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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 ug/ml $\pm$ 2.2 ($\pm$ SE), the CBZ-Epox level was 1.6 ug/ml $\pm$ 0.6 and the CBZ-Epox/CBZ ratio was 0.19$\pm$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 doe 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 $\pm$ 0.05; CBZ and valproate, 0.33 $\pm$ 0.15; CBZ and phenytoin, 0.35 $\pm$ 0.11; CBZ and phenobarbital or primidone, 0.29 $\pm$ 0.05; CBZ and more than one additional anticonvulsant, 0.44 $\pm$ 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 durgs. 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

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-diol) from CBZ-Epox (Bertilsson and Tomson 1986).

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 adversive side effect of CBZ (Gillham *et al.* 1988).

Several stduies 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; McKauge *et al.*, 1981; Schoeman *et al.*, 1984a, b; Furlanut, 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 meaurable; 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 phenytion and five patients with CBZ and phenobarbital/primidone. The other 20 patients were taking more than two antiepileptic durgs 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

Treatment Group	No. of Patients
Monotherapy	80
CBZ* & ethosuximide	20
CBZ & phenytoin	8
CBZ & valproate	8
CBZ & phenobarbital/primidone	5
Polytherapy**	20
Total	141

*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 meansured 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/,l 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

Seizure Type*	No. of Patients
Partial simple	6
Partial complex	50
Generalized tonic clonic	32
Myoclonic	1
Absence	3
Tonic	3
Unclear	3
Total	98

*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 the 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 Antieptileptic 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

	CBZ (ug/ml)	CBZ-Epox (ug/ml)	CBZ-Epox /CBZ
Mean ± SD	8.2 ± 2.2	1.6 ± 0.6	0.19 ± 0.5
Range	2.4 – 14.8	0.5 – 4.3	0.07 – 0.37

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

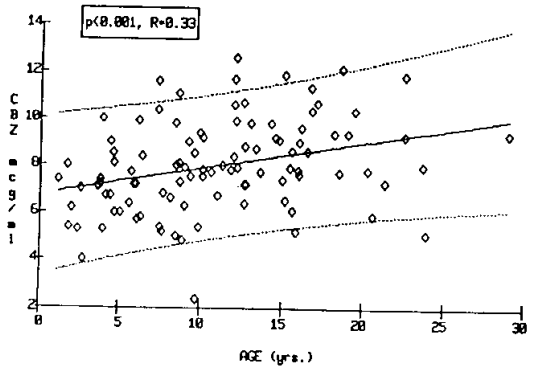

Fig. 1. Correlation between age of the patients and serum levels of carbamazepine

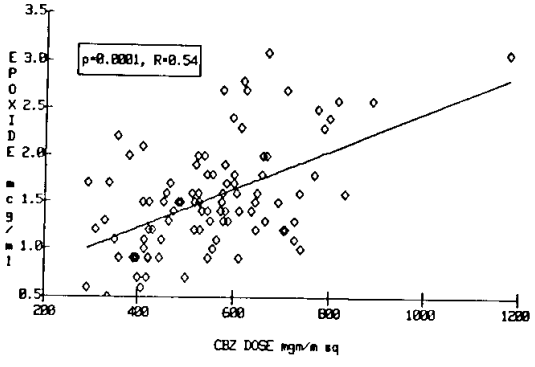

Fig. 2. Correlation between dose of carbamazepine and serum levels of carbamazepine-10, 11-epoxide.

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 valproated or two additional antiepileptic drugs.

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

Eight patients had levels of CBZ-Epox grater than 4.0 ug/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-

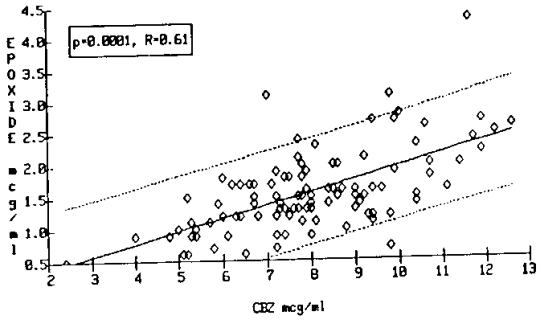

Fig. 3. Correlation between serum levels of carbamazepine and carbamazepine-10, 11-epoxide

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 absences 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% (Bertilsson and Tomson 1986).

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

Dependent Variables Independant Varitables	CBZ	CBZ-Epox	CBZ-Epox/CBZ
Age	$P < 0.05$	NS	$P < 0.0005$
Interval	NS	$P < 0.01$	$P < 0.001$
Dose/m2	$P < 0.001$	$P < 0.0001$	NS

*NS: not significant

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

Treatment	No. of Patients	Age (mean ± S.D)	Dose (mg/m2)	Interval (hours)	CBZ level (ug/ml)	CBZ-Epox (ug/ml)	CBZ-Epox/CBZ
CBZ	80	11 ± 5.7	193 ± 49	5.7 ± 2.3	8.2 ± 2.2	1.6 ± 0.6	0.19 ± 0.05
CBZ + ETX	20	11.5 ± 5.7	245 ± 59 (P 0.01)	5.4 ± 2.7 (NS)	7.7 ± 2.1 (NS)	1.7 ± 0.6 (NS)	0.23 ± 0.05 (P < 0.05)
CBZ VPA	8	14.2 ± 5	238 ± 58 (NS)	7.8 ± 1.7 (NS)	7.8 ± 1.7 (NS)	2.7 ± 1.3 (P < 0.05)	0.33 ± 0.15 (P < 0.05)
CBZ + PHT	8	12.1 ± 8.5	350 ± 134 (NS)	5.1 ± 2.5 (NS)	7.4 ± 3.5 (NS)	2.5 ± 1.4 (NS)	0.35 ± 0.11 (P < 0.01)
CBZ + PHB/PRM	5	11 ± 8.9	366 ± 126 (P < 0.05)	4.3 ± 2.4 (NS)	7.3 ± 2.7 (NS)	2.1 ± 0.9 (NS)	0.29 ± 0.05 (P < 0.05)
Polytherapy	20	13.8 ± 7.5	276 ± 112 (P < 0.05)	5 ± 2.2 (NS)	7.1 ± 1.9 (NS)	3.1 ± 1.2 (P < 0.001)	0.44 ± 0.17 (P < 0.001)

*ETX: ethosuximide, VPA: valproate, PHT: phenytoin PHB; phenobarbital, PRM: primidone

Table 6. Patients with CBZ-Epox levels more than 4.0 ug/ml

No. of Patients	Dose (mg/kg)	Dose (mg/m2)	CBZ (ug/ml)	CBZ-Epox (ug/ml)	CBZ-Epox/CBZ	Additional Anticonvulsants
1	23.7	264	6.6	4.0	61%	VPA
2	26.4	324	11.5	4.6	40%	VPA
3	20.8	306	4.8	4.2	87.5%	VPA, PHT
4	51.5	495	13.2	5.5	41.7%	PHT
5	37.2	295	7.3	5.1	70%	VPA, PHB
6	37.7		11.6	4.3	37%	–
7	26.8	247	8.6	4.7	54.7%	VPA, ETX
8	43.4	492	12.9	6.1	47.3%	VPA

only contributes to its anticonvulsant and antineuralgic properties but is also implicated in its neurotoxic side effects (Rane *et al.*, 1975; Gillham *et al.*, 1988). Because of this strong evidence for CBZ-Epox being an active metabolite, several studies have addressed the possible fators 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.*, 1984 a, b; Furlanut *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 (Pynnonen *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 (Pynnonen *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 showed 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 matabolism 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 includes 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 ug/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 apporximately 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 barbirturates and least with ethosuximide. The addition of more than one antieptic 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 ug/ml were most often on valproate in addition to CBZ.

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= 국문초록 =

Carbamazepine과 Carbamazepine-10, 11-epoxide의 혈청농도에 미치는 영향

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Carbamazepine-10, 11-epoxide (CBZ-Epox)는 carbamazepine (CBZ)의 대사산물로서 CBZ과 유사한 항경련 작용과 독성효과를 나타낸다. CBZ 단독요법 혹은 타항경련제와 병용하여 CBZ을 복용하고 있는 141명의 소아와 젊은 성인 (1-29세)을 대상으로 항정상태에서의 CBZ과 CBZ-Epox의 혈청농도를 HPLC방법으로 측정하였다. CBZ 단독요법을 시행한 환자 수는 80명이었고 20명은 ethosuximide, 8명은 valproate, 8명은 phenytoin 5명은 phenobarbital이나 primidone 그리고 20명은 2가지 이상의 타항경련제를 CBZ과 같이 사용하고 있었다.

CBZ 단독요법군에서 CBZ의 평균치는 8.2 ug / ml ± 2.2 였고 CBZ-Epox는 1.6 ug / ml ± 0.6, CBZ-Epox / CBZ의 비는 0.19 ± 0.5였다. CBZ-Epox / CBZ의 비에 의미있게 영향을 미치는 요인은 환자의 연령, 마지막 투약시간과 채혈시간의 간격, 그리고 체표면적당의 용량이었다. 다변수분석결과 CBZ-Epox / CBZ비에 의미있게 영향을 미치는 요인은 마지막 투약시간과 채혈시간의 간격 그리고 환아의 연령이었다.

복합요법을 시행하고 있는 환자군은 CBZ-Epox / CBZ가 단독요법군에 비하여 의미있게 높았고, 그 비는 ethosuximide 병용군은 0.23 ± 0.05, valproate 병용군은 0.33 ± 0.15, phenytoin 병용군은 0.35 ± 0.11, phenobarbital이나 primidone 병용군은 0.29 ± 0.05, 두가지 이상 항경련제 병용군은 0.44 ± 0.17이었다. 따라서 CBZ군과 CBZ-Epox의 혈청 농도는 환자의 연령, CBZ 용량 및 타항경련제와의 병용에 의하여 영향을 받음을 알 수 있었고 특히 CBZ과 더불어 여러 항경련제를 복합 사용하는 경우 CBZ-Epox의 독성효과를 피하기 위하여서도 약물농도의 감시가 중요할 것이다.