Replacing Carbamazepine Slow-Release Tablets With Carbamazepine Suppositories: A Pharmacokinetic and Clinical Study in Children With Epilepsy

Jan Arvidsson, MD; Heimo L. Nilsson, PhD; Per Sandstedt, MD, PhD; Gunilla Steinwall, MD; Bernt Tonnby, MD; Gerard Flesch, PhD

ABSTRACT

A suppository for rectal administration of carbamazepine has been developed for situations in which it is unsuitable to use the oral route of administration. In an open, controlled, within-patient study, the pharmacokinetics, clinical efficacy, and tolerability of carbamazepine slow-release tablets were compared with those of carbamazepine suppositories in children with epilepsy. The pharmacokinetic part of the study comprised 22 children, and an additional nine children were included in the clinical part of the study. Treatment with slow-release tablets was replaced for 7 days with carbamazepine suppositories in bioequivalent dosage. Clinical factors such as the rate of seizures and the local tolerability were studied, and an overall assessment of efficacy was made. In the pharmacokinetic part, 24-hour plasma concentration curves for carbamazepine and carbamazepine-10,11-epoxide were recorded. The plasma concentration profiles (minimum, maximum, and mean concentrations, fluctuation index, and area under the curve) for carbamazepine and the other metabolites did not show any significant differences between oral and rectal administration when the suppository dose was increased by 25% compared to the tablets. No increase in seizure frequency was detected, and the overall assessment was very good to good in 25 of the 29 epileptic children. Increased flatulence during treatment with suppositories was noted in two children, one had anal irritation, and one had nausea/vomiting. Treatment with carbamazepine slow-release tablets in children with epilepsy can be replaced by carbamazepine suppositories in 25% higher dosage, with good clinical effect and appropriate pharmacokinetic values, when it is unsuitable to use the common oral route of administration. (J Child Neurol 1995;10:114-117).

Carbamazepine is used in children and adults as an effective antiepileptic drug in the treatment of both partial and generalized tonic-clonic seizures.1 To overcome the problems of interdosage fluctuations of the diurnal concentration of carbamazepine with conventional tablets, a slow-release formulation has proven effective.2 In cases in which the patients are unable to take carbamazepine orally—for example, in connection with general anesthesia, unconsciousness, or vomiting—it would be a great advantage to use a preparation employing a parenteral mode. In children with frequent seizures, it may also be a good idea to start the drug treatment with a parenteral or rectal loading dose before oral medication is started.3 Administration of carbamazepine as suppositories has been studied by Johannessen et al.4 They showed in three children that treatment using this mode of administration for 4 days gave 30% to 50% lower plasma concentration levels than an oral mixture.

A new carbamazepine suppository has been developed. The bioavailability of the suppositories has been studied in healthy volunteers after a single dose and found to be about 25% lower than that of conventional carbamazepine tablets.5 A satisfactory dose proportionality was found in the dose range of 100 to 300 mg with the suppository.

Two sizes of the suppositories, 125 mg and 250 mg, to be equivalent to 100 mg and 200 mg tablets, were developed. The aim of the present study was (1) to evaluate the pharmacokinetic variables by comparing carbamazepine suppositories with slow-release carbamazepine tablets in children with epilepsy, and (2) to evaluate the clinical efficacy and the general tolerability of the suppositories.
MATERIAL AND METHODS

Twenty-nine children, 17 boys and 12 girls, between 4 and 16 years of age were included in this multicenter study, in which three different Swedish pediatric departments participated. All the children had the diagnosis of epilepsy, with either generalized tonic-clonic seizures or partial seizures, simple or complex, with or without secondary generalization. In the pharmacokinetic part of the study, 22 children participated, and seven additional patients were evaluated only clinically. No patients withdrew prematurely from the study (Table 1).

The children were selected from patients treated with slow-release carbamazepine tablet monotherapy for a long time in a maximum daily dose of 800 mg. All the children had good seizure control. The daily oral dose had been constant for at least 4 weeks preceding the trial, and all patients had steady-state levels of carbamazepine. No other drugs known to interact with carbamazepine were allowed during the last 4 weeks. No clinically significant abnormal laboratory findings, eg, in liver function and blood picture, were allowed.

Study Design

The study design was an open, within-patient trial. The children were not randomly selected. The trial was approved by the Ethical Review Board, and ethical considerations were satisfied by the parents indicating their willingness to let their children take part in the study. The number of seizures was counted and recorded in a calendar the last 7 days before switching to suppositories. Carbamazepine slow-release tablets (Tegretol Retard) were replaced by carbamazepine suppositories (Ciba-Geigy) for 7 days. The suppository dose was 25% higher, according to the guidelines from previous single-dose studies. The dose was divided in two to four parts (Table 2). After 7 days, the child returned to the previously given carbamazepine slow-release dose.

In the pharmacokinetic study, a 24-hour plasma concentration profile was made on day 0 (tablets) and day 7 (suppositories) at the following nominal times immediately before and at 2, 4, 6, 8, 10, 12, 16, 20, and 24 hours after the first daily dose. Blood samples were placed in lithium heparin tubes and centrifuged immediately. The plasma fraction was separated and transferred to plain tubes for storage at -20°C and subsequent analysis. Carbamazepine (G 32 883) and the two metabolites (10,11-epoxycarbamazepine [GP 49 023, pharmacologically active] and 10,11-dihydro-10,11-trans-dihydroxycarbamazepine [CGP 10 000, pharmacologically inactive]) were measured by high-performance liquid chromatography at the Pharmacological Chemistry Laboratories of Ciba-Geigy, Basel.

Clinical Assessment: Efficacy and Tolerability

Seizure frequency was recorded by means of seizure calendars and by clinical interviews with the patient and with at least one of the parents. The overall efficacy was assessed on a four-point scale: very good, good, moderate, and poor. Adverse events during the treatment with carbamazepine suppositories were recorded, and an overall assessment of the tolerability was made, using a similar four-point scale. Medical history was recorded and medical examinations were done before substitution of treatment and after the 7 days of treatment with suppositories.

Calculations and Statistics

A comparison of the diurnal plasma concentration profiles for the carbamazepine suppositories and the slow-release formulation was carried out, using the following variables: the peak concentration (Cmax), the lowest concentration (Cmin), the area under the curve over 24 hours (AUC), the average plasma concentration (Cmean), and the fluctuation index (FI). For calculation of the area under the curve, trapezoidal approximation was applied; furthermore,

\[ C_{\text{mean}} = \frac{AUC}{24 \text{ hr}} \quad \text{and} \quad FI = \frac{(C_{\text{max}} - C_{\text{min}})}{(AUC/T)} \]

where T = the time period. A Bayesian approach was then used for the statistical analysis.

RESULTS

Pharmacokinetics

The plasma concentrations of carbamazepine and the active metabolite 10,11-epoxy-carbamazepine are illustrated in Figures 1 and 2 and Table 3. On average, there was a tendency toward a slight decrease in the peak concentration, mean concentration, and area under the curve for carbamazepine when suppositories were given, com-
pared to slow-release tablets (Table 3). The 24-hour curve in two different individuals could vary, as shown by the examples in Figure 3. None of the pharmacokinetic variables of suppositories and tablets differed statistically significantly, and they were well within the 90% confidence interval (Table 4). The plasma concentrations of the pharmacologically inactive metabolite (CGP 10 000) were low.

Clinical Assessment: Efficacy and Tolerability
The study was not designed to evaluate the efficacy with regard to seizure change during treatments, and thus a statistical comparison between the treatments carbamazepine suppositories and the carbamazepine slow-release tablets cannot be made. However, recording of seizures during the two study periods showed the same rate of seizures during the two periods (Table 5).

The side effects reported during treatment with suppositories were: increased flatulence in two children, in one child from day 1 to day 7 and in one child from day 2 to day 6. One child had local anal irritation from day 1 to day 4. A causal relationship with the suppositories was judged possible. One child had 2 days of nausea, and one had a short episode of vomiting for half a day during the trial, but these events were probably not connected with the suppository treatment.

DISCUSSION
The main objective of this investigation was to perform a pharmacokinetic study of carbamazepine suppositories and compare them with slow-release carbamazepine tablets in children with epilepsy. Basically, carbamazepine has very poor solubility in water, and the development of a parenteral formulation has been difficult. It is, however, soluble in more polar organic solvents, like propylene glycol and ethanol. In addition to different kinds of tablets, a carbamazepine syrup, 20 mg/mL, is available in many countries (dissolved in propylene glycol at acidic pH). Johannessen et al have given one healthy volunteer the syrup rectally and found appropriate serum levels of the drug.

The suppositories in this trial were given with a 25% higher dose than that of the slow-release tablets. The dose recommendations were based on previous studies carried out in volunteers. This dose was well chosen, because there was only a small, nonsignificant decrease in the pharmacokinetic variables in our study. Also, the compliance of the children and the parents was very good, and there were no dropouts. Another type of carba-

![Figure 1. Individual carbamazepine concentrations in children with epilepsy treated with slow-release tablets and suppositories](image1)

![Figure 2. Area under the curve (AUC) from diurnal plasma concentration profiles in children with epilepsy treated with carbamazepine slow-release tablets and suppositories](image2)

![Figure 3. Two children with epilepsy having different diurnal plasma concentration profiles when treated with carbamazepine slow-release tablets (CBZ-SR) and suppositories (CBZ-supp)](image3)
mazepine suppositories, which Johannessen et al. used in three healthy subjects, gave a bioavailability of about 67% compared to the tablets. When they tried these suppositories on three children with epilepsy for 4 days, the serum concentration was reduced by 50% compared to conventional carbamazepine tablets.

In our study, the fluctuation index between slow-release carbamazepine tablets and carbamazepine suppositories shows a higher value for suppositories, but this was not statistically significant.

The clinical efficacy (seizure control) of carbamazepine slow-release tablets and suppositories was comparable in this study. The local tolerability was generally good. A few patients experienced increased flatulence, and one had anal irritation. The overall side effects were mild, if any.

As a conclusion, this trial shows that it is possible to use carbamazepine suppositories instead of carbamazepine slow-release tablets when it is necessary to replace the oral mode for a short period of time. The suppositories seem to have the same good clinical effect as carbamazepine given as slow-release tablets. The pharmacokinetic variables do not differ statistically from the slow-release form. The bioavailability of the carbamazepine suppository formulation is lower than that of slow-release tablets, and hence a 25% higher dose of carbamazepine must be given.

References