Pharmacokinetic interactions of carbamazepine with some antiepileptic drugs during epilepsy treatment in children and adolescents

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Abstract

Purpose: The aim of the study was to obtain pharmacokinetic data for carbamazepine (CBZ) and its fractions not bound with proteins in bitherapy with lamotrigine (LTG), topiramate (TPM), vigabatrin (VGB) or valproic acid (VPA) in children and adolescents treated for epilepsy.

Material and methods: The participants of the presented investigations were fifty-five patients with epilepsy who were under control of The Department of Developmental Neurology, University of Medical Sciences in Poznań. All of patients were treated with CBZ in bitherapy with LTG, TPM, VGB or VPA. The blood samples were taken under steady-state conditions, before the morning dose and subsequently every 3 or 2 for 24 h. The plasma levels of CBZ were determined using TDX analyzer (Abbott Diagnostic Division, USA). Free CBZ fraction was isolated with the use of ultrafiltration system (Amicon, USA). For pharmacokinetic calculations of total and free CBZ, one-compartment model was used according to standardized procedure.

Results: No significant differences in pharmacokinetic parameters of unbound CBZ in four groups of patients on bitherapy with CBZ and LTG, TPM, VGB or VPA were found. The changes in pharmacokinetics of total CBZ were related with difference in CBZ concentrations, area under curve (AUC), L/D/kg ratios and clearance (Cl)/kg. CBZ+VGB bitherapy led to higher total CBZ concentrations. In the group on bitherapy with CBZ+VPA, no increase in unbound CBZ was detected.

Conclusions: Pharmacokinetic interactions of CBZ with LTG, TPM, VGB or VPA in children are associated only with the changes in total CBZ parameters.

Key words: carbamazepine, interactions, lamotrigine, topiramate, vigabatrin, valproic acid.

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Introduction

Treatment of epilepsy in most of children involves long-term therapy with one or more of antiepileptic drugs (AEDs). Interactions between AEDs can results from either pharmacodynamic or pharmacokinetic mechanisms [1]. Pharmacodynamic interactions between drugs with similar or opposing pharmacological mechanism of actions take place at the cellular levels (cellular targets) and are associated with no changes in the plasma levels of these drugs. Pharmacokinetic interactions can occur when one drug interferes with another one and alters the level of the drug or its metabolite or both of them [1,2]. This kind of interactions between AEDs most commonly occurs due to displacement of a drug from binding with plasma proteins or modification of hepatic metabolism. Interactions involving protein binding displacement are prominent only among the highly protein-bound AEDs (more than 90%), i.e. phenytoin (PHT), tiagabine (TGB) or valproic acid (VPA) [1,2,3]. For drugs with low intrinsic hepatic clearance (Cl), like AEDs, the addition of displacing agent causes a decrease in the total drug concentration in plasma and no changes of free drug concentrations. As concentration of unbound fraction represents the pharmacologically active drug, the clinical effects of AED should also be unchanged. Clinically important interactions involving hepatic metabolism occur when a drug reduces (enzyme inhibition) or enhances (enzyme induction) the activity of pathways responsible for the metabolism of co-administered drugs. The magnitude of both inhibition or induction and their clinical relevance depend on age of children, genetic and envi-

Table 1. **The age of patients treated with CBZ and other AEDs**

Bitherapy	Number of patients	Age range (years)	Mean age ±SD	Sex M/F
CBZ+VPA	28	6.3 - 18.2	13.6 ± 2.9	14/14
CBZ+LTG	10	11.6 - 17.8	15.5 ± 1.9	3/7
CBZ+TPM	11	9.9 - 17.1	13.9 ± 3.5	5/6
CBZ+VGB	6	11.4 - 17.6	15.9 ± 4.4	2/4

ronmental influences, doses and pharmacological activity of the metabolites [1,4,5].

Classic AEDs are often involved in many interactions due to their pharmacokinetic properties. These drugs carbamazepine (CBZ), PHT, phenobarital (PB), primidone (PRM) are potent inducers of cytochrome P 450 (CYP450) and can enhance the metabolism of other AEDs lamotrigine (LTG), topiramate (TPM), and TGB [1,6]. VPA inhibits the metabolism of PB, LTG and CBZ and increases a risk of toxicity of these drugs. VPA is a protein-binding displacer.

The new AEDs exhibit fewer potential interactions than the classic AEDs. They are eliminated by the renal system and are not protein-bound (except TGB). Oxcarbazepine (OXC), felbamate (FBM) and TPM have mild inducing properties and may cause CYP2C19 inhibition thus the metabolism of PHT may be altered. Gabapentin (GBP), vigabatrin (VGB), and leviteracetam (LEV) exhibit few or no interaction with AEDs. FBM, LTG, TGB, TPM and zonisamide (ZNS) may be induced by classic AEDs with enzyme-inducting properties.

CBZ is widely used in the treatment of partial and generalized seizures. Polytherapy of CBZ with conventional AEDs like: PHT, PB or PRM is related with decreased plasma levels of CBZ [7] but some authors did not observe any changes in CBZ level [8]. The main effect of these interactions is an increase in carbamazepine-10,11-epoxide (CBZ-E) level due to induction of CYP3A4 [7]. PHT levels during bitherapy with CBZ may increase or decrease [9]. CBZ may inhibit or induce PHT biotransformation [10]. The decrease in PRM and increase its active metabolite – PB were noticed during bitherapy with CBZ+PRM [9]. CBZ+PB bitherapy was little clinical value because the increase in CBZ level is small and CBZ does not influence PB concentration [7,9].

Co-medication with CBZ+VPA leads to both pharmacodynamic and pharmacokinetic effects. Pharmacodynamic, synergistic interaction results in enhanced antiepileptic efficacy of this combination [11,12]. Protein binding of CBZ is changed during bitherapy with VPA and the unbound fraction of CBZ can increase [13]. Some authors did not observe these changes [7] or found only temporary increase in free CBZ level [14]. VPA inhibits the metabolism of CBZ-E and toxic plasma concentrations of CBZ-E may be observed [7,15]. Bernus et al. [16] described the inhibition of glucuronidation of CBZ-10, 11-trans-diol, and probably inhibition of the conversion CBZ-E to trans-diol derivative, rather than simple inhibition of epoxide hydrolase.

CBZ+LTG bitherapy is related with shortening in t½ of LTG and neurotoxic side effects [9]. The mechanism of these changes is unknown [9]. The ratio CBZ/CBZ-E concentration is lowered during co-medication with LTG [8]. The data about concentrations of these drugs during bitherapy are divergent [9]. The pharmacodynamic interaction may result in neurotoxic symptoms [1,17]. CBZ-E is pharmacologically active metabolite of CBZ but some authors do not agree with opinion about its role in epilepsy treatment and side effects [8,18]. Winnicka et al. [19] did not observe relationship between side effects and increase in CBZ plasma levels.

The effect of VGB therapy on CBZ concentration is somehow controversial. Some studies did not show any influence on CBZ levels [9]. However, Jędrzejczak et al. [20] reported an increase in CBZ concentration after VGB addition. Sanchez-Alcaraz et al. [21] reported also an increase in CBZ clearance during its bitherapy with VGB.

Sisodiya et al. [22] described some patients with neurotoxic side effects after combining LEV with CBZ without any changes in concentrations of both AEDs and CBZ-E. TPM is a weak inducer of isoenzymes of CYP450 and its addition to CBZ does not change pharmacokinetic parameters of total an unbound CBZ [23,24]. Pharmacokinetics of CBZ did not change during treatment with TGB but t½ and Cl of TGB increased when this combination was used due to the same metabolic pathway (CYP3A4) [25]. Addition of OXC to CBZ therapy can lead to small decrease in serum CBZ concentration [26,27].

The aim of the study was to obtain pharmacokinetic data for CBZ and its fractions not bound with proteins in bitherapy with LTG, TPM, VGB or VPA in children and adolescents treated for epilepsy.

Material and methods

The participants of the study were fifty-five patients with epilepsy who were under care of The Department of Developmental Neurology, K. Marcinkowski University of Medical Sciences in Poznań. All patients were treated with CBZ in bitherapy with LTG, TPM, VGB or VPA. The age of patients and AEDs doses are presented in *Tab. 1* and *2*. One-way analysis of variance showed statistically significant differences mean age of patients ($p < 0.001$, F=5.038, df=7:136). Post hoc Tukey tests did not show any differences.

One-way analysis of variance showed statistically significant difference in CBZ doses (p=0.01, F=2.272, df=7:136) but in *post-hoc* tests found no differences in CBZ doses.

Twelve patients had primary generalized epilepsy and 43 patients suffered from focal seizures. The blood samples were taken under steady-state conditions before the morning dose and subsequently every 3 or 2 h for 24 h. The last changes in

Table 2. **Doses of CBZ and other AEDs**

Bitherapy	CBZ dose range mg/kg	Mean CBZ dose mg/kg	Dose range of co-administered AEDs mg/kg	Mean doses of co-administered AEDs mg/kg
CBZ+VPA	5.0-22.2	14.4±7.6	4.5-40.0	20.7±8.1
CBZ+LTG	4.8-17.9	10.6±4.3	1.9-7.0	3.5±1.8
CBZ+TPM	5.8-22.0	12.7±5.3	3.3-12.1	5.9±2.7
CBZ+VGB	9.6-21.4	13.3±4.4	17.5-72.0	38.4±18.2

Table 3. **Pharmacokinetic parameters of unbound CBZ in patients on bitherapy with other AEDs**

Parameter	CBZ+LTG	CBZ+TPM	CBZ+VGB	CBZ+VPA	Analysis of variance		
					Df	F	p
AUC [μgh/ml]	18.10±5.98	22.13±7.82	20.98±7.25	19.26±7.87	3;54	0.623	0.603
t½ [h]	24.36±14.87	18.85±9.58	18.42±4.53	22.08±15.17	3;54	0.341	0.796
k [1/h]	0.05±0.03	0.05±0.03	0.04±0.01	0.05±0.03	3;54	0.415	0.743
Cl/kg [ml/h/kg]	292.94±97.22	318.07±148.89	323.51±55.95	379.06±202.89	3;54	0.834	0.481
Vd/kg [l/kg]	11.45±9.75	8.35±4.65	8.61±2.14	12.31±10.85	3;54	0.645	0.590
C_{min} [μg/ml]	1.28±0.37	1.60±0.58	1.52±0.53	1.44±0.64	3;54	0.57	0.683
C_{mean} [μg/ml]	1.49±0.49	1.82±0.65	1.73±0.60	1.71±0.70	3;54	0.46	0.688
C_{max} [μg/ml]	1.77±0.70	2.14±0.77	2.04±0.78	1.99±0.77	3;54	0.423	0.737
FI	0.38±0.23	0.35±0.16	0.34±0.12	0.46±0.43	3;54	0.484	0.695
L/D/kg [μg/ml/mg/kg]	0.15±0.05	0.18±0.13	0.13±0.02	0.14±0.07	3;54	0.683	0.567

Table 4. **Pharmacokinetic parameters of total CBZ in patients on bitherapy with other AEDs**

Parameter	CBZ+LTG	CBZ+TPM	CBZ+VGB	CBZ+VPA	Analysis of variance		
					Df	F	p
AUC [μgh/ml]	117.02±51.46	87.39±21.76	128.30±19.95	77.31±23.47	3;54	7.650	0.0001*
t½ [h]	17.55±8.09	25.16±8.17	13.96±7.50	17.39±1.07	3;54	0.209	0.890
k [1/h]	0.06±0.03	0.06±0.04	0.06±0.02	0.06±0.04	3;54	0.913	0.439
Cl/kg [ml/h/kg]	47.59±14.12	75.22±29.91	53.21±17.75	88.63±41.93	3;54	4.424	0.008*
Vd/kg [l/kg]	1.13±0.53	2.85±3.66	1.15±0.87	2.06±1.28	3;54	1.821	0.155
C_{min} [μg/ml]	7.81±3.59	6.07±1.80	8.52±1.08	5.68±2.12	3;54	3.842	0.015*
C_{mean} [μg/ml]	9.59±4.24	7.20±1.84	10.52±1.60	6.92±2.51	3;54	4.582	0.006*
C_{max} [μg/ml]	11.37±4.78	8.38±1.98	12.70±2.21	8.26±3.07	3;54	4.913	0.004*
FI	0.49±0.27	0.42±0.23	0.48±0.15	0.50±0.30	3;54	0.222	0.880
L/D/kg [μg/ml/mg/kg]	0.95±0.41	0.67±0.35	0.86±0.30	0.54±0.20	3;54	5.846	0.002*

* Difference statistically significant at p≤0.05

dosage were done two months before the study. The plasma levels of CBZ were determined using TDX analyzer (Abbott Diagnostic Division, USA). Free CBZ fraction was isolated with the use of ultrafiltration system (Amicon, USA). Diurnal fluctuations of free and total CBZ were presented with the use of fluctuation index (FI), i.e. the difference between maximum concentration (C_{max}) and minimum concentration (C_{min}), which is the percentage of C_{min} (FI = C_{max} - C_{min}/C_{min}%). For pharmacokinetic calculations of total and free CBZ, one-compartment model was used according to standardized procedure. Pharmacokinetic parameters: area under curve (AUC), elimination rate constant (k), half-life (t½), volume of distribution (Vd), Cl, level/dose (L/D) ratio and free fraction (FF) (AUC free/AUC total ratio) were compared using analysis of variance and *post-hoc* test (Tukey test, p=<0.05).

Results

Pharmacokinetic parameters for unbound CBZ in bitherapy and results of analysis of variance were presented in *Tab. 3*. CBZ achieved after the doses used in all patients were in therapeutic range (1.1 do 3.2 μg/ml) [28]. The unbound CBZ levels were below therapeutic concentrations only in some cases, but the C_{mean} values were always in therapeutic range. Pharmacokinetic parameters calculated for unbound CBZ in four groups of patients did not differ significantly.

Pharmacokinetic parameters for total CBZ in bitherapy are presented in *Tab. 4*.

Mean values of C_{min}, C_{max} and C_{mean} of total CBZ used with TPM or VPA were in therapeutic range, 4-10 μg/ml [28]. The values above 10 μg/ml and below 4 μg/ml were measured only

in few cases in the groups on CBZ+VPA and CBZ+LTG bitherapy. In a case of bitherapy with CBZ+LTG, the C_{max} of total CBZ was higher than therapeutic value averaging 11.37±4.78 μg/ml. The C_{max} values of C_{min}, C_{max} and C_{mean} were the highest in CBZ+VGB bitherapy group. Two of them, maximum and mean levels of CBZ, were the highest among observed groups of bitherapy (*Tab. 4*).

C_{min} was the lowest in groups on CBZ+VPA bitherapy while in the patients on CBZ+VGB bitherapy it was the highest. C_{min} for CBZ+LTG and CBZ+TPM did not differ from the others C_{min} values.

Analysis of variance for C_{mean} showed the difference between all patient groups. The lowest C_{mean} resulted from CBZ+VPA treatment and differed from the highest C_{mean} in CBZ+VGB group. However, these values did not differ from C_{mean} in CBZ+TPM or CBZ+LTG groups. Total CBZ concentration in the group treated with CBZ+TPM was different from that in CBZ+VGB bitherapy while the result of CBZ+LTG treatment did not differ from the co-medication with VGB and VPA.

C_{max} of CBZ varied in different treatment, it was the highest in CBZ+VGB group. This value differed from C_{max} of CBZ during co-medication with CBZ and VPA or TPM. CBZ C_{max} was not changed by LTG and VGB co-medication. The lowest levels of CBZ were measured in CBZ+VPA – treated group and were different from C_{max} in patients on bitherapy with VGB+CBZ.

The value for bitherapy CBZ+LTG was the highest and differed from values those for CBZ+VPA – treated group. L/D/kg for bitherapy with CBZ and VGB or TPM did not differ.

The CBZ AUC was the highest in patients on bitherapy with CBZ+VGB and the smallest in those receiving bitherapy with CBZ+VPA. AUC of CBZ+TPM – treated group differed from the value in patients receiving CBZ+VGB. There was no difference in AUC values between VPA versus TPM co-medication with CBZ, and TPM vs LTG as well as LTG vs VGB.

Cl of CBZ significantly differed between the groups. The highest values of Cl were calculated for CBZ+VPA group and the lowest Cl of CBZ accompanied add-on therapy with LTG. Vd did not differ statistically significantly in all patient groups as demonstrated by analysis of variance and *post-hoc* tests.

Analysis of variance revealed statistically significant (p=0.018) differences in FF between all groups of patients. There were no differences between the groups on bitherapies. The highest values of FF were calculated for CBZ+TPM (0.25±0.07 μg/ml) and CBZ+VPA (0.25±0.09 μg/ml) groups and the lowest for CBZ+VGB (0.17±0.06 μg/ml) and CBZ+LTG (0.17±0.06 μg/ml) treated groups (data are not shown).

Discussion

Epilepsy treatment with CBZ is related with an autoinduction. The autoinduction of CBZ leads to a decrease in CBZ levels and shortening of t½ [28,29]. Metabolism of CBZ accelerates during treatment and the doses of this drug may be too low to achieve the therapeutic effect [29,30]. Cl values may increase two times after one month of treatment but no changes were observed after four months [26]. Cloyd and Remmel [31]

reported cases with three times higher Cl in initial weeks of CBZ therapy. The range of autoinduction depends on CBZ dose. The increase in CBZ dose does not elevate plasma CBZ concentration at the beginning of treatment [28].

The fluctuations of concentration of total and unbound CBZ were found in therapeutic range in the patients participating in this study. No differences in pharmacokinetic parameters of unbound CBZ between all groups on bitherapies: CBZ+LTG, CBZ+TPM, CBZ+VGB and CBZ+VPA were found. The changes in pharmacokinetic parameters of total and unbound CBZ in each of bitherapy groups are discussed below.

CBZ+LTG

No differences of unbound CBZ were observed between all groups. The lowest concentrations of CBZ were probably related with the smallest doses of CBZ used in add-on therapy with LTG, however, no differences were calculated in CBZ doses. In the earlier reports on interaction CBZ+LTG, the authors suggested an increase in CBZ-E level [32], but later observations did not confirm this conclusion [1,17]. Eriksson et al. [33] described no changes in CBZ and CBZ-E concentrations after LTG addition. This study and observations of others authors [34] excluded any pharmacokinetic interaction between CBZ and LTG. CBZ+LTG bitherapy leads to pharmacodynamic interaction with a possibility of neurotoxic side-effects [17,35].

The doses of CBZ used in patients receiving CBZ+LTG were lower than the doses in those treated with CBZ+VPA but without significant differences. Usually, in co-medication with CBZ and VPA, the lower concentrations of CBZ were estimated [36].

No changes in Cl were observed in comparison with CBZ+TPM and CBZ+VGB groups. The lower values of Cl in CBZ+LTG bitherapy group might be related with lower doses of CBZ used with LTG.

The interactions of AEDs during absorption are very rare [2]. LTG does not change the absorption or elimination of CBZ. It was demonstrated by double-blind, randomized study in volunteers presented by Malminiemi et al. [37]. Protein-binding interactions commonly occur when two highly protein-bound drugs (>90%) are co-administered and compete for a limited number of binding sites. Bitherapy with CBZ+LTG does not change pharmacokinetic parameters of both CBZ and its active metabolite CBZ-E. LTG is a weak inducer of UGT while CBZ induces both CYP450 isoenzymes and UGT, so the interaction between these two AEDs may appear [4,38]. LTG is metabolized via conjugation with UGT and it neither influences nor inhibits CYP450 isoenzymes. CBZ is metabolized by CYP450 system and induces P450 isoenzymes, which do not metabolize LTG [2]. No change was observed in pharmacokinetics of free CBZ fraction in CBZ+LTG group comparing with other groups. Finally, no interactions during elimination were reported [2], and LTG did not influence elimination of CBZ [37].

CBZ+TPM

Co-medication with both of these two drugs was used for the treatment of epileptic patients with simple or complex focal/partial seizures. However, the indications of TPM usage

are broader, since they were applied to manage, a lot of epileptic seizures and epileptic syndromes [39] and status epilepticus [40]. Mean doses of TPM and CBZ were in therapeutic range. There were no significant differences in CBZ doses between all bitherapy groups.

Some changes in pharmacokinetic parameters of unbound and total CBZ were observed in the group CBZ+TPM. No reports were found about parallel comparison of four groups of patients treated with CBZ in combination with different AEDs. Co-medication with CBZ and VGB, VPA, LTG or TPM did not lead to any changes in pharmacokinetic parameters of unbound CBZ. Sachdeo et al. [23] reported no influence of TPM addition on pharmacokinetics of total and free CBZ and CBZ-E. Neurotoxic side effects connected with CBZ appeared when TPM was used as add-on therapy with CBZ. Reduction of CBZ dosage resulted in a disappearance of these symptoms [41]. Maximum and mean CBZ concentrations and AUC did not differ from the respective value obtained in CBZ+VGB bitherapy group.

CBZ+VGB

Fluctuation of pharmacokinetic parameters in CBZ+VGB were analyzed only in six patients. The small number of patients was connected with some limitation of the use of VGB to few epileptic syndromes. West syndrome (WS) was the special indication to use VGB [42]. Apart from this indication, VGB is often used in the treatment pharmacoresistant focal seizures [25]. The limitation of VGB therapy is related with some unwanted effects, especially with appearance of visual defects in 30% of patients treated with VGB [43].

Combination of CBZ with VGB is very effective due to specific mechanism of action of these two AEDs. Combining a sodium channel blocker with drug enhancing GABAergic inhibition may be useful in patients with generalized tonic-clonic seizures and partial seizures [11]. Bitherapy with VGB did not cause any differences in pharmacokinetic parameters of unbound CBZ. During treatment with CBZ+VGB, we can expect higher concentration of CBZ than during other bitherapies with CBZ. Similar conclusions were drawn by Jędrzejczak et al. [20]. The authors noticed 10% increase in CBZ concentration after addition of VGB to CBZ therapy. A negative correlation between the increase and the initial level of CBZ prior to VGB addition was found. However, the trial of these authors comprised only adult patients, and they did not measure unbound CBZ levels. Neurotoxic symptoms of CBZ in bitherapy with VGB have been reported sometimes, but without any pharmacokinetic consequences [9,45,46].

Searching for any pharmacokinetic interactions between CBZ and VGB, Sanchez-Alcaraz et al. [21] investigated pharmacokinetics of CBZ during monotherapy and after addition of VGB. Co-medication with VGB and CBZ was connected with a decrease in L/D ratio and with an increase in Cl by about 35%. Furthermore, the plasma levels of CBZ in some patients lowered to subtherapeutic values. The monitoring of CBZ concentration after addition VGB is important for this type of bitherapy. The explanation of interaction of CBZ with VGB is difficult. VGB is not metabolized in the liver, does not bind to plasma proteins and the major route for its elimination is *via* renal excretion of the unchanged compound [1]. The reports

about VGB interaction are ambiguous [20,21]. The reason of this discrepancy in the observations may be different time of blood sampling and the fact that CBZ concentrations were measured before autoinduction period [29].

CBZ+VPA

Bitherapy with CBZ and VPA is the combination of AEDs which was used most often in the patients participating in the present study. CBZ doses did not differ from other groups in this study.

CBZ is used in the treatment of partial epilepsy more often than VPA but VPA was not more effective in generalized tonic-clonic seizures [47]. Combination of these AEDs has been used for treatment of epileptic seizures for many years [12]. There were no serious side-effects. Some authors underline not only pharmacokinetic but pharmacodynamic interactions that increase antiepileptic properties of these AEDs [48]. Deckers et al. [11] reported that combination of CBZ+VPA appeared to be associated with an improvement in effectiveness. Froscher [49] mentioned bitherapy CBZ with VPA as very useful in drug-resistant seizures.

VPA is highly bound to plasma proteins. VPA can displace drugs from their plasma protein-binding sites and their free fraction may dramatically increase [7]. Despite VPA capability of increasing unbound CBZ levels, no changes in free CBZ levels were obtained. Literature data indicate that sometimes unbound CBZ concentrations remained unchanged [50] and this interaction is doubtful [51]. Kozik et al. [14] reported an increase in unbound CBZ level during bitherapy with VPA at the beginning of treatment with CBZ+VPA and, then, a decrease in the concentrations to the values before bitherapy. The lack of high unbound CBZ levels in CBZ+VPA bitherapy, patients even considering mechanism of displacement of other drugs by VPA, may be explained by the fact that the study was conducted after stabilizing of concentrations all AEDs. This interaction has small clinical significance and it does not increase unbound CBZ levels.

The changes in CBZ levels have been described as decreased [52], increased or cure changed by VPA [51,53]. The L/D/kg ratio was the lowest and differed from L/D/kg ratio calculated for CBZ+LTG. These values usually decrease in polytherapy [52,54]. The lowest L/D/kg for CBZ+VPA, despite similar CBZ doses, are connected with low concentrations of CBZ in bitherapy with VPA. Liu and Delgado [52] explained this phenomenon as increases in CBZ Cl due to heteroinduction of CBZ while in patients treated with CBZ+VPA as an increase in unbound CBZ. CBZ Cl in the group was the highest and differed from Cl in patients on CBZ+LTG bitherapy. The changes in this parameter were observed also during treatment with other AEDs [46]. The interaction between CBZ and VPA was described as very complicated due to various values of total CBZ concentrations but the final effect depended on the examined population [54]. The lack of any influence of VPA on CBZ levels was explained as an effect of unchanged activity of CYP3A4 isozyme by VPA [2]. Because of inhibition of epoxide hydrolase, VPA can significantly inhibit Cl of CBZ-E [51]. Although the measured CBZ concentrations remain stable, toxicity may still occur. CBZ-E is an active metabolite of CBZ and, despite its antiepileptic activ-

ity, is responsible for side-effects [18]. Newer study does not confirm these results but reports that side-effects may be connected with high CBZ levels [19]. Bernus et al. [16] described the inhibition of glucoronidation of CBZ-10, 11-trans-diol, and probably inhibition of the conversion CBZ-E to trans-diol derivative, rather than simply inhibiting epoxide hydrolase.

Conclusions

There were no significant differences in pharmacokinetic parameters of unbound CBZ between four groups of patients on bitherapy with CBZ and LTG, TPM, VGB or VPA. The changes in pharmacokinetics of total CBZ were related with differences in CBZ concentrations, AUC, L/D/kg ratios and Cl/kg. In the group CBZ+VPA, no increase in unbound CBZ was detected. CBZ+VGB bitherapy may lead to higher total CBZ concentrations than other types of bitherapy.

References

1. Patsalos PN. The importance of drug interactions in epilepsy therapy. Epilepsia, 2002; 43: 365-89.

2. French JA, Gidal EB. Antiepileptic drug interaction. Epilepsia, 2000; 41, Suppl. 8: 30-6.

3. Bourgeois BF. Important pharmacokinetic properties of antiepileptic drugs. Epilepsia, 1995; 36, Suppl. 5: 1-7.

4. Andreson GD. A mechanistic approach to antiepileptic drug interactions. Ann Pharmacother, 1998; 325: 554-8.

5. Faught E. Pharmacokinetic consideration in prescribing antiepileptic drugs. Epilepsia, 2001; 42, Suppl. 4: 19-23.

6. Hachad H, Ragueneau-Majlessi I, Levy RH. New antiepileptic drugs. Review on drug interactions. Ther Drug Monit, 2002; 29: 91-103.

7. Liu H, Delgado MR, Browne RH. Interaction of valproic acid with carbamazepine and its metabolites concentrations, concentrations ratios, and level/dose ratios in epileptic children. Clin Neuropharmacol, 1995; 8: 1-12.

8. Potter JM, Donnelly A. Carbamazepine-10,11-epoxide in therapeutic drug monitoring. Ther Drug Monit, 1999; 206: 652-7.

9. Reimers A. Drug interactions and non-interactions with carbamazepine. Desitin Arzneimittel GmbH, Hamburg, 2000.

10. Lakehal F, Wurden CJ, Kalhorn TF, Levy RH. Carbamazepine and oxcarbazepine decrease phenytoin metabolism trough inhibition of CYP2C19. Epilepsy Res, 2002; 52: 79-83.

11. Deckers CLP, Czuczwar SJ, Hekster YA, Keyser A, Kubova H, Meinardi H, Patsalos PN, Renier WO, van Rijn CM. Selection of antiepileptic drug polytherapy based on mechanisms of action. The evidence reviewed. Epilepsia, 2000; 41: 1364-74.

12. Froscher W. Synergistic and additive efects of antiepileptic drugs in epileptic patients. Epileptologia, 1998; 62: 31-42.

13. Pisani F, Caputo M, Fazio A, Oteri G, Russo MF, Spina E, Perucca E, Bertilsson L. Interaction of carbamazepine-10,11-epoxide, an active metabolite of carbamazepine, with valproate: a pharmacokinetic study. Epilepsia, 1990; 31: 339-42.

14. Kozik A, Orzechowska-Józwenko K, Ujma-Czapska B, Unholt J, Hurkacz M. Results of free carbamazepine monitoring in children with epilepsy. Epileptologia, 1994; 2: 271-81.

15. Svinarov DA, Pippenger CE. Valproic acid-carbamazepine interaction: is valproic acid a selective inhibitor of epoxide hydrolase? Ther Drug Monit, 1995; 217-20.

16. Bernus I, Dickinson RG, Hooper WD, Eadie MJ. The mechanism of the carbamazepine-valproate interaction in humans. Brit J Clin Pharmacol, 1997; 441: 21-7.

17. Besag FM, Berry DJ, Pool F. Carbamazepine toxicity with lamotrigine: pharmacokinetic pharmacodynamic interaction? Epilepsia, 1998; 39: 183-7.

18. Semah F, Gimenez F, Longer E. Carbamazepine and its epoxide: an open study of efficacy and side effects after carbamazepine dose increment in refractory partial epilepsy. Ther Drug Monit, 1994; 16: 537-40.

19. Winnicka RI, Topaciński B, Czymczak WM, Szymańska B. Carbamazepine poisoning, elimination kinetics and quantitative relationship with carbamazepine-10,11-epoxide. J Toxicol Clin Toxicol, 2002; 406: 759-65.

20. Jędrzejczak J, Dławichowska E, Owczarek K, Majkowski J. Effect of vigabatrin addition on carbamazepine blood serum levels in patients with epilepsy. Epilepsy Res, 2000; 39: 115-20.

21. Sanchez-Alcaraz A, Quintana B, Lopez E, Rodrigeuz J, Llopis P. Effect of vigabatrin on the pharmacokinetics of carbamazepine. J Clin Pharm Ther, 2002; 27: 427-30.

22. Sisodiya SM, Sander JW, Patsalos PN. Carbamazepine toxicity during combination therapy with leviteracetam: a pharmacodynamic interaction. Epillepsy Res, 2002; 48: 217-9.

23. Sachdeo RC, Sachdeo SK, Walker SA, Kramer LD, Nayak RK, Doose DR. Steady-state pharmacokinetics of topiramate and carbamazepine in patients with epilepsy during monotherapy and concomitant therapy. Epilepsia, 1996; 37: 774-80.

24. Świąder M, Kotowski J. Interaction of topiramate with conventional antiepileptic drugs in mice. Eur J Pharmacol, 2000; 399: 35-41.

25. Bialer M, Johannessen SI, Kupferberg MJ, Levy RH, Loiseau P, Perucca E. Progress report on new antiepileptic drugs: a summary of the Sixth Eilat Conference (EILAT VI). Epilepsy Res. 2002; 5: 31-71.

26. McKee PJW, Blacklaw J, Forrrest G, Gillham RA, Walker SM, Connelly D, Brodie MJ. A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients. Brit J Clin Pharmacol, 1995; 37: 27-32.

27. Perucca E. The clinical pharmacokinetics of the new antiepileptic drugs. Epilepsia, 1999; 40: 7-13.

28. Taylor WJ, Caviness MHD. A textbook for the clinical application of therapeutic drug monitoring. Abbott Laboratories, Diagnostic Division, Iriving, 1986.

29. Arroyo S, Sander WAS. Carbamazepine in comparative trials. Pharmacokinetic characteristics too often forgotten. Neurology, 1999; 53: 1170-4.

30. Battino D, Estienne M, Avanzini G. Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part II. Phenytoin, carbamazepine, sulthiame, lamotrigine, vigabatrin, oxcarbazepine and felbamate. Clin Pharmacokinet, 1995; 29: 341-69.

31. Cloyd JC, Remmel RR. Antiepileptic drug pharamacokinetics and interactions: imapact on treatment of epilepsy. Pharmacotherapy, 2000; 20: 139-51.

32. Warner T, Patsalos PN, Prevett M, Elyas AA, Duncan JS. Lamotrigine-induced carbamazepine toxicity: an interaction with carbamazepine-10,11-epoxide. Epilepsy Res, 1992; 11: 147-50.

33. Eriksson AS, Hoppu K, Nergarhd A, Boreus L. Pharmacokinetic interaction between lamotrigine and other antiepileptic drugs in children with intractable epilepsy. Epilepsia, 1996; 37, Suppl. 3: 769-73.

34. Gidal BE, Rutecki PR, Shaw R, Maly MM, Pitterle ME. Effect of lamotrigine/carbamazepine serum concentration ratios in adult patients with epilepsy. Epilepsy Res, 1997; 283: 207-11.

35. Yuen AWC. Lamotrigine. Interactions with other drugs. In: Antiepileptic Drugs. Eds. Levy RH, Mattson RH, Meldrum BS. Raven Press, New York, 1995.

36. Spina E, Pisani F, Perucca E. Clinically significant pharmacokinetic drug interactions with carbamazepine. An update. Clin Pharmacokinet, 1996; 313: 198-214.

37. Malminiemi K, Keranen T, Kerttula T, Mailanen E, Yliato P. Effects of short-term lamotrigine treatment on pharmacokinetics of carbamazepine. Int J Clin Pharmacol, 2000; 3811: 540-5.

38. Anderson G, Gidal BE, Messenheimer IA, Gilliam FG. Time course of lamotrigine deinduction, impact of step-wise withdrawal of carbamazepine or phenytoin. Epilepsy Res, 2002; 493: 211-7.

39. Mikaeloff Y, de Saint-Martin A, Mancini J, Peudenier S, Pedespan JM, Vallee L, Motte J, Bourgeois M, Arzimanoglou A, Dulac, O, Chiron O. Topiramate: efficacy and tolerbility in children according to epilepsy syndromes. Epilepsy Res, 2003; 53: 225-32.

40. Towne AR, Garnett LK, Waterhouse EJ, Motron LD, DeLorenzo RJ. The use of topiramate in refractory status epilepticus. Neurology, 2003; 60: 332-4.

41. Mack CJ, Kuc S, Mulicrone SA, Pilley A, Grunewald RA. Interaction of topiramate with carbamazepine: two case reports and a review of clinical experience. Seizure, 2002; 11: 464-7.

42. Mikati MA, Lepejian GA, Holmes GL. Medical treatment of patients with infantile spasm. Clin Neuropharmacol, 2002; 252: 61-70.

43. Kalviainen R, Nousiainen I, Mantyjarvi M, Nikoskelainen E, Partanen K, Riekkienen P Sr. Vigabatrin, a GABAergic antiepileptic drug, causes concentric visual field defects. Neurology, 1999; 53: 922-6.

44. Appelton R, Gibbs J. Epilepsy in childhood and adolescence, Martin Dunitz Ltd, 1998.

45. Spina E, Perucca E. Clinical siginficance of pharmacokinetic interaction between antiepileptic and psychotropic drugs. Epilepsia, 2002; 43: Suppl. 2: 37-44.

46. Liu H, Delgado MR. The influence of polytherapy on the relationships between serum carbamazepine and its metabolites in epileptic children. Epilepsy Res, 1994; 17: 257-69.

47. Marson AG, Williamson PR, Clough H, Hutton JL, Chadwick DW. Carbamazepine versus valproate monotherapy for epilepsy, a meta-analysis. Epilepsia, 2002; 435: 505-13.

48. Ketter TA, Pazzaglia PJ, Post RM. Synergy of carbamazepine and valproic acid in affective illness: case report and review of the literature. J Clin Pharmacol, 1992; 12: 276-81.

49. Froscher W. Clinical experience with synergistic and additive effects of antiepileptic drugs in epileptic patients new developments. Epileptologia, 2000; 83: 221-7.

50. McKee PJW, Blacklaw J, Butler E, Gillham RA, Brodie MJ. Variability and clinical revalence of the interaction between sodium valproate and carbamazepine in epileptic patients. Epilepsy Res, 1992; 11: 193-8.

51. Rambeck B, Salke-Treumann A, May T, Boenigk HE. Valproic acid-induced carbamazepine-10,11-epoxide toxicity in children and adolescents. Eur Neurol, 1990; 30: 79-83.

52. Liu H, Delgado MR. Improved therapeutic monitoring of drug interactions in epileptic children using carbamazepine polytherapy. Ther Drug Monit, 1994; 162: 132-8.

53. Riva R, Albani F, et al. Pharmacokinetic interaction between antiepileptic drugs. Clinical consideration. Clin Pharmacokinet, 1996; 316: 470-93.

54. Svinarov DA, Pippenger CE. Relationships between carbamazepine-diol, carbamazepine-epoxide, and carbamazepine total and free steady-state concentrations in epileptic patients. The influence of age, sex, and comedication. Ther Drug Monit, 1996; 8: 660-5.