Factors Influencing the Serum Levels of Carbamazepine and Carbamazepine-10, 11-Epoxide

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Abstract-Carbamazepine-10,11-epoxide (CBZ-Epox), a metabolite of carbamazepine (CBZ), is known to have toxic effects as well as some antiepileptic property similar to CBZ.

The serum levels of CBZ and CBZ-Epox at the steady state were measured by HPLC assay for 141 children and young adults (1-29 years) who were on CBZ monotherapy or in combination with other antiepileptic drugs. Eighty patients were on CBZ monotherapy. In addition to CBZ, 20 patients were on ethosuximide, eight on valproate, eight on phenytoin, five on phenobarbital or primidone and 20 on more than one additional antiepileptic drug.

In patients on CBZ monotherapy, the mean CBZ level was 8.2 µg/ml ± 2.2 (± SE), the CBZ-Epox level was 1.6 µg/ml ± 0.6 and the CBZ-Epox/CBZ ratio was 0.19±0.5. On univariate analysis, factors that significantly* influenced the CBZ-Epox/CBZ ratio were the age of the patient, the time interval between the last dose and blood sampling, and the dose/surface area. Multivariate analysis demonstrated that the only factors that significantly* influenced the CBZ-Epox/CBZ ratio were the time interval between the last dose and blood sampling and the age of the patients.

Patients on polytherapy had significantly* higher CBZ-Epox/CBZ ratios than patients on monotherapy. The ratios were as follows: CBZ and ethosuximide, 0.23 ± 0.05; CBZ and valproate, 0.33 ± 0.15; CBZ and phenytoin, 0.35 ± 0.11; CBZ and phenobarbital or primidone, 0.29 ± 0.05; CBZ and more than one additional anticonvulsant, 0.44 ± 0.17.

CBZ and CBZ-Epox levels are invariably affected by the age of the patients, the CBZ dose and co-medication with other antiepileptic drugs. Careful monitoring is mandatory in the latter group to avoid toxicity. *p < 0.01, unpaired t-test

Key Words: Carbamazepine, Carbamazepine-10, 11-epoxide, Antiepileptic drugs, Therapeutic drug monitoring.

INTRODUCTION

Carbamazepine (CBZ) has been widely used as an anticonvulsant of first choice since the late 1970's especially for the complex partial seizure (Cereghino et al., 1974; Schain et al., 1977; Sillanpaa et al., 1979; Huf and Schain 1980; Gram et al., 1982; Callaghan et al., 1985, Mattson et al., 1985).

The predominant metabolic pathway of CBZ involves the enzymatic conversion of CBZ to carbamazepine-10, 11-epoxide (CBZ Epox). This reaction is catalyzed by hepatic mono-oxygenase, whereas hepatic epoxide hydrase catalyzes the formation of 10,11-dihydroxy CBZ (CBZ-Epox).
CBZ is unique among the anticonvulsants because of this metabolite CBZ-Epox. CBZ-Epox is an active metabolite and contributes to antiepileptic activity as well as the adverse side effect of CBZ (Gilham et al. 1988).

Several studies regarding the CBZ and CBZ-Epox serum levels in epileptic children have addressed factors that modified the levels of CBZ, CBZ-Epox and the ratio of CBZ-Epox/CBZ. These studies, however, have utilized small numbers of patients, and the results have often been conflicting (Eichelbaum et al., 1976; McKague et al., 1981; Schoeman et al., 1984a, b; Furlanet, 1985; Bertilsson and Tomson, 1986).

The authors present the results of the measurement of the serum level of CBZ and CBZ-Epox in epileptic children and attempt to define the factors influencing the level of these substances.

**MATERIALS AND METHODS**

The inclusion criteria of the study population were all the patients treated as outpatients of the Pediatric Neurology Clinic of University of Minnesota Hospital over a period of 12 months, who were on CBZ with or without other antiepileptic drugs, and who had their CBZ and CBZ-Epox serum levels measured. These serum levels were in a steady state since the patients had taking CBZ for more than six weeks, and there had been no change in dosage in the week prior to the measurement of the levels.

The exclusion criteria were those for whom the times of the last dose and/or blood sampling were not available; those whose CBZ-Epox levels in the serum were not measurable; and if other antiepileptic drug serum levels were so low that non-compliance was suspected.

The final study population was 141 patients. The patients were subdivided according to antiepileptic medications. Eighty patients were treated with CBZ alone, 20 patients with a combination of CBZ and ethosuximide, eight patients with CBZ and valproate, eight patients CBZ and phenytoin and five patients with CBZ and phenobarbital/primidone. The other 20 patients were taking more than two antiepileptic drugs in addition to CBZ (Table 1).

Of those 80 patients who were treated with CBZ alone, 44 were males and 36 females. The mean age was 11±5.7 years and they ranged from 1 to 24 years.

**Table 1. Final population according to treatment**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>80</td>
</tr>
<tr>
<td>CBZ* &amp; ethosuximide</td>
<td>20</td>
</tr>
<tr>
<td>CBZ &amp; phenytoin</td>
<td>8</td>
</tr>
<tr>
<td>CBZ &amp; valproate</td>
<td>8</td>
</tr>
<tr>
<td>CBZ &amp; phenobarbital/primidone</td>
<td>5</td>
</tr>
<tr>
<td>Polytherapy**</td>
<td>20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>141</strong></td>
</tr>
</tbody>
</table>

*CBZ: carbamazepine
**more than one additional anticonvulsants besides CBZ

The type of epilepsy was classified according to the International Classification proposed by the International League Against Epilepsy (1981). Complex partial seizures were the most frequent seizure type treated with CBZ.

The mean daily dose of CBZ for patients on CBZ alone was 18.0 ± 5.5 mg/kg. The dose for body surface area was 537 ± 139 mg/m2.

Blood samples were drawn 5.7 ± 2.3 hours after each dose of CBZ.

The serum levels of CBZ and CBZ-Epox were measured by the HPLC assay as described by Meijer (1981).

For those 80 patients who were on CBZ monotherapy, several factors were analyzed that could possibly have affected the CBZ and CBZ-Epox serum levels and thus the CBZ-Epox/CBZ ratio.

**RESULTS**

**CBZ Monotherapy**

The seizure type of patients on monotherapy with CBZ, that is, 80 patients, are presented in Table 2. Complex partial seizures are the most frequent seizure type, followed by generalized tonic-clonic seizure and simple partial seizures. Seventeen of the patients had more than one seizure type, so that the total numbers are greater than 80.

The mean serum level of CBZ was 8.2 ± 2.2 ug/1 and that of CBZ-Epox 1.6 ± 0.6 ug/ml. the mean ratio of the CBZ-Epox/CBZ was 20% (Table 3).

The results of the multivariate analysis are shown in Table 4. The factors that significantly influenced the CBZ-Epox/CBZ ratio were the age of the patients and the time interval between the last dose and blood sampling.
Table 2. Seizure types of patients on monotherapy

<table>
<thead>
<tr>
<th>Seizure Type*</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial simple</td>
<td>6</td>
</tr>
<tr>
<td>Partial complex</td>
<td>50</td>
</tr>
<tr>
<td>Generalized tonic clonic</td>
<td>32</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>1</td>
</tr>
<tr>
<td>Absence</td>
<td>3</td>
</tr>
<tr>
<td>Tonic</td>
<td>3</td>
</tr>
<tr>
<td>Unclear</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>98</strong></td>
</tr>
</tbody>
</table>

*17 patients had more than one type of seizure.

The regression analysis of the serum levels of CBZ and the age of the patients are shown on Fig. 1. The younger the patients, the lower the levels of CBZ. The serum levels of CBZ-Epox, however, did not show a significant correlation with age. As we might expect, the serum level of CBZ-Epox was related to the dose of CBZ ($p = 0.001$) (Fig. 2). Also, the serum levels of CBZ-Epox showed a significant correlation with the serum levels of CBZ ($p = 0.0001$) (Fig. 3).

**CBZ and Other Antiepileptic Drugs (Polytherapy)**

The polytherapy group of patients who were treated with other antiepileptic drugs was compared with the monotherapy group (Table 5).

Table 3. Levels of CBZ and CBZ-Epox and the ratio of CBZ-Epox/CBZ

<table>
<thead>
<tr>
<th></th>
<th>CBZ (μg/ml)</th>
<th>CBZ-Epox (μg/ml)</th>
<th>CBZ-Epox/CBZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>8.2 ± 2.2</td>
<td>1.6 ± 0.6</td>
<td>0.19 ± 0.5</td>
</tr>
<tr>
<td>Range</td>
<td>2.4 – 14.8</td>
<td>0.5 – 4.3</td>
<td>0.07 – 0.37</td>
</tr>
</tbody>
</table>

*CBZ-Epox: Carbamazepine-10, 11-epoxide

Fig. 1. Correlation between age of the patients and serum levels of carbamazepine

The serum levels of CBZ did not reveal significant differences between each group. The serum levels of CBZ-Epox, however, were elevated significantly in the patients who were taking valproate or two additional antiepileptic drugs.

The ratio of CBZ-Epox/CBZ was significantly higher in the patients taking phenytoin, valproate, phenobarbital, or ethosuximide in order of decreasing significance.

Fig. 2. Correlation between dose of carbamazepine and serum levels of carbamazepine-10, 11-epoxide

Eight patients had levels of CBZ-Epox greater than 4.0 μg/ml. Seven of them were taking more than one antiepileptic drug, most frequently valproate (Table 6).

**DISCUSSION**

CBZ has become one of the most widely used anticonvulsants in the world.

The drug was synthesized by Schindler in 1953 as part of a program investigating ana-
logues of chlorpromazine. Its anticonvulsant properties remained undetected for some years, and the first clinical study in epilepsy was not done until 1963.

CBZ has a proven efficacy in the prophylaxis of generalized tonic clonic and partial seizures (Gram et al., 1982; Callaghan et al., 1985; Mattson et al., 1985) but is not an appropriate treatment for absence or myoclonic epilepsy. It remains the drug of choice for trigeminal neuralgia, and there is much interest in its psychotropic properties (Crawford and Silverston, 1987).

The pharmacokinetics of CBZ are great relevance to its clinical use. Oral absorption is slow, with concentrations peaking around four hours after a dose; overall bioavailability, however, approaches 90% (Beritilson and Tomson 1988).

CBZ is eliminated by liver mono-oxygenase in the form of CBZ-Epox, a metabolite that not

**Table 4. Multivariate analysis of serum levels of CBZ, CBZ-Epox and ratio of CBZ-Epox/CBZ for 80 pts. on monotherapy**

<table>
<thead>
<tr>
<th>Dependent Variables</th>
<th>CBZ</th>
<th>CBZ-Epox</th>
<th>CBZ-Epox/CBZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>P &lt; 0.05</td>
<td>NS</td>
<td>P &lt; 0.0005</td>
</tr>
<tr>
<td>Interval</td>
<td>NS</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Dose/m²</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.0001</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS: not significant

**Table 5. Comparison between monotherapy group of patients and polytherapy group**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Mean ± S.D.</th>
<th>Age (years)</th>
<th>Dose (mg/m²)</th>
<th>Interval (hours)</th>
<th>CBZ level (ug/ml)</th>
<th>CBZ-Epox (ug/ml)</th>
<th>CBZ-Epox/CBZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>80</td>
<td>11 ± 5.7</td>
<td>193 ± 49</td>
<td>5.7 ± 2.3</td>
<td>8.2 ± 2.2</td>
<td>1.6 ± 0.6</td>
<td>0.19 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>CBZ + ETX</td>
<td>20</td>
<td>11.5 ± 5.7</td>
<td>245 ± 59</td>
<td>5.4 ± 2.7</td>
<td>7.7 ± 2.1</td>
<td>1.7 ± 0.6</td>
<td>0.23 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>CBZ + VPA</td>
<td>8</td>
<td>14.2 ± 5</td>
<td>238 ± 58</td>
<td>7.8 ± 1.7</td>
<td>7.8 ± 1.7</td>
<td>2.7 ± 1.3</td>
<td>0.33 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>CBZ + PHT</td>
<td>8</td>
<td>12.1 ± 8.5</td>
<td>350 ± 134</td>
<td>5.1 ± 2.5</td>
<td>7.4 ± 3.5</td>
<td>2.5 ± 1.4</td>
<td>0.35 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>CBZ + PHB/</td>
<td>5</td>
<td>11 ± 8.9</td>
<td>366 ± 126</td>
<td>4.3 ± 2.4</td>
<td>7.3 ± 2.7</td>
<td>2.1 ± 0.9</td>
<td>0.29 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>PRM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polytherapy</td>
<td>20</td>
<td>13.8 ± 7.5</td>
<td>276 ± 112</td>
<td>5 ± 2.2</td>
<td>7.1 ± 1.9</td>
<td>3.1 ± 1.2</td>
<td>0.44 ± 0.17</td>
<td></td>
</tr>
</tbody>
</table>

*ETX: ethosuximide, VPA: valproate, PHT: phenytoin, PHB: phenobarbital, PRM: primidone*
only contributes to its anticonvulsant and antineuralgic properties but is also implicated in its neurotoxic side effects (Rane et al., 1975; Gilham et al., 1988). Because of this strong evidence for CBZ-Epox being an active metabolite, several studies have addressed the possible factors that modify the serum levels of CBZ-Epox and the ratio of CBZ-Epox/CBZ (Eichelbaum et al., 1976; McKauge et al., 1981; Elyas et al., 1982; Schoeman et al., 1984a, b; Furlanet et al., 1985).

Bertilson et al. (1986) reported that children metabolize CBZ faster than adults and may require larger doses to achieve comparable serum levels. It was also stated that children form relatively more CBZ Epox compared to adults (Pynnönen et al., 1978; Miura, 1981; McKauge et al., 1981). Younger children were found to have a lower plasma content of CBZ but higher levels of CBZ-Epox compared with older children (Pynnönen et al., 1978; Miura, 1981). On the contrary, the CBZ-Epox/CBZ ratio decreased with age due to increased CBZ levels, and CBZ-Epox levels did not show age dependency. This relationship, however, has not been found by any other authors (Eichelbaum et al., 1976). These studies have been performed with relatively small numbers of patients and the results are conflicting.

Regarding the relationship between CBZ and CBZ-Epox, our study showed that the CBZ-Epox/CBZ ratio is higher in younger children because of relatively low CBZ levels that might reflect the faster metabolism of CBZ in them than the metabolism of CBZ-Epox.

Autoinduction of metabolism produces a variable but dose-dependent fall in steady-state concentrations which can result in breakthrough seizures (Macphee and Brodie, 1985). Our study population does not include that problem since all the patients were taking CBZ more than six weeks prior to enrollment for this study.

Interactions between CBZ and other antiepileptic drugs are complex and are a good reason in themselves for preferring monotherapy (Eichelbaum et al., 1979; Baciewicz, 1986). CBZ increases the clearance of clonazepam, ethosuximide and sodium valproate. (Mattson et al., 1980) Mutual enzyme induction or inhibition in patients treated with concomitant phenobarbital, phenytoin or primidone can result in the rise or fall in steady-state concentrations of either or both anticonvulsants (Zielinski and Haidukewych, 1987). This is another situation in which monitoring CBZ concentrations can be helpful (Brodie and Feely, 1988). Sodium valproate, in addition, inhibits the breakdown of CBZ and, probably more importantly, that of its active epoxide metabolite (Macphee et al., 1988). Our study demonstrated that CBZ-Epox levels more than 4.0 µg/ml is most frequently associated with polytherapy, especially valproate.

In conclusion, our study demonstrated the following characteristics regarding the serum levels of CBZ and CBZ-Epox. The average ratio of CBZ-Epox/CBZ in children and young adults was approximately 20% for the patients on monotherapy of CBZ. The ratio of CBZ-Epox/CBZ was higher in younger children because of a relatively lower CBZ level. The ratio of CBZ-Epox/CBZ increased progressively following an oral dose of CBZ due to a rise in the level of CBZ-Epox. The dose of CBZ did not affect the ratio of CBZ-Epox/CBZ. The addition of a second drug to CBZ increased the ratio of CBZ-Epox/CBZ. This effect was most prominent with valproate, phenytoin, less with barbiturates and least with ethosuximide. The addition of more than one antiepileptic drug markedly elevated the ratio of CBZ-Epox/CBZ. Patients on
phenytoin and barbiturates required higher doses of CBZ to achieve a given CBZ level. The group of patients who had toxic levels of CBZ-Epox above 4.0 μg/ml were most often on valproate in addition to CBZ.

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= 국문조목 =

Carbamazepine과 Carbamazepine-10, 11-epoxide의 혈청농도에 미치는 영향

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황용승* Lawrence A. Lockman**

Carbamazepine-10, 11-epoxide (CBZ-Epox)는 carbamazepine (CBZ)의 대사산물로서 CBZ와 유사한 항경련 작용과 독성효과를 나타낸다. CBZ 단독요법 혹은 다파경련제 병용하여 CBZ를 복용하고 있는 141명의 소아와 청소년 성인 (1-29세)을 대상으로 항경련제에서의 CBZ와 CBZ-Epox의 혈청농도를 HPLC방법으로 측정하였다. CBZ 단독요법은 시행한 환자 수는 80명이었고 20명은 ethosuximide, 8명은 valproate, 8명은 phenytoin 5명은 phenobarbital이나 primidone 그리고 20명은 2가지 이상의 다파경련제를 CBZ와 같이 사용하고 있었다.
CBZ 단독요법군에서 CBZ의 평균지는 8.2 μg / ml ± 2.2 엠포 CBZ-Epox는 1.6 μg / ml ± 0.6, CBZ-Epox / CBZ의 비는 0.19 ± 0.5였다. CBZ-Epox / CBZ의 비에 의하여 생활중 환자에서는 오일은 환자의 연령, 비자약 두약기간과 복용기간의 전략, 그리고 복용방법적용의 영향이었다. 두약 수준의결과 CBZ-Epox / CBZ비에 의하여 생활중 환자는 오일은 비자약 두약기간과 복용기간의 전략, 그리고 복용방법적용의 영향이었다.

복합요법은 시행하고 있는 환자들은 CBZ-Epox / CBZ가 단독요법군에 비하여 더 많이 포함되었고 그 비는 ethosuximide 복용군은 0.23 ± 0.05, valproate 복용군은 0.33 ± 0.15, phenytoin 복용군은 0.35 ± 0.11, phenobarbital이나 primidone 복용군은 0.29 ± 0.05, 두약 시 이의 항경련제 복용군은 0.44 ± 0.17였다. 따라서 CBZ군과 CBZ-Epox의 혈청농도는 환자의 연령, CBZ 복용량 및 항경련제 복용방법에 의하여 생활중 주요요법이 안될 수 있었고 특히 CBZ가 더하여 여러 항경련제 복합단용하는 경우 CBZ-Epox의 독성효과를 비해하기 위해서 약물농도의 감시가 중요할 것이다.