The effect of valproic acid on plasma level of carbamazepine and carbamazepine-10, 11-epoxide in long-term treatment with slow-release drug formulations in pediatric patients: the importance of TDM

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The effect of valproic acid (VPA) on plasma level of carbamazepine (CBZ) and carbamazepine-10,11-epoxide (CBZ-E) in long-term treatment was evaluated.

Method: A total of 262 samples were obtained predose from 175 pediatric patients (< 15 years). Daily dose (PDD), dose related to bodyweight (DBW), plasma levels (PL) of CBZ, CBZ-E, CBZ level/dose ratio, CBZ-E level/dose ratio and CBZ-E/CBZ ratio, the distribution of PL according to the therapeutic range 4–9 mg/L, and seizure frequency were compared. A detailed analysis was done in 11 individuals who served as their own control.

Results (given as mean ± SD): Patients on a CBZ + VPA regimen were treated with higher daily doses: PDD 557 ± 204 vs. 400 ± 187 mg, respectively, $p < 0.001$; DBW 20.2 ± 10.5 vs. 13.5 ± 5.8 mg/kg, respectively, $p < 0.001$. The mean CBZ PL and the distribution of PL according to the therapeutic range were not different: 5.1 ± 1.4 vs. 5.3 ± 1.9 mg/L, respectively. There was 86% of therapeutic PL CBZ + VPA and 77% in monotherapy. No toxic level was found. CBZ-E PL remained unchanged in CBZ + VPA (1.2 ± 0.8 vs. 1.1 ± 0.9 mg/L, respectively) as did the CBZ-E/CBZ ratio (0.24 ± 0.12 vs. 0.22 ± 0.19, respectively).

The CBZ level/dose was decreased in CBZ + VPA: $10.3 \times 10^{-3} \pm 4.2 \times 10^{-3}$ vs. $14.9 \times 10^{-3} \pm 6.4 \times 10^{-3}$ mg×L^{-1}/mg, respectively, $p < 0.001$; so was the CBZ level/DBW: 0.31 ± 0.17 vs. 0.44 ± 0.19 mg×L^{-1}/mg×kg^{-1}, $p < 0.001$. These findings suggest an inductive effect of VPA on CBZ metabolism. Similar outcomes were found in 11 individuals who served as their own control: CBZ level/dose $10.9 \times 10^{-3} \pm 3.7 \times 10^{-3}$ vs. $15.0 \times 10^{-3} \pm 5.7 \times 10^{-3}$, respectively, $p < 0.01$; CBZ level/DBW 0.35 ± 0.10 vs. 0.40 ± 0.14, respectively, $p < 0.05$.

Dose-dependent adverse drug reactions (ataxia, headache) were reported in four individuals on CBZ monotherapy. No difference in the mean PL of CBZ or CBZ-E was found, while the CBZ-E/CBZ ratio and CBZ-E level/dose ratio were increased: $6.8 \times 10^{-3} \pm 1.6 \times 10^{-3}$ vs. $3.1 \times 10^{-3} \pm 3.6 \times 10^{-3}$, and 0.32 ± 0.06 vs. 0.21 ± 0.20, $p < 0.05$). No difference in seizure frequency was found.

Conclusion: The CBZ-VPA interaction is considerable, but it is sufficiently eliminated due to TDM dose adjustment.

Key words: carbamazepine, carbamazepine-epoxide, valproic acid, drug-drug, interaction, slow-release drug formulations.

Vliv kyseliny valproové na hladinu karbamazepinu a karbamazepin-10,11-epoxidu při dlouhodobé léčbě přípravky s pomalým uvolňováním u dětí, význam TDM

Účel studie: Hodnocení vlivu kyseliny valproové (VPA) na hladinu karbamazepinu (CBZ) a karbamazepin-10,11-epoxidu (CBZ-E) při dlouhodobé léčbě přípravky s pomalým uvolňováním.

Metoda: U 262 vzorků odebraných před podáním od 175 dětských pacientů (< 15 let) byla hodnocena celková denní dávka (PDD), dávka na kg (DBW), koncentrace CBZ, CBZ-E, poměry CBZ koncentrace/PDD, CBZ-E koncentrace/PDD, CBZ-E/CBZ a rozložení koncentrací CBZ ve vztahu k terapeutickému rozmezí 4–9 mg. Podrobná analýza byla provedena u 11 pacientů, kteří byli vlastní kontrolou.

Výsledky (uvedeny jako průměr ± směrodatná odchylka): Ačkoliv pacienti léčení CBZ + VPA užívali vyšší dávky než pacienti na monoterapii: PDD 557 ± 204 vs. 400 ± 187 mg, p < 0.001; DBW 20.2 ± 10.5 vs. 13.5 ± 5.8 mg/kg, p < 0.001, nebyl zaznamenán rozdíl v průměrné koncentraci CBZ (5.1 ± 1.4 vs. 5.3 ± 1.9 mg/l), CBZ-E (1.2 ± 0.8 vs. 1.1 ± 0.9 mg/l), poměru CBZ-E/CBZ (0.24 ± 0.12 vs. 0.22 ± 0.19) ani v rozložení koncentrací podle terapeutického rozmezí. V terapeutickém optimu bylo 86 % vs. 77 % koncentrací. Koncentrace nad horní hranicí terapeutického rozmezí se nevyskytovaly. U CBZ + VPA byly nižší poměry koncentrace CBZ/PDD: $10.3 \times 10^{-3} \pm 4.2 \times 10^{-3}$, vs. $14.9 \times 10^{-3} \pm 6.4 \times 10^{-3}$ mg × L^{-1}/mg, p < 0.001; CBZ/DBW: 0.31 ± 0.17, vs. 0.44 ± 0.19 mg × l^{-1}/mg × kg^{-1}, p < 0.001. Obdobně u 11 pacientů, kteří byli vlastní kontrolou: poměr koncentrace CBZ/PDD $10.9 \times 10^{-3} \pm 3.7 \times 10^{-3}$ vs. $15.0 \times 10^{-3} \pm 5.7 \times 10^{-3}$, p < 0.01; CBZ/DBW 0.35 ± 0.10 vs. 0.40 ± 0.14, p < 0.05. Zdá se, že VPA má indukční efekt na metabolismus CBZ. Na dávce závislé nežádoucí účinky (ataxie, bolest hlavy) byly popsány u 4 pacientů na monoterapii. Koncentrace CBZ a CBZ-E se nelišila od pacientů bez NÚL, byl však vyšší poměr CBZ-E/CBZ $6.8 \times 10^{-3} \pm 1.6 \times 10^{-3}$ vs. $3.1 \times 10^{-3} \pm 3.6 \times 10^{-3}$, a CBZ-E/PDD 0.32 ± 0.06 vs. 0.21 ± 0.20, p < 0.05.

Závěr: Významná interakce mezi CBZ a VPA byla úspěšně eliminována úpravou dávkování pomocí TDM.

Klíčová slova: karbamazepin, karbamazepin-epoxid, kyselina valproová, interakce, léčivé přípravky s pomalým uvolňováním.

Introduction

Carbamazepine (CBZ) and valproic acid (VPA) are the drugs of choice in the treatment of epilepsy. Their concomitant administration is quite common (1–3).

CBZ is extensively metabolized in the liver, primarily by CYP 3A4, to active carbamazepine-10,11-epoxide (CBZ-E) (4, 5) whereas CYP2C8 is a minor pathway (5). CBZ-E is further metabolized by epoxide-hydrolase to inactive 10,11-dihydro-carbamazepine (carbamazepine-diol), which is consequently conjugated with glucuronic acid by uridine diphosphate glucuronosyltransferase (UGT) (4, 5). In long-term treated patients, 30–50% of carbamazepine-diol is excreted directly into urine (5).

Even though CBZ and VPA have been in use since the 1960s (1, 6), there is no consensus regarding the clinical relevance of VPA effects on carbamazepine metabolism (5), with both increases and decreases in the CBZ level having been observed (7). Carbamazepine-10,11-epoxide level was reported to be increased with concurrent use of valproate (3, 5, 7, 8).

CBZ is known as an inducer of cytochrome CYP3A4, CYP2C and epoxide hydrolase (9), and its own metabolism is susceptible to autoinduction after repeated administration (2, 7, 8). The autoinduction is reported to be finished after one month of drug administration (5). CBZ-E also induces its own metabolism in a way similar to CBZ (10). VPA is an inhibitor of epoxide hydrolase (1, 9, 11) and nonspecifically inhibits all steps of the epoxide-diol pathway of CBZ metabolism in children (12). Significant positive correlations have been found between the VPA level and CBZ-E/CBZ ratio, as well as the CBZ level/dose ratio in children (13).

The aim was to study the effect of valproic acid on carbamazepine concentration during long-term treatment in pediatric epileptic patients.

Material and method

Request and reply forms for therapeutic drug monitoring of antiepileptic drugs examined during the period 1997–2002 were used as a data source. A total of 262 of samples taken predose obtained from 175 pediatric patients (i. e., younger than 15 years) were included. The characteristic of the cohort is given in Table 1. Eleven patients treated with both CBZ monotherapy and CBZ + VPA were included in both groups. These 11 patients who served as their own control were also analyzed in detail.

Inclusion criteria: Long-term treatment with slow-release forms of carbamazepine (Timonil, Tegretol, Neurotop) or valproic acid (Depakine, Orfiril, Convulex).

Exclusion criteria: Suspected non-compliance (i. e., a plasma level of CBZ < 1 mg/L and of VPA < 10 mg/L), once daily treatment regimen. Patients treated with other drugs were excluded with an exception of magnesium, nootropics (piracetam, pyritinol), and vitamins.

Dosage (absolute daily dose, dose related to body weight), plasma levels of CBZ, CBZ-E, CBZ level/dose ratio, CBZ-E level/dose ratio, CBZ-E/CBZ, and CBZ + CBZ-E were evaluated. The distribution of plasma levels according to the therapeutic range 4–9 mg/L and the incidence of adverse drug reactions, such as nystagmus, dizziness, bradypsychia, ataxia, headache, and nausea, were analyzed.

The frequency of seizures was divided into four categories: occurrence of seizures daily, monthly, several seizures per year, and being seizure-free more than one year. Statistics were calculated from answered questions only.

All samples were included in patients examined repeatedly, while means per patient were used in a detailed analysis of 11 individuals who served as their own control.

Analysis of plasma levels

CBZ and CBZ-E plasma levels were determined using high-performance liquid chromatography (HPLC) (14). Plasma levels of VPA were assayed with gas-liquid chromatography (GLC) (15). Both methods were fully validated and participated in external quality control schemes – RfB Referenzinstitut für Bioanalytik.

Statistics

Differences between means were compared using the Student's t-test (two-tailed). The Chi-square test was used to analyze the distribution of plasma levels according to the therapeutic range (16) and for seizure frequency (17).

Results

The patients on the CBZ + VPA regimen were treated with significantly higher daily doses (absolute as well as related to the body weight) while mean plasma levels of CBZ and CBZ-E were not different (Table 2). The dose of valproic acid was (mean ± SD) 691 ± 218 mg, DBW was 25.15 ± 11.83 mg.kg^{-1}, and VPA level was 52.57 ± 17.25 mg.L^{-1}.

PŮVODNÍ PRÁCE ›

THE EFFECT OF VALPROIC ACID ON PLASMA LEVEL OF CARBAMAZEPINE AND CARBAMAZEPINE-10, 11-EPOXIDE IN LONG-TERM TREATMENT
WITH SLOW-RELEASE DRUG FORMULATIONS IN PEDIATRIC PATIENTS; THE IMPORTANCE OF TDM

The concentration ratio of CBZ-E/CBZ was unchanged. The CBZ level/dose ratio as well as CBZ-E level/dose ratio were lower in patients on the CBZ+VPA regimen (Table 3). This suggests an increased clearance of CBZ and CBZ-E.

The distribution according to the therapeutic range was similar in both regimens. No level was found above the older upper margin, i. e., 12 mg/L. When the CBZ + CBZ-E level was counted together, 6 (3%) levels above 12 mg/L in CBZ monotherapy were found (Table 4). Generally, CBZ levels tended to target concentrations at the lower end of the therapeutic range (Fig. 1).

Adverse drug reactions were found in four individuals on CBZ monotherapy (Table 5). No difference in mean CBZ or CBZ-E levels was found when compared with patients without toxic events, while the CBZ-E/CBZ ratio and CBZ-E level/dose ratio were increased ($6.82 \times 10^{-3} \pm 1.61 \times 10^{-3}$ vs. $3.14 \times 10^{-3} \pm 3.62 \times 10^{-3}$, and 0.321 ± 0.061 vs. 0.214 ± 0.197, $p < 0.05$).

Information on seizure frequency was given in 148 request forms (56%). The difference between CBZ and CBZ+VPA was not significant (Table 6).

Analysis of 11 patients who served as their own control

The cohort characteristic and dosage of CBZ in 11 patients that served as their own control is given in Table 7. The VPA dosage and plasma levels are given in Table 8. Six patients only reached the therapeutic range 50–100 mg/L.

Patients treated with CBZ+VPA received significantly higher daily doses, while CBZ levels, CBZ-E levels, and CBZ-E/CBZ ratios were not different. All levels reached the therapeutic range 4–9 mg/L in monotherapy, while two dropped below when VPA was added (Table 9). A significantly lower mean CBZ level/dose ratio as well as mean CBZ level/DBW ratio were found in the CBZ+VPA group (Table 1). No adverse drug reactions were reported in this cohort.

Discussion

The CBZ plasma level and the distribution of plasma levels according to the therapeutic range were similar in both regimens. The lack of an effect of VPA on plasma level of CBZ is apparent at first sight. However, these findings are a result of significantly higher daily doses as well as DBW in the CBZ+VPA group. The CBZ level/dose ratio was significantly decreased in CBZ + VPA in the whole cohort as well as in 11 patients who served as their own control. This reflects increased CBZ clearance. Similar findings were described by Levy et al (18) in a cohort of seven patients (both children and adults), by Liu et al (13) in children, and by Rambeck et al (19) in adults. Shoeman et al (20) also found a decreased CBZ level which, however, was not significant. By contrast, Svinarov et al (12) found an increased CBZ level/dose ratio in CBZ + VPA in children, but a decreased ratio in adults two months after treatment initiation. Potter et al (3) reported similar mean CBZ concentrations in both CBZ and CBZ + VPA groups, but information on the dosage is lacking. Bernus et al (21) reviewed five studies with no appreciable change in the CBZ plasma level.

Tab. 1. *The characteristic of the cohort*

	CBZ alone	CBZ+VPA
number of patients	143	32
number of samples	209	53
age [yr][†]	8.8 ± 3.2	10.0 ± 2.6**
weight [kg][†]	32.2 ± 13.6	30.7 ± 11.1

[†]*values are given as mean ± SD, ** p < 0.01*

Tab. 2. *The dosage and plasma levels of carbamazepine and carbamazepine-10,11-epoxide*

	CBZ	CBZ+VPA	difference
dose [mg]	400 ± 187	557 ± 204	39% ***
dose related to body weight [mg/kg]	13.5 ± 5.8	20.2 ± 10.5	50% ***
CBZ level [mg/L]	5.3 ± 1.9	5.1 ± 1.4	−3%
CBZ-E level [mg/L]	1.1 ± 0.9	1.2 ± 0.8	10%
CBZ-E/CBZ	0.22 ± 0.19	0.24 ± 0.12	12%
CBZ+CBZ-E [mg/L]	6.3 ± 2.3	6.3 ± 1.6	−1%

*The values are given as mean ± SD, *** p < 0.0001; ** p < 0.01*

Tab. 3. *Level/dose ratios of carbamazepine and carbamazepine-10,11-epoxide*

	CBZ	CBZ+VPA	difference
CBZ level/dose [mg × L⁻¹/mg]	$14.9 \times 10^{-3} \pm 6.4 \times 10^{-3}$	$10.3 \times 10^{-3} \pm 4.2 \times 10^{-3}$	−31%***
CBZ level/DBW [mg × L⁻¹/mg × kg⁻¹]	0.44 ± 0.19	0.31 ± 0.17	−29%***
CBZ-E level/dose [mg × L⁻¹/mg]	$3.2 \times 10^{-3} \pm 3.6 \times 10^{-3}$	$2.4 \times 10^{-3} \pm 1.5 \times 10^{-3}$	−24%*
CBZ-E level/DBW [mg × L⁻¹/mg × kg⁻¹]	$90.1 \times 10^{-3} \pm 90.3 \times 10^{-3}$	$72.8 \times 10^{-3} \pm 52.0 \times 10^{-3}$	−19%

*The values are given as mean ± SD; *** p < 0.0001; * p < 0.05, DBW – dose related to body weight*

Tab. 4. *The distribution of CBZ concentrations related to therapeutic range (TR) 4–9 mg/L*

	regimen		plasma level			
		0–3.9	4–9	>9	> 12 mg/L
CBZ level	CBZ	49 (23%)	153 (73%)	7 (3%)	0
	CBZ + VPA	10 (19%)	43 (81%)		
CBZ+CBZ-E level	CBZ	24 (11%)	157 (75%)	28 (13%)	6 (3%)
	CBZ + VPA	4 (7.5%)	49 (92.5%)		

Tab. 5. *The type of adverse drug reaction in relation with CBZ and CBZ-E levels and their ratios in order to CBZ level*

Patient No.	CBZ level	CBZ-E level	CBZ-E/CBZ	CBZ + CBZ-E	adverse drug reaction
1	2.8	1.0	0.357	3.8	headache
2	5.1	1.3	0.255	6.4	ataxia
3	8.1	2.3	0.284	10.4	ataxia
4	10.1	3.9	0.386	14	ataxia

Tab. 6. *Seizure frequency*

	NR/total	daily	monthly	yearly	none
CBZ	90/209	10 (8%)	37 (31%)	51 (43%)	10 (18%)
CBZ + VPA	24/53	5 (21%)	9 (31%)	12 (41%)	5 (7%)

NR not reported. Percentages are calculated from answered questionnaires only.

Tab. 7. *The cohort characteristics of 11 patients treated with both CBZ and CBZ+VPA*

No.	gender	age [yr]	body weight [kg]	CBZ dose [mg]		CBZ DBW [mg/kg]	
				CBZ	CBZ + VPA	CBZ	CBZ + VPA
1	F	9	26	200	200	7.69	7.69
2	M	5	23	288	500	14.32	17.45
3	F	10	33	300	375	9.68	10.97
4	F	7	27	325	375	13.18	11.36
5	F	8	27	375	675	18.75	22.27
6	M	11	31	375	600	13.06	17.71
7	F	7	20	412	375	20.09	19.74
8	M	10	43	488	638	11.72	14.56
9	M	10	30	525	525	18.10	17.50
10	M	12	50	525	750	10.71	15.00
11	M	10	24	600	700	31.58	25.83
mean ± SD		9 ± 2	30 ± 8	401 ± 122	519 ± 172**	15.4 ± 6.6	16.4 ± 5.2**

**p < 0.01, DBW – dose related to body weight

Tab. 8. *The dosage and plasma levels of valproic acid*

No.	dose [mg]	DBW [mg/kg]	plasma level [mg/L]
1	75	2.9	33.0
2	750	26.7	57.5
3	525	15.4	57.2
4	500	15.2	42.7
5	750	25.0	68.8
6	750	21.9	46.6
7	500	26.3	40.0
8	438	9.9	39.8
9	250	8.3	39.1
10	500	10.0	36.0
11	600	22.5	35.8
mean ± SD	513 ± 211	16.7 ± 8.2	45.1 ± 11.3

DBW – dose related to body weight

Tab. 9. *Plasma levels of carbamazepine, carbamazepine-10,11-epoxide and CBZ-E/CBZ ratio in 11 patients treated with both CBZ and CBZ + VPA*

No	CBZ level [mg/L]		CBZ-E level [mg/L]		CBZ-E/CBZ	
	CBZ	CBZ + VPA	CBZ	CBZ + VPA	CBZ	CBZ + VPA
1	5.2	3.8	0.6	0.4	0.12	0.11
2	6.0	4.6	1.18	0.8	0.19	0.19
3	4.7	5.1	0.9	0.7	0.19	0.14
4	4.6	2.4	0.7	1.1	0.15	0.46
5	6.5	6.5	1.6	1.8	0.25	0.28
6	4.8	5.0	0.25	1.1	0.05	0.21
7	4.4	5.0	1.4	2.3	0.32	0.46
8	5.7	6.6	1.15	1.7	0.20	0.28
9	8.6	6.7	0.9	1.1	0.10	0.16
10	4.0	4.6	0.8	0.8	0.20	0.17
11	5.3	5.6	1.7	0.8	0.32	0.14
mean ± SD	5.4 ± 1.3	5.1 ± 1.2	1.0 ± 0.4	1.1 ± 0.6	0.19 ± 0.08	0.24 ± 0.12

Liu et al (13) also mentioned a significant decrease in the CBZ level/dose ratio in the presence of VPA.

An increase in the CBZ-E level and CBZ-E/CBZ ratio in CBZ + VPA reported by Liu et al (13) and Potter et al (3) was not observed in our study.

Liu et al further described a CBZ-E/dose increase while we found a significant decrea-se. The effect of a different drug formulation is questionable.

Two steps of CBZ-VPA interaction might explain the conflicting reports: initially, the CBZ level rose because of either enzymatic inhibition or protein binding displacement due to VPA, followed by enzymatic induction due to CBZ. Enzymatic inhibition is generally caused by competition at the en-zyme site (2) and occurs immediately after treatment initiation, while enzymatic induction requires the synthesis of a new protein, which may take several days or weeks (13). This mechanism is supported by the finding of Liu et al (13) who found a significant decrease in the CBZ level/dose ratio in CBZ+VPA and together positive correlation between this ratio and VPA level. They also described a significantly increased CBZ free fraction as a result of relatively decreased total CBZ level with almost unchanged free CBZ concentration. An increase in the free fraction described by Levy et al (18) was also suggested as a reason for CBZ level decrease in the presence of VPA.

A third mechanism involved may be incomplete absorption described in high doses of CBZ (10) which might be deepened with lower bioavailability of retard tablets, that we found in our previous study (22). Lower bioavailability might also explain the lower CBZ level/dose ratio when compared with the observation by Liu et al (13).

Similarly to us, Potter et al (3) pointed out that clinicians tended to target concentrations at the lower end of the therapeutic range.

When therapeutic drug monitoring is performed, the dose of CBZ is stepwise increased according to the TDM outcomes, similar CBZ levels are reached, and the clinical effect of the interaction is thus eliminated.

The TDM outcomes must be interpreted in relation with dosage, otherwise incorrect conclusions might be drawn.

Limitations: Non-adherence of physicians to some questions on the request forms (mentioned also by Morris et al. (23), especially those regarding seizure frequency or occurrence of ADRs, represents a difficulty for data evaluation. In the case of ADRs, we cannot distinguish whether they were not reported because they did not occur or because of simple non-adherence. Considering this fact, we decided to show the percentage of the incidence of ADRs from the whole group.

Potential under-reporting of ADRs or inaccuracies regarding seizure frequency on the request form are inherent to the retrospective and pragmatic nature of this study.

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Tab. 10. *Level/dose ratios of carbamazepine and carbamazepine-10,11-epoxide in 11 patients treated with both CBZ and CBZ + VPA*

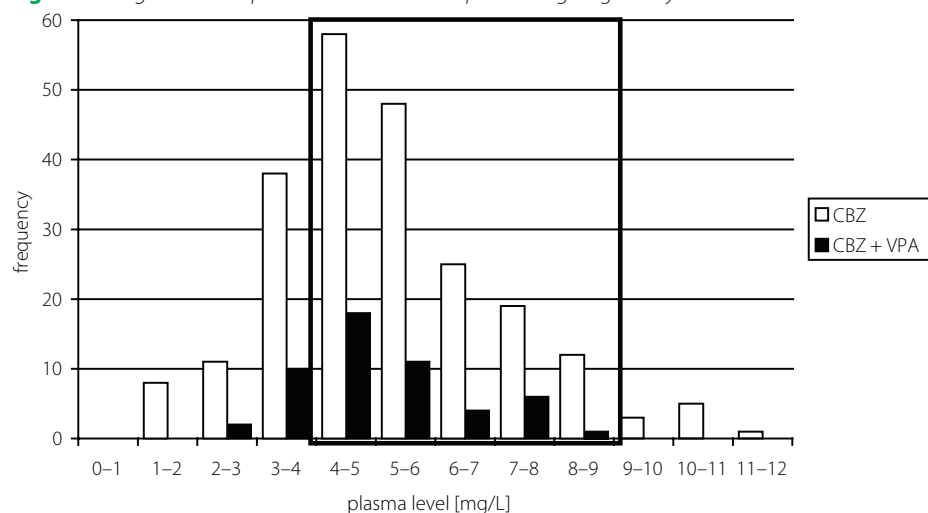| No	CBZ level/dose [mg × L⁻¹/mg]		CBZ-E level/dose [mg × L⁻¹/mg]		CBZ level/DBW [mg × L⁻¹/mg × kg⁻¹]		CBZ-E level/DBW [mg × L⁻¹/mg × kg⁻¹]	
	CBZ	CBZ + VPA	CBZ	CBZ + VPA	CBZ	CBZ + VPA	CBZ	CBZ + VPA
1	26.0×10^{-3}	19.0×10^{-3}	30×10^{-3}	2.0×10^{-3}	0.676	0.494	78.0×10^{-3}	52.0×10^{-3}
2	23.4×10^{-3}	10.7×10^{-3}	48×10^{-3}	1.8×10^{-3}	0.430	0.298	81.8×10^{-3}	48.8×10^{-3}
3	15.7×10^{-3}	13.3×10^{-3}	30×10^{-3}	1.8×10^{-3}	0.486	0.454	93.0×10^{-3}	61.8×10^{-3}
4	14.5×10^{-3}	6.4×10^{-3}	21×10^{-3}	2.9×10^{-3}	0.352	0.211	51.9×10^{-3}	96.8×10^{-3}
5	17.3×10^{-3}	10.8×10^{-3}	43×10^{-3}	2.9×10^{-3}	0.347	0.321	85.3×10^{-3}	87.5×10^{-3}
6	12.9×10^{-3}	8.3×10^{-3}	07×10^{-3}	1.8×10^{-3}	0.367	0.287	20.2×10^{-3}	60.3×10^{-3}
7	10.4×10^{-3}	13.3×10^{-3}	34×10^{-3}	6.1×10^{-3}	0.215	0.253	69.3×10^{-3}	116.5×10^{-3}
8	11.6×10^{-3}	10.3×10^{-3}	23×10^{-3}	2.6×10^{-3}	0.484	0.458	96.2×10^{-3}	114.7×10^{-3}
9	16.4×10^{-3}	12.8×10^{-3}	17×10^{-3}	2.1×10^{-3}	0.475	0.383	49.7×10^{-3}	62.9×10^{-3}
10	7.6×10^{-3}	6.1×10^{-3}	15×10^{-3}	1.1×10^{-3}	0.373	0.307	74.7×10^{-3}	53.3×10^{-3}
11	8.8×10^{-3}	8.3×10^{-3}	28×10^{-3}	1.1×10^{-3}	0.168	0.217	53.8×10^{-3}	29.1×10^{-3}
mean ± SD	$15.0 \times 10^{-3} \pm 5.7 \times 10^{-3}$	$10.9 \times 10^{-3} \pm 3.7 \times 10^{-3}$**	$27 \times 10^{-3} \pm 12 \times 10^{-3}$	$2.4 \times 10^{-3} \pm 1.4 \times 10^{-3}$	0.397 ± 0.139	0.345 ± 0.099*	$68.5 \times 10^{-3} \pm 22.7 \times 10^{-3}$	$71.3 \times 10^{-3} \pm 28.5 \times 10^{-3}$

*DBW – dose related to body weight, ** p < 0.01, * p < 0.05*

Conclusion

The CBZ-VPA interaction is complicated, both increase and decrease in the CBZ level might occur. When therapeutic drug monitoring is performed, the dose of CBZ is balanced according to the TDM outcomes, similar CBZ levels are reached, and the clinical effect of the interaction is eliminated. It is important to interpret TDM outcomes in relation with dosage and concomitant therapy. Due to a CBZ level balance, the incidence of adverse drug reactions remained unchanged in CBZ + VPA.

Fig. 1. *Histogram of CBZ plasma levels. The therapeutic range is given by box*

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