The Pharmacology of Chewable Versus Regular Carbamazepine in Chronically Treated Children With Epilepsy

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ABSTRACT: We report the first comparison of Chewable and Regular Carbamazepine (CBZ) tablets in children with epilepsy. Forty-four children receiving chronic monotherapy CBZ participated. In month 1 children received regular CBZ; in month 2, the same dose of Chewable CBZ. Once per week fasting predose CBZ and CBZ epoxide serum levels were determined. In a subset of 15 children, at the end of each month serum levels were obtained every 2 hours for 12 hours beginning pre-dose. Standards for CBZ and CBZ epoxide were tested in each centre. Overall, weekly levels showed no consistent differences between the month on chewable CBZ and regular CBZ. Seizure control and rates of reported side effects were similar. In five patients chewable CBZ produced higher peak CBZ levels while five had higher peaks with regular CBZ. In conclusion, regular and chewable CBZ often have unpredictable differences in peak but not trough levels of CBZ suggesting that peak level side effects with one form of CBZ might be alleviated by changing to the other.

RESUME: Pharmacologie de la carbamazépine à mâcher versus régulière chez les enfants traités de façon chronique pour épilepsie. Nous rapportons la première comparaison de la carbamazépine (CBZ) en tablettes à mâcher et régulière chez les enfants épileptiques. Quarante-quatre enfants recevant de la CBZ en monothérapie chronique ont participé à l'étude. Pendant le premier mois, les enfants ont reçu la CBZ régulière; pendant le deuxième mois, la même dose de CBZ à mâcher. On a procédé à des déterminations hebdomadaires des taux sériques de CBZ et d'époxyde de CBZ à jeun, avant la prise de CBZ. À la fin de chaque mois, des taux sériques ont été obtenus aux 2 heures pendant 12 heures, commençant avant la première dose, dans un sous-groupe de 15 enfants. Des standards de CBZ et d'époxyde de CBZ ont été mesurés dans chaque centre. Dans l'ensemble, les taux hebdomadaires n'ont pas montré de différence constante entre le mois où les enfants recevaient de la CBZ à mâcher et de la CBZ régulière. Le contrôle des crises et les taux d'effets secondaires rapportés ont été similaires. Chez cinq patients, la CBZ à mâcher a produit des pics plus élevés de CBZ, alors que cinq ont eu des pics plus élevés avec la CBZ régulière. Donc, la CBZ régulière et à mâcher ont souvent des différences imprévisibles dans le pic mais non dans les niveaux courants de CBZ suggérant que les effets secondaires lors du pic avec une présentation de CBZ pourraient être atténués en changement à l'autre présentation.


Carbamazepine (CBZ) is one of the most frequently used antiepileptic medications in children. It exists in several formulations including a regular tablet, a chewable tablet, a suspension (in the U.S.A.), and a controlled release form (in Canada and other countries). There have been no studies comparing the pharmacology of the regular tablet with the chewable tablet in chronically treated children. In this study we report a multicentre study that compares the chewable and regular form of the drug.

METHODS

The study was carried out in 5 centres across Canada. The study was approved by the institutional review board in each centre and informed consent was obtained. Children aged less than 16 years were eligible, if they had epilepsy and had been treated for at least 6 months with CBZ as monotherapy. Patients were excluded who received other medications on a regular basis or had any progressive systemic or neurologic diseases.
The study was divided into 2, one month, study periods. In the first month the children received regular CBZ (Tegretol TM). They received their usual daily dose for 4 consecutive weeks with fasting CBZ and CBZ 10-11 epoxide serum levels obtained weekly. At the end of the first 4 weeks in two centres only, study patients spent 12 hours at the hospital between 8 AM and 8 PM. Blood was obtained for CBZ and CBZ 10-11 epoxide levels every 2 hours with the first sample before the morning dose of CBZ.

In the second month all study patients were switched to the identical dose of chewable CBZ (Tegretol Chewtabs TM) with the same daily dosing schedule. Again AM fasting serum levels were obtained weekly for 4 further weeks. At the end of the second month the same children who had 12 hour curves obtained on regular CBZ underwent the same 12 hour serum sampling following chewable CBZ.

CBZ and CBZ 10-11 epoxide levels were determined using high pressure liquid chromatography.\(^2,3\) For the two centres performing 12 hour curves standard CBZ concentration samples were analyzed in the two laboratories for comparison of consistency of technique. The results were essentially identical (less than 5% variation).

In one of the centres performing the 12 hour curves, samples from 2 patients were split and the carbamazepine 10-11 epoxide levels were measured in each of the two laboratories for evidence of consistency. Again there were no significant measurement differences between centers.

Compliance was assessed by weekly pill counts.

**RESULTS**

Forty-four patients, 23 boys and 21 girls entered the study. Thirty patients dropped out (1 on regular CBZ and 2 on chewable CBZ) for reasons unrelated to medication side effects. The average age of patients was 11 ± 3 (STD) years. The average daily dose was 565 ± 188 mg (range 200-1100 mg/day).

The total number of seizures reported by patients during the first and second months was essentially the same (Table 1, p=NS, paired t-test).

Side effects were noted with similar frequency with the chewable and regular CBZ. Tiredness and drowsiness were reported in 4 patients all on regular CBZ, while 4/5 patients with reported behaviour disturbance received chewable CBZ.

Mean weekly fasting CBZ and CBZ 10-11 epoxide serum levels were virtually identical between the two study months. There were no significant trends noted across the visits (Table 2). Weekly pill counts showed excellent compliance with only 3 patients showing a single week with < 80% of prescribed pills taken.

Twelve hour curves were carried out in 15 children all of whom received CBZ monotherapy. Their average daily dose was 13.5 mg/kg/day (range 4.4 - 20.6 mg/kg/day). Ten children received twice daily dosing and five children, three times daily dosing.

When the data were combined for all patients the 12 hour curves were very similar for regular versus chewable CBZ (P=NS for paired t-tests for each sampling time).

For each case with 12 hour curves, the following were compared for the two 12 hour curves – Cmin, Tmax, Cmax, area under the curve (times 0 - 12 hours), and peak/trough ratio (Table 3). The mean values of each of these measurements did not appear to show significant differences between regular and chewable CBZ (paired t-tests). Nonetheless, despite the lack of difference in overall mean values, for some individual patients the differences were quite marked.

Among the 10 patients with twice daily dosing, there were 5 with clinically important higher peak CBZ levels with chewable than with regular CBZ by an average of 26%. The curve for one such patient is illustrated (Figure 1).

Two children on twice daily dosing had higher peak CBZ serum levels with regular than with chewable CBZ, by an average of 17%.

Among the 5 patients on 3 times a day dosing regimens, 3 showed higher peaks with regular CBZ, averaging 26% higher. The curve for one such patient is illustrated (Figure 2).

**Table 1: Total Number of Seizures on Regular vs Chewable Carbamazepine**

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Total Seizures Regular Carbamazepine</th>
<th>Total Seizures Chewable Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex Partial</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Simple Partial</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Generalized</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Absence **</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Uncategorized</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 2: Mean Fasting Serum Levels for all Patients (obtained weekly) in micromoles/litre**

<table>
<thead>
<tr>
<th>CBZ Serum Level</th>
<th>CBZ 10-11 Epoxide Serum Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular CBZ</td>
<td>27.5 ± 14.9 STD</td>
</tr>
<tr>
<td>Chewable CBZ</td>
<td>26.3 ± 8.0 STD</td>
</tr>
</tbody>
</table>

\(**\) patients with absence had more than one seizure type and received an anti-absence medication plus carbamazepine

**Table 3: Mean Serum Levels for 12 Hour Curves in Micromoles/L (STD)**

| Cmin | Tmax | Cmax | Peak/Trough Ratio | Auc |
|------|------|======|-------------------|-----|
| Reg CBZ 27 (6.7) | 6 (2.3) | 37 (8.3) | 1.39 (0.2) | 376 (88) |
| Chew CBZ 24.3 (5.2) | 5.6 (2.3) | 36 (70) | 1.5 (0.32) | 367 (125) |
| Reg Epox 4.8 (1.3) | 6.4 (4) | 6 (1.4) | 1.3 (0.15) |
| Chew Epox 4.1 (1.5) | 5.6 (2.6) | 5.6 (2.1) | 1.4 (0.15) |

Reg CBZ = serum CBZ level when patients received regular CBZ
Chew CBZ = serum CBZ level when patients received chewable CBZ
Reg Epox = serum CBZ 10-11 epoxide level when patients received regular CBZ
Chew Epox = serum CBZ 10-11 epoxide level when patients received chewable CBZ

Cmin = minimum serum level (predose trough level)
Cmax = maximum serum level (peak level)
Auc = area under the 12 hour serum level curve (time 0-12 hours)
CHEWABLE VS REGULAR CBZ
2 DAILY DOSES

serum level mm/l

chewable CBZ level
chewable CBZ epoxide
regular CBZ level
regular CBZ epoxide

* cbz 200 mg

Figure 1 — 12 hour curves for one patient on twice daily dosing.

CHEWABLE VS REGULAR CBZ
3 DAILY DOSES

serum level mm/l

chewable CBZ level
chewable CBZ epoxide
regular CBZ level
regular CBZ epoxide

* cbz 200 mg
** cbz 300 mg

Figure 2 — 12 hour curves for one patient on three times/day dosing.
CONCLUSION

This study suggests that, on average, the pharmacokinetics of chewable and regular CBZ are very similar in chronically treated children with epilepsy. Similarities include bioavailability (judged by mean values of area under the curve during 12 hours serum level profiles) and half life (judged by mean values for AM fasting levels). The efficacy of these two formulations of CBZ in this group of children with epilepsy appeared to be essentially equal.

The mean values do, however, obscure the findings for individual patients. Five of our patients on twice daily dosing had higher peak serum levels on chewable CBZ – a difference that may be clinically important. On the other hand, three children on three times a day dosing had a similar difference with the higher peaks with regular CBZ. It is unclear whether such variations are related to fundamental differences in the way the two preparations are absorbed and/or metabolized by these individual patients. It is possible that patients on the same formulation of CBZ everyday have great variation of peak levels depending on diet or other factors. We are unaware of other studies with CBZ that have repeated 12 hour curves in the same patient. Diet, however, may change the absorption pattern of other anticonvulsant drugs. For example tube feeding may inhibit the absorption of phenytoin.

Only one other published study has examined the difference between regular and chewable CBZ. Maas et al. studied 10 adult volunteers for 48 hours after a single dose of 200 mg of CBZ. On one occasion they took regular CBZ and on another occasion chewable CBZ. These volunteers were naive to CBZ and would not be expected to have any of the P450 enzyme induction noted in chronic use. Maas noted greater bioavailability and higher peak levels with the chewable CBZ – results that resemble five of our cases noted above.

Careful psychological studies have found that peak levels of CBZ may be associated with diminished cognitive performance.

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REFERENCES


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