A Comparison of Two Brands of Carbamazepine in Young Patients With Epilepsy

Alicia Christopher, Marc Levine and Doreen McConnell

ABSTRACT

Anecdotal reports in the literature have led to concern regarding the safety of interchanging brands of carbamazepine in patients with epilepsy. To address this concern two different brands of regular compressed tablets of carbamazepine (Apotex and Ciba-Geigy) were studied in a group of ten institutionalized young patients with epilepsy. Patients were maintained on a constant regimen of the Apotex brand (Apo-carbamazepine^R) of carbamazepine and were then changed to the Ciba-Geigy brand (Tegretol^R) on the same dosage regimen. Steady-state serum carbamazepine concentrations and seizure frequencies were compared in the patients on the two brands of carbamazepine. The results of our study failed to show any differences between the two brands. When the potential effect of a brand change is a concern in patients on chronic therapy, studies such as this, done at steady-state, are relatively straightforward to accomplish and can adequately address the question of interchangeability of products for which serum drug assays are available.

Key Words: *anti-epileptic drugs, carbamazepine, epilepsy, interchangeability*

RÉSUMÉ

La publication de rapports anecdotiques force à s'interroger sur le risque éventuel que pose la substitution d'une marque de carbamazépine par une autre dans le traitement de l'épilepsie. On a étudié les effets de deux marques de comprimés ordinaires de carbamazépine (Apotex et Ciba-Geigy) chez un groupe de dix jeunes épileptiques hospitalisés. Les patients on d'abord reçu un régime constant d'Apo-carbamazépine^R (Apotex), puis du Tegretol^R (Ciba-Geigy) selon le même schéma posologique. Une comparaison de la concentration sérique de la carbamazépine à l'état d'équilibre et de la fréquence des crises d'épilepsie observées pour chaque traitement ne révèle aucune différence entre les deux marques. Pour évaluer les conséquences éventuelles d'un changement de formulation chez les malades qui reçoivent un traitement chronique, ce type d'étude, effectuée à l'état d'équilibre, s'avère relativement simple et suffit à résoudre la question de l'interchangeabilité des produits dont on peut effectuer le dosage sérique.

Mots clés: *antiépileptiques, carbamazépine, épilepsie, interchangeabilité*

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INTRODUCTION

With the large number of generic drugs available on the market, the question often arises whether or not these and brand name products can be safely interchanged without compromising therapy. Current regulations at the Health Protection Branch require bioequivalence studies to be carried out in a small number of subjects. These studies are often carried out in fasting, young, healthy adults using single doses of the drug.[1] Usually the C_{max} (maximum serum concentration) and the AUC (area under the serum concentration-time curve) of the generic brand are compared to those of the proprietor's brand, using protocols which involve multiple blood sampling after single doses.[1,2] The T_{max} (time taken to reach peak plasma concentration) values are not part of the standards for bioequivalence of drugs for oral use. Concern about differences in bioavailability of drugs such as antiepileptics is important because changes in formulation which affect steady-state serum drug concentrations may lead to exacerbation of seizures or adverse effects. A simplified approach to the investigation of clinical interchangeability of products which can be applied in hospital practice would be intuitively attractive.

Carbamazepine is an antiepileptic drug which is very effective for the treatment of partial and generalized tonic-clonic seizures and is now one of the most frequently used drugs in the pediatric population. The pharmacokinetics of carbamazepine in children and

adults have been well characterized.[3,4] Younger patients exhibit shorter half-lives, higher clearances and higher dosage requirements relative to body weight than older adults. The usual therapeutic range is 25-50 μmol/L. Carbamazepine is known to induce its own hepatic metabolism such that, after a few weeks of therapy, the steady-state serum concentration of carbamazepine may drop significantly and a dose increase may be required to maintain the desired concentration.[4]

The absolute bioavailability of carbamazepine from compressed tablets is not known since there is no intravenous form available for comparison. One comparative study showed that the bioavailability of carbamazepine from compressed tablets was about 80% relative to a propylene glycol solution of the drug.[5] Single dose studies have been performed in healthy volunteers to compare the bioequivalence of different brands of carbamazepine. Bhatia et al[6] found that in six healthy adult volunteers there was a significant difference in the AUC of two brands of carbamazepine available in India. Pynnonen et al[7] also found differences amongst carbamazepine preparations manufactured in Finland. These differences, for the most part, were in the rate rather than the extent of absorption.

Since carbamazepine is not completely absorbed due to poor water solubility, it is possible that different formulations may not be bioequivalent. Anecdotal reports in the literature have suggested that changes in carbamazepine brand can lead to exacerbation of seizures.[8-10] These case reports, though not well documented, do suggest clinically important differences in bioavailability. It would seem most appropriate to conduct comparisons of carbamazepine products by studying patients at steady-state, rather than relying solely on the results of single dose studies in healthy adult volunteers. We, therefore, undertook the present study to determine whether interchanging two popular brands of carbamazepine tablets, available on the Canadian market, would affect the steady-state serum concentration of carbamazepine in a group of institutionalized young patients with epilepsy. Seizure frequency was also documented during the study.

METHODS

Patients

This study was approved by the University of British Columbia Clinical Screening Committee for Research Studies Involving Human Subjects, and written informed consent was obtained from either the parents or the legal guardians of the young patients.

Ten handicapped young patients with a history of epilepsy being treated with carbamazepine were recruited to participate in this study over a 20 month period (Table I). All of these patients were residents at Sunny Hill Hospital for Children, a 75-bed long-term care and rehabilitation facility. All ten patients had been taking carbamazepine for at least six months and had been on the same daily dose and regimen of carbamazepine of the Apotex brand for at least two months prior to the study. All of the patients' medications were administered by registered nurses. Five of the patients required their carbamazepine tablets to be crushed. This had been done prior to the study and was continued during both phases of the study. No doses of carbamazepine were missed or vomited during the course of the study. Five of the patients were on other antiepileptic drugs (Table I) and most of them were taking other medications as well, but there were no changes to any of these during the study. There were no significant changes in prescribed diet in each individual patient from one study period to the next.

Protocol

Each patient was followed for an eight-week period consisting of two phases, during which the patient's dose and dosage interval remained constant:

Phase I: Patients were receiving Apo-carbamazepine[R] (regular compressed tablets, Apotex) for two weeks, at which time capillary blood was drawn by finger prick just prior to the morning dose to determine serum carbamazepine concentrations. This was repeated 14 days later at the same time of the day.

Phase II: After completing phase I, patients were switched to Tegretol[R] (regular compressed tablets, Ciba-Geigy) and maintained on the same dosage regimen. Fourteen days later, serum carbamazepine concentrations were determined prior to the morning dose at the same time as in phase I. This was repeated after another 14 days of therapy with Tegretol[R].

Capillary blood was collected into unheparinized Microtainer Tubes[R] made by Becton Dickinson. Serum carbamazepine concentrations were determined by the EMIT[R] method using the Dupont[R] aca IV analyzer on the morning that serum samples were drawn. The day-to-day coefficient of variation of the assay was 2.8-4% over a concentration range of 19-60 μmol/L.

Seizure frequency in these patients was monitored during each four-week period by the nursing and educational staff. The date, time of day, duration and description of each observed seizure were recorded in the patient's chart. The four-week pre-study seizure frequency was obtained retrospectively from the chart.

Table I: Demographics of Patients Enrolled in the Study

Patient	Diagnosis and Seizure Type	Sex	Age (yrs)	Other Anti-epileptic Drugs	Carbamazepine Dosage Regimen	Carbamazepine Dose mg/kg/day
1	Cerebral Palsy Grand Mal Seizures	M	19	none	300 mg at 0630 hours and 1800 hours	24
2	Cerebral Palsy Grand Mal Seizures	F	19	phenobarbital	400 mg at 0730 hours and 300 mg at 1930 hours	21
3	Cerebral Palsy Grand Mal Seizures	F	18	divalproex	200 mg at 0800 hours, 1330 hours and 1930 hours	20
4	Tuberous Sclerosis Grand Mal Seizures	M	19	valproic acid clonazepam	300 mg at 0630 hours, 1330 hours and 2200 hours	23
5	Head Injury Grand Mal Seizures	F	16	none	300 mg at 0600 hours, 200 mg at 1200 hours and 300 mg at 2000 hours	17
6	Cerebral Palsy Grand Mal Seizures	M	21	clonazepam	300 mg at 0800 hours and 2000 hours	20
7	Head Injury Grand Mal Seizures	M	13	none	300 mg at 0800 hours and 200 mg at 1400 hours	24
8	Cerebral Palsy Grand Mal Seizures	F	19	none	200 mg at 0800 hours and 300 mg at 2000 hours	12
9	Post-Reye's Syndrome disease Petit Mal Seizures	F	9	nitrazepam	250 mg at 0600 hours, 1400 hours and 2200 hours	36
10	Cerebral Palsy Myoclonic Seizures	M	13	none	300 mg at 0800 hours, 200 mg at 1200 hours and 300 mg at 1700 hours	35

All of the patients in this study were wheelchair-dependent and mentally retarded with minimal communication skills. We, therefore, did not include an assessment of side effects by the patients in the study since they could not reliably communicate such information.

Statistical Analysis

The primary end point of the study was the steady-state serum carbamazepine concentration. Patient sample size was estimated on the basis of a power analysis that ten patients would give more than 80% probability (power ≥ 0.8) and 20 patients would give more than 90% probability (power ≥ 0.9) of detecting a difference in steady-state serum concentration of 15-20% or more. Therefore, our target recruitment was between 10 and 20 patients. Serum carbamazepine concentrations were compared using one-way ANOVA with repeated measures. Seizure frequency was a secondary end point and comparisons were made using the Wilcoxon matched-pair ranked-sum test. Statistical significance was set at $p < 0.05$.

RESULTS

All patients completed the protocol without interruption, with the exception of patient #10, whose dose required modification from 700 to 800 mg/day due to exacerbation of seizures. This prompted a temporary withdrawal of the patient from the study. After a sufficient period had elapsed to permit re-establishment of steady-state and evaluation of his seizure control, the protocol was re-initiated and was completed in the standard fashion eight weeks later.

The patients' serum carbamazepine concentrations measured during both phases of the study are shown in Table II. There was no change in mean serum carbamazepine concentration at any time, indicating that the patients were at steady-state at the outset and that the change in formulation had no effect on carbamazepine concentration.

The patients' seizure frequencies recorded prior to and during the study period are shown in Table III. Although the mean number of seizures was similar during the two phases of the study, the data were not normally distributed. There was no difference in seizure frequency during the two phases of the study. The seizures recorded prior to the study were included for comparison. However, since they were obtained retrospectively, they were not included in the statistical analysis.

DISCUSSION

The results of our study indicate that a change in brand of carbamazepine had no effect on the steady-state serum concentration. There was also no apparent difference in seizure frequency during either phase of the study. For practical purposes, it is concluded that the two formulations under study are clinically interchangeable. No conclusions can be drawn regard-

ing their bioequivalence, since this was outside the scope of the present study. It is possible, for example, that the extent of absorption was higher in phase II of the study but this effect was masked by a corresponding increase in drug clearance through enhancement of hepatic enzyme induction. Our objectives did not include a detailed analysis of the serum concentration-time profiles or examination of pharmacokinetic changes.

Some intra-patient variability was observed between the 14 and 28 day samples taken in each of the two phases of the study. This is to be expected with carbamazepine, in part because the drug has low water solubility and is erratically, and possibly incompletely absorbed.[4,11] In addition, many children have a relatively low elimination half-life for carbamazepine.[4,11,12] Thus, the nature and timing of the previous evening meal may have a noticeable effect on the measured serum carbamazepine concentration the next morning. However, the variability in the group mean carbamazepine level, as measured by the coefficient of variation, was similar in the two phases of the study (Table II).

A fundamental assumption of our study design was that patients were at steady-state when the blood samples were collected. In children on long-term therapy carbamazepine half-lives are reported to be in the range of 2.5-15 hours.[11] Under the conditions of our two phase protocol, the time to steady-state with both formulations was projected as three to five days maximum. Changes in effective dose may lead to alterations in the degree of induction of hepatic cytochrome P-450, but this process is essentially complete within two weeks.[13]

There are a number of reported cases in the literature of patients stabilized on one brand of carbamazepine who began to have seizures when the brand of the drug was changed.[8-10] Sachdeo et al[9] reported that five adult epileptic patients, who were seizure-free on the Ciba-Geigy brand of Tegretol^{R}, had recurrent seizures when switched to a generic brand of carbamazepine. Their seizures stopped when the patients were switched back to Tegretol^{R}. The authors did not include in their report any data on serum concentrations of carbamazepine or other variables such as changes in dosing interval or changes in other medications which may affect serum carbamazepine concentrations or patient compliance. Therefore, it is difficult to draw conclusions from these case reports. Koch et al[10] reported the case of an epileptic woman who had been stabilized on Tegretol^{R} and was seizure free. She began to have seizures and experienced an apparent reduction in serum carbamazepine concentration when she was switched to a generic brand of the drug. She was initially receiving carbamazepine (Tegretol^{R}) 400 mg/24 hr (interval not indicated) for an indefinite period of time. The serum carbamazepine concentration was reported to be 41 μmol/L and one month later on the same brand the

Table II: Serum Carbamazepine Concentrations* During the Two Phases of the Study

Patient	Phase I — Apotex Brand		Phase II — Ciba-Geigy Brand	
	Day 14 (μmol/L)	Day 28 (μmol/L)	Day 14 (μmol/L)	Day 28 (μmol/L)
1	24.0	24.1	33.1	39.0
2	31.0	34.3	34.1	25.1
3	47.1	36.5	42.6	53.3
4	46.1	41.8	38.2	40.8
5	31.6	32.4	31.4	35.6
6	43.1	33.2	46.3	44.0
7	31.6	32.0	32.2	30.4
8	30.9	28.4	22.0	32.1
9	37.6	36.6	33.0	25.9
10	27.0	22.4	30.0	36.0
Means ± SD	35.0 ± 8.0	32.2 ± 5.9	34.3 ± 6.8	36.2 ± 8.6
C.V.**(%)	22.9	18.3	19.8	23.8

* No significant change ($p>0.05$) in mean serum carbamazepine concentration occurred.
** Coefficient of variation.

Table III: Recorded Seizures During Four Weeks Before and During Phase I and Phase II of the Study

Patient	Number of Seizures Recorded		
	Apotex Brand	Ciba-Geigy Brand	Pre-Study (retrospective
1	0	0	0
2	4	8	0
3	5	3	3
4	26	17	29
5	0	0	0
6	0	0	0
7	0	1	3
8	0	1	0
9	12	14	6
10	0	0	0
Mean ± SD	4.7 ± 8.4*	4.4 ± 6.4*	4.1 ± 9

* There was no significant difference in the occurrence of seizures between the two phases of the study.

serum carbamazepine concentration was reported to be 30.9 μmol/L. Shortly thereafter, the generic brand was dispensed and the patient began to have seizures. The serum carbamazepine concentration on the generic brand was reported to be unmeasurable. When the patient was restarted on Tegretol[R] the daily dose was increased by 50 percent to 600 mg/24 hr (interval not indicated) with a serum concentration of 47 μmol/L after 72 hours. All serum concentrations were reported to be from morning predose samples. This case is one of the most detailed in the literature, but is still difficult to interpret. There was variation in serum carbamazepine concentration when the patient was initially on Tegretol[R], suggesting that she was not at steady-state or that there was some degree of noncompliance. The fact that carbamazepine was unmeasurable in her serum around the time of her recurrence of seizures also indicates that compliance may have been a problem. In cases such as this, without proper documentation of the duration of therapy, the dosage interval, concurrent medications, and compliance, no conclusions can be drawn about the effect of a change in the brand of medication. In addition, other changes in the patient's medication regimen may result in induction or inhibition of carbamazepine metabolism which would also alter serum concentration.

In order to properly compare two brands of carbamazepine, rigorous testing at true steady-state serum concentrations at the same time of day, and the same dose and dosage interval should be carried out. Standardization of timing of carbamazepine doses is particularly important since some patients, especially younger ones, have relatively short elimination half-lives and different rates of absorption of carbamazepine.[3-5] Changes in dose and/or interval in patients with short half-lives can account for differences in serum carbamazepine concentrations and may result in breakthrough seizures in unstable patients.

After the present investigation was begun, two other groups reported that a change in carbamazepine brand did not change serum carbamazepine concentration or seizure frequency.[14-15] As a result of our study, clinicians at Sunny Hill Hospital for Children consider the two brands of carbamazepine used in this study to be clinically interchangeable in young patients with epilepsy. However, the approach taken in this study addresses a larger question, namely, how should pharmacists and physicians deal with isolated reports of problems which are ascribed to changes in brands of medication in individual patients? This is particularly important for patients taking drugs such as carbamazepine where changes in steady-state serum concentrations can lead to exacerbation of symptoms (seizures in this case) or clinically important toxicity. In situations like this, studies should be carried out at steady-state in order to objectively address the question of interchangeability and the rationale for product substitution in clinical practice. Studies such as this are relatively straightforward, inexpensive to perform and would inject a tone of rationality into an often emotional debate of the bioequivalence and interchangeability of drug products.

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