, the authors concluded that the rectal route is an acceptable short-term alternative to the oral route for patients who require maintenance therapy.[5] Similar results were obtained by Neuvonen and Tokola.[9] Successful use of rectal carbamazepine in the clinical setting has been described by others.[6-8] However, to the authors' knowledge, this is the first report of successful use of the commercially available Tegretol suspension in the clinical setting. This information may prove useful in settings where facilities for timely extemporaneous compounding of suppositories or gels are lacking.

The presence of sorbitol in Tegretol suspension may be a cause for concern. Intestinal necrosis has been reported with rectal and, less frequently, oral administration of mixtures of sorbitol and sodium polystyrene sulfonate[13-16] in uremic patients. While the outcome of colonic necrosis is potentially serious, it is important to note that these cases involved coadministration of sorbitol with another compound; a literature search failed to reveal any reports of an association between intestinal necrosis and sorbitol given orally or rectally without sodium polystyrene sulfonate. Furthermore, the quantity of sorbitol administered to a patient receiving a 200-mg dose of Tegretol suspension (1.2 g*) would in most cases be much less than doses typically administered in conjunction with sodium polystyrene sulfonate. Nevertheless, the possibility of colonic necrosis should be borne in mind; the patient described in this report was switched to oral carbamazepine as soon as it was clinically feasible to do so.

*Lan Huong Nguyen, Medical Information Specialist, Novartis Pharmaceuticals Canada. Personal communication, July 28, 1999.

The reason for "subtherapeutic" levels of carbamazepine and carbamazepine epoxide on October 22 (day 11) is unknown. It is possible that several consecutive doses of carbamazepine were expelled by the patient before absorption began. Nevertheless, the patient suffered no increase in seizure frequency in the 4 days after this "subtherapeutic" concentration was observed, so its significance is questionable.

The reason for the patient's markedly elevated phenobarbital concentration on admission is also unknown; recommendation for close follow-up was given to his primary caregiver upon discharge.

References

1. Agurell S, Berlin A, Ferngren H, Hellstrom B. Plasma levels of diazepam after parenteral and rectal administration in children. *Epilepsia* 1975;16:277-83.
2. Vajda FJ, Mihaly GW, Miles JL, Donnan GA, Bladin PF. Rectal administration of sodium valproate in status epilepticus. *Neurology* 1978;28:897-9.
3. Kanazawa O, Sengoku A, Kawai I. Treatment of childhood epilepsy with rectal valproate: case reports and pharmacokinetic study. *Brain Dev* 1987;9:615-20.
4. Graves NM, Holmes GB, Kriel RL, Jones-Saete C, Ong B, Ehresman DJ. Relative bioavailability of rectally administered phenobarbital sodium parenteral solution. *DICP* 1989;23:565-8.
5. Graves NM, Kriel RL, Jones-Saete C, Cloyd JC. Relative bioavailability of rectally administered carbamazepine in humans. *Epilepsia* 1985;26:429-33.
6. Storey P, Trumble M. Rectal doxepin and carbamazepine therapy in patients with cancer. *N Engl J Med* 1992;327:1318-9.
7. Olson WL. Carbamazepine suppository. *Neurology* 1990;40:1472-3.
8. Brouard A, Fontan JE, Masselin S, Terrier JL. Rectal administration of carbamazepine gel. *Clin Pharm* 1990;9:13-4.
9. Neuvonen PJ, Tokola O. Bioavailability of rectally administered carbamazepine mixture. *Br J Clin Pharmacol* 1987;24:839-41.
10. Warren DE. Practical use of rectal medications in palliative care. *J Pain Symptom Manage* 1996;11:378-87.
11. Kerr D. Re: Practical use of rectal medications in palliative care [letter]. *J Pain Symptom Manage* 1997;13:250.
12. Graves NM, Kriel RL. Rectal administration of antiepileptic drugs in children. *Pediatr Neurol* 1987;6:321-6.
13. Wootton FT, Rhodes DF, Lee WM, Fitts CT. Colonic necrosis with Kayexelate-sorbitol enemas after renal transplantation. *Ann Intern Med* 1989;111:947-9.
14. Gardiner GW. Kayexelate (sodium polystyrene sulphonate) in sorbitol associated with intestinal necrosis in uremic patients. *Can J Gastoenterol* 1997;11:573-7.
15. Gerstman BB, Kirkman R, Platt R. Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. *Am J Kidney Dis* 1992;20;159-61.
16. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. *Am J Surg Pathol* 1997;21:60-9.

John R. Manderville, BscPharm, is a Staff Pharmacist in the Department of Pharmacy, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia.

James R.P. Godin, BscPharm, is a Staff Pharmacist in the Department of Pharmacy, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia.

Kathryn L. Slayter, PharmD, is with the the Department of Pharmacy and the Department of Medicine, Division of Infectious Diseases, Queen Elizabeth II Health Sciences Centre, and the College of Pharmacy, Dalhousie University, Halifax, Nova Scotia.

Address correspondence to:
John R. Manderville
Department of Pharmacy
Queen Elizabeth II Health Sciences Centre
1796 Summer Street
Halifax NS
B3H 3A7

e-mail: John.Manderville@cdha.nshealth.ca

Acknowledgements
No sources of financial support or competing interests declared.