Paediatric and Perinatal Drug Therapy, 2002; 5 (1)

Long-term Use Of Rectal Carbamazepine in a Patient with Intractable Epilepsy

M Mallewa
The Roald Dahl EEG Unit, Neurology Department, Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP, UK

R Appleton Corresponding Author
The Roald Dahl EEG Unit, Neurology Department, Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP, UK. Tel +44 (0) 151 252 5851; Fax +44 (0) 151 252 5152 Email: Richard.Appleton@RLCH-TR.NWEST.NHS.UK

A Aindow
Department of Pharmacy, Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP, UK

Abstract

A patient was initially treated with oral carbamazepine (CBZ) and oral phenobarbitone (PB) with incomplete seizure control. The patient subsequently developed persistent vomiting due to marked gastro-oesophageal reflux, which necessitated treatment with rectal CBZ and intravenous PB for the subsequent 10 weeks. There was no difference in seizure control or drug levels before and during treatment with rectal CBZ and intravenous PB. The patient developed perianal erythema and excoriation after nine weeks of treatment with this regime. Following fundoplication and insertion of a feeding gastrostomy tube, the patient was recommenced on oral CBZ and PB, with no significant effect on seizure control. As far as we are aware this is the longest period a patient has received rectal CBZ.

Paed Perinatal Drug Ther 2002; 5: 25–27

Key words: Carbamazepine – rectal formulation – suppositories – epilepsy – children – bioavailability

Introduction

Carbamazepine (CBZ) as a rectal solution or as a suppository may be administered rectally when oral administration is not possible[1]. The bioavailability of rectally administered CBZ is reported to be approximately 70% of the tablet (but not necessarily the liquid) preparation although absorption is considered to be more consistent than with the oral route[2,3]. It is therefore recommended that rectal dosing should be 25% higher than the oral dosing. However, these data have been based largely on healthy, adult volunteers and using only a few doses.

We report an 18 month old patient with PEHO Syndrome (Progressive encephalopathy, Edema, Hypsarrhythmia and Optic atrophy) in whom CBZ suppositories were given rectally for 10 weeks with no apparent deterioration in seizure control and without adverse side effects. As far as we are aware this is the longest period a patient has received rectal CBZ.

Case report

The patient was born at term following an uneventful pregnancy. No resuscitation was required and at two days of age the patient developed frequent focal and generalised tonic

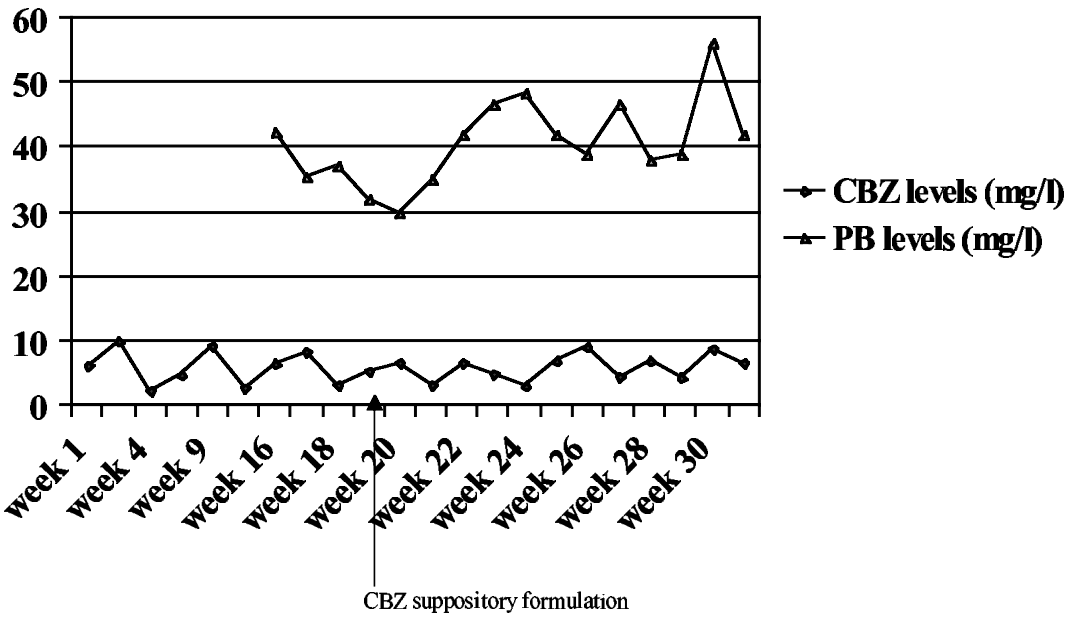

Figure 1. Carbamazepine and phenobarbitone levels (mg/l): February – September 2001

and clonic but no myoclonic seizures, which were refractory to the following anti-epileptic drugs used either singly or in combination: phenytoin, vigabatrin, clonazepam, pyridoxine (given orally for four weeks), biotin, folinic acid, predinisolone (given orally for two weeks) and lamotrigine. Sodium valproate was discontinued after five days because of a marked increase in seizure frequency and vomiting but without any evidence of hepatic dysfunction or an acute metabolic encephalopathy.

A combination of high dose phenobarbitone (PB) (20mg/kg/day) and high dose CBZ (45mg/kg/day) resulted in improved seizure control. Microcephaly developed from nine months and optic atrophy and hand and foot oedema developed from 14 months of age. Electroencephalography (EEG) showed hypsarrhythmia and multifocal spike activity at different stages during the first year of life. Numerous metabolic studies (including skin and muscle biopsies measuring mitochondrial respiratory chain enzyme activity) gave normal or negative results. Sequential brain magnetic resonance imaging (MRI) showed progressive cerebral and marked cerebellar atrophy but no evidence of cerebral dysgenesis or a metabolic disorder. The patient's clinical features and neuro-imaging findings were felt be consistent with PEHO Syndrome.

In February 2001, at seven months of age, the patient was commenced on oral CBZ liquid and a dose of 100 mg four times daily resulted in improved seizure control. Blood levels of CBZ varied between 3 and 6 mg/l (therapeutic range for our laboratory, 4–12 mg/l). The patient received PB simultaneously in a dose of 70 mg given twice daily, giving blood levels of 35–50 mg/l (therapeutic range for our laboratory, 20–40 mg/l).

In July 2001 the patient developed frequent and persistent vomiting due to marked gastro-oesophageal reflux. Other causes of vomiting were excluded including metabolic and infective causes and non-toxic levels of both CBZ (levels between 3 and 5 mg/l) and PB (levels between 30 and 42 mg/l). In view of the persistent vomiting, which was resistant to anti-reflux and anti-emetic medication, the patient received total parenteral nutrition, intravenous PB and rectal CBZ suppositories, the latter in a dose of 125 mg given four times daily. The patient's weight at the time that rectal CBZ was introduced was 8 kg. Rectal CBZ was given in this dose for a total of 10 weeks.

Blood levels of PB and CBZ before and during this period are shown in Figure 1. The patient's seizure control showed no change while receiving rectal CBZ and intravenous PB and no obvious local (perianal) or systemic adverse effects after the first eight weeks of using CBZ rectally. By the end of the ninth week the patient developed erythema and excoriation of her anus that was considered to represent a direct effect of the CBZ suppositories. In view of this and the fact that the patient's reflux had resolved following fundoplication and insertion of a feeding

gastrostomy tube, rectal CBZ was gradually replaced with oral CBZ liquid over a ten day period. The change to oral CBZ and oral PB was not associated with any change in the patient's seizure frequency or the development of any adverse side effects.

Discussion

Limited pharmacokinetic data have suggested that there is no major difference between the oral (tablet) and rectal (solution or suppository) formulations of CBZ, but the reduced rectal bioavailability necessitates a 25% higher dose of the rectal formulation[2,3]. The prolonged use of CBZ suppositories in our patient appears to be the longest reported use of this formulation in a patient with epilepsy and demonstrates that it seemed to be as effective as the oral liquid formulation in suppressing epileptic seizures and was also well tolerated.

This patient required considerably higher than usual doses of CBZ (50 mg/kg/day) with the oral formulation, and more than 62 mg/kg/day with the suppositories, reasons for which could have included auto-induction and the simultaneous use of high dose PB[4,5]. Further studies are required, ideally in less complex children with less refractory epilepsies, in order to obtain a clearer picture of the role of long-term rectal CBZ in children with epilepsy.

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