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Therapeutic Drug Monitoring of Antiepileptic Drugs in Real Clinical Practice in Russia

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Abstract

Introduction: *Anticonvulsants refer to drugs with interindividual variability of plasma concentrations and clinical efficacy. Therapeutic drug monitoring (TDM) is an important tool for optimizing pharmacotherapy with anticonvulsants in real clinical practice. The aim of the study was to analyze the results of TDM of valproates (VPA) and carbamazepine (CBZ) in epilepsy adults in clinical practice in Russia.*

Methods: *observation study in 800 epilepsy adults (mean age 35.5±0.5) the rate of achievement the therapeutic concentrations (TC) of VPA and CBZ in different drug forms using high performance liquid chromatography; range of TC for VPA 50-150 mg/l, for CBZ 4-12 mg/l.*

Results: *The frequency of achievement TC on VPA was 66.4% in average dose – 1325.1±29.6 mg/day with no difference between sustain-released and immediate-released drug forms. Gender differences of VPA concentrations were identified: women mean Cmin and Cmax were higher than in men with significantly lower daily dose. The frequency of sub-TC VPA was 16.3% and over-TC – 1% (Cmax 164.2±2.4mg/l); the toxic concentration for CNS (175 mg/l) was not achieved. In VPA doses<500mg/day there was no patients with TC; in 1001–1500 mg/day TC have 75%, in doses 1501–2000mg/day – 97%; in >2000 mg/day – 86% and there was high risk of over-TC (4%). The frequency of achievement TC range VPA monotherapy was 2 times more than in combination VPA+CBZ (67% versus 34%). The frequency of achievement TC range on CBZ was 78.6%, the average daily dose was 922.2±23.0 mg/day with significantly higher rate of TC range achievement when using sustain-release forms of CBZ. The frequency of sub-TC CBZ was 6.3%, over-TC – 1.25%. In patients with over-TC mean dose was 1250 mg/day, Cmin 13.5±0.2mg/l, Cmax 15.1±0.7mg/l. At initial doses<600 mg/day 64.3% patients have TC; in doses>600 mg/day – 87%. In daily doses 600-1200 mg and >1200 mg 1.3% and 4.1% patients have over-TC by both Cmin and Cmax, only by Cmax – 8.8% and 18.4%, respectively.*

Conclusion: *the frequency of TC on VPA and CBZ is high with rare cases of over-TC, but there was problem of paradox low concentrations in single cases. CBZ have less predictable concentrations in therapeutic doses range than VPA.*

Keywords: Therapeutic Concentration Range, Carbamazepine, Valproic Acid, Epilepsy.

Introduction

Therapeutic drug monitoring (TDM), or measuring drug concentration in serum or plasma (or other body liquids), serves to increase the clinical efficacy of pharmacotherapy and to prevent toxicity. Today TDM is an actual tool for pharmacotherapy individualization. There are some reasons for carrying TDM in clinical practice: wide inter-patient variability in pharmacokinetics of drugs, a close correlation between the concentration and toxic effects, or a narrow therapeutic range of drugs, and the availability of affordable and validated method for concentration evaluation. These reasons are present when using antiepileptic drugs (AEDs). More than 30 years TDM is used to manage the efficacy and safety of AEDs: original guidance for applying TDM were developed in different countries but in 2008 international guidance was adopted by International League Against Epilepsy [1-3]. They level of evidence for TDM of AEDs was defined category 2 (recommended for therapy optimization).

Two drugs are the most widely used and have proven efficacy in treatment for various clinical forms of epilepsy in children and adults: carbamazepine (CBZ) and valproic acid (VPA). Both drugs characterized by narrow therapeutic range and high

inter-patients variability of serum concentration. The feature of CBZ pharmacokinetics is auto induction of metabolism during prolonged use (mainly by cytochrome P450), which can modify its efficiency and requires TDM. VPA has a concentration-dependent pharmacokinetics, due to bound to serum proteins and clearance. For example, VPA has a high bound to serum proteins (87-95%) and characterized by saturation kinetics after binding to protein when the concentration is 100 mg/l; further increasing of VPA dose may lead to rapid and unpredictable growth of VPA free fraction. VPA clearance is slow (6-20 ml/hr/kg), it is carried out in several metabolic ways in liver (50% glucuronization, 40% β-oxidation, 10% - with cytochrome P450), and it is also dependent on dose and concentration; moreover, VPA inhibits the metabolism of many hepatic enzymes, including metabolism auto inhibition [4-6]. It is recommended to control the concentration of VPA in first 6 months of the therapy.

Indications for TDM of AEDs are the following [3,7]:

- Suspicion of toxicity or adverse drug reactions (ADRs);
- Suspected low compliance of patients;
- At the beginning of the treatment before achieving steady state (first 72-96 hours);
- While achieving steady state (after 5T½);
- Long-term treatment with good efficiency - 1 per year for adults and 1 every 6 months in children, as well as 1 every 3 months when modifying pharmacotherapy, or when suspiciondrug interactions and changes in the pharmacokinetics of drugs (hepatic or gastrointestinal diseases, pregnancy and so on) of interest is to study AEDs concentrations in real clinical practice of epileptic patient's treatment.

Methods

The design was an observation study of TDM of AEDs in real clinical practice in Russian population. The material of the study was TDM data of epileptic adult patients, conducted in pharmacokinetic laboratory at Clinical pharmacology Department of Russian National Research Medical University named after N.I. Pirogov for the period 2009-2016. TDM data of 800 patients were included in the analysis, of which 295 VPA treated patients, 319 CBZ treated patients and 186 patients with VPA+CBZ combination. VPA was represented by 9 tradenames, 85% of them were sustain-release formulations. CBZ was represented by 5 tradenames, 65% of which were sustain-release formulations. General characteristics of patients presented in (Table 1).

Characteristics of patients	VPA (n=295)	CBZ (n=319)
Mean age (years)	31,2±0,62	39,4±0,77
Range of age (years)	18 - 70	18 - 80
Men/Women	139 / 156	154 / 164
The range of daily doses (mg)	300 - 3000	150 - 2000
The number of patients with monotherapy	165	224
The number of patients treated with combined therapy (non-CBZ):	130	95
- combination of 2 AEDs	- 101	- 66
- combination of 3 AEDs	- 24	- 26
- combination of 4 AEDs	- 5	- 3
The number of patients treated with combination VPA+CBZ	187	

Concentrations of CBZ and VPA were measured using high performance liquid chromatography (HPLC) [8]. Were studied two blood samples at steady state: before taking usual dose of the drug (Cmin), and 2-5 hours after taking usual dose (Cmax)? The therapeutic concentrations (TC) range of VPA considered 50-150 mg/l concentration above 175 mg/l is toxic for CNS4. The TC range of CBZ considered within 4-12 mg/l for all patients the concentration above 15 mg/l was toxic. Mean TC were calculated in M±m; Cmax/Cmin ratio was calculated for assessing the degree of concentration fluctuations; significant differences in p-value [8].

Results TDM for VPA

The analysis of VPA concentrations in the whole group of patients showed, that 66.4% achieved Cmin and Cmax in TC range with an average daily dose of 1201.4 mg. Frequency of achieving TC range in Cmax level was higher - 82.7% (Table 2). The range of VPA daily dose needs to achieve TC range was 600-3000 mg: dose of 600-750 mg/day was used only in 9 patients (4.5%); doses above 2000 mg/day, which exceed the average therapeutic dose - in 20 patients (10%); 2 women used dose of 3000 mg/day.

Table 2: Compare dosages and concentrations in VPA treated patients

Groups of patients	Mean daily dose (mg)	Range of daily doses (mg)	Cmin (mg/l)	Cmax (mg/l)	Cmax/Cmin ratio
All patients	1201,4±25,3	300-3000	61,6±1,4	76,3±1,7	1,20±0,03
Patients achieved TC range (n=196)	1325,1±29,6	600-3000	73,7±1,2	89,1±1,6	1,22±0,01
Patients not achieved TC range (n=48)	819,8±49,5	300-1500	28,2±1,5	35,0±1,6	1,44±0,15
Patients with over-TC range (n=3)	1800±300	1500-2400	109,6±15,1	164,2±2,4	1,55±0,21

Some gender differences of VPA concentrations were identified. Thus, in women mean daily dose were significantly lower than in men (1156.4 versus 1252.2 mg/day, p<0, 05), but mean Cmin and Cmax were higher in women: 63.1 versus 59.9 mg/l and 78.5 versus 73.8 mg/l, respectively (p>0, 05). As a result, the frequency of achieving TC range in women was also higher than in men - 69% versus 63.3%, respectively.

VPA level of TC range achieving was not dependent on drug formulations. Thus, using sustain-released formulations of VPA showed the same level of TC range achievement, as immediate-release drug forms, although there was a trend toward a higher frequency of Cmin and Cmax achieving in the TC range with sustain-released formulations, that particularly important for the residual concentration. Analysis of the TDM of VPA in monotherapy and in combination with CBZ showed that the mean values of Cmin and Cmax in the therapeutic range were 2 times more frequent than in the combination VPA+CBZ (67% versus 34%, p<0.01) (Table 3). There was no any influence on doses, Cmin and Cmax of VPA in combination with other AEDs that showed stability of VPA pharmacokinetics and the absence of pharmacokinetic drug-drug interactions with other non-CBZ AEDs.

Table 3: Comparison dosages and concentrations in patients receiving monotherapy and combination VPA with CBZ or other AEDs

Groups of patients	Mean daily dose (mg)	Cmin (mg/l)	Cmax (mg/l)	Patients achieved TC (%)
Patients received monotherapy VPA (n=165)	1330,5±41,1	75,0±1,8	90,7±2,2	67%
Patients received VPA with non-CBZ AEDs (n=130)	1318,4±42,7	72,2±1,7	87,2±2,1	67%
Patients received combination VPA+CBZ (n=186)	1576,2±64,4*	66,8±2,4**	84,1±3,1**	34%*

Note: * p<0.001 and ** p<0.05 between groups of monotherapy and combined therapy.

Analysis of cases failure to achieve TC range showed that in 96 patients Cmin was 35.3 ± 1.1 mg/l and in 48 of these Cmax remained 35 ± 1.6 mg/l, which is less than the lower limit (16.3 %). Mean daily dose of VPA without providing TC range amounted 819.8 mg and was independent of the drug formulations, and the multiplicity of taking. At the same time, in 21 (43%) of 48 patients with sub-TC of VPA daily dose was within the average therapeutic (more than 1000 mg/day). It should be noted that in 3 women taking VPA in doses of 500, 1000 and 1500 mg/day as monotherapy the level of Cmax and Cmin remained extremely low - less than 11 mg/l, which may be indicative of pharmacogenetic disorders of VPA metabolism (UGT1A and CYP2C19) [5, 9, 10]. Among patients with sub-TC of VPA the rate of combined therapy was 39.6%, significantly lower than in the group achieved TC range, so the low concentration could not be explained by pharmacokinetic interactions with other AEDs.

Cases of VPA over-TC were observed in 3 (1%) women while taking doses 1500 and 2400 mg/day (Cmax reached 160, 164, and 168.6 mg/l). However, toxic concentration for CNS (above 175 mg/l) was not achieved in any case.

It is important to note that the dosage ranges for patients with over-TC and TC range coincided completely, and dosage ranges for patients with over-TC and sub-TC did not coincide at all.

TDM results were further analyzed considering the average TC doses of VPA used in clinical practice. Usually, initial drug dose do not exceed 1000 mg/day (10-15 mg/kg for adult), subsequently the dose titrated according to clinical effectiveness, so the average dose is 1000-2000 mg/day (20-30 mg/kg). Accordingly, achieving VPA TC range by using the initial dosages (less than 1000 mg/day) were indicated only in 8% of patients and the average therapeutic doses (1000-2000 mg/day) were achieved in 58%. For more detailed description TDM results in different range of VPA doses we choice five daily dosage ranges: doses less than 500 mg/day (n=18), doses 501-1000 mg/day (n=124), doses 1001-1500 mg/day (n=115), doses 1501-2000 mg/day (n=31), doses 2001 mg/day and more (n=7). At doses less than 500 mg/day, which used in 6% of patients, the VPA TC range was not achieved in any patient. In these cases, a TDM completely unnecessary, as there are low VPA concentration (Cmin=27.2±2.5 mg/l, Cmax=35.1±3.0 mg/l), even when combined therapy with other AEDs (it was used in half of these patients). The use of VPA in the dose range 501-2000 mg/day showed the best result of TC range achievement in the vast majority of patients. Moreover, even with VPA doses 501-1000 mg/day (mean 915.7 mg/day), which were used in 42% of patients, the rate of TC range achievement was 60% (mean concentrations Cmin=55.8±1.8 mg/l, Cmax=69.7±2.3 mg/l). The use of doses 1001-1500 mg/day (mean 1372.0 mg/day) provides achievement of the TC range in 75% of patients (mean concentrations Cmin=65.8±2.1 mg/l, Cmax=81.8±2.6 mg/l). At the same time, in this group in 2 women using combined therapy there was an over-TC - Cmax reached 168.5 and 164 mg/l. These cases may be due to pharmacokinetic interactions with other AEDs that are substrates for the same metabolizing hepatic enzymes and alter their activity (lamotrigine - UGT, topiramate - β-oxidation and CYP2C19) [7]. In addition, the possible cause is a pharmacogenetic variations of hepatic enzymes activity involved in VPA metabolism, that lead to over-TC even when average therapeutic dose is taken [5,9].

The highest rate of TC range achievement was showed at doses 1501-2000 mg/day (mean 1835.5 mg/day) and amounted 97% at mean concentrations Cmin=81.5±3.5 mg/l and Cmax=96.8±4.0 mg/l. In this group only one patient at VPA dose 1650 mg/day combined with lamotrigine had sub-TC range Cmin (35 mg/l), while Cmax reached 59.7 mg/l. Although higher VPA doses (more than 2000 mg/day, mean 2578.6 mg/day) associated with high rate of TC range achievement - 100% patients in this group, but it increases the risk of over-TC: in 1 woman at VPA daily dose 2400 mg in monotherapy Cmax was 160 mg/l. In such clinical situations when it is necessary the use VPA doses over 2000 mg, TDM is especially required to control the safety of therapy.

Thus, the analysis of VPA TDM in real clinical practice revealed the importance of this method for optimization therapy in epileptic adults. Some cases of unnecessary TDM were identified, when low doses were used (up to 500 mg/day). Was shown the average

therapeutic dosage range providing a TC range of VPA (501-2000 mg/day) in real clinical practice, which was independent on different VPA drug formulations. However, in rare cases we identified paradoxical low concentration values, even when using the average daily dosages and rare cases of over-TC, even when receiving low dose of VPA (interesting that all of these patients were women), that justifies carrying TDM when therapeutic doses of 500-1500 mg/day administrated. Carrying TDM is strongly recommended if VPA doses are over 2000 mg/day to control pharmacotherapy safety because the risk of overdose.

Results TDM for CBZ.

Analysis of CBZ concentrations in the whole group of patients showed mean Cmin and Cmax achievement in TC range with an average daily dose of 881.5 mg. The rate of TC range achievement, in contrast to VPA group, was higher and amounted 78.6%, and even more patients achieved therapeutic value of Cmax - 86.5%. To achieve a TC range, patient required higher daily dose of CBZ - 922.2 mg. Daily dose range for patients with TC range was very broad - 200-2000 mg/day; in 24 person (9.5%) daily dose was less than 400 mg, in 2 patients it was 200 mg and in 2 patients - 300 mg (Table 4).

Table 4: Comparison dosages and concentrations in CBZ treated patients.

Groups of patients	Mean daily dose (mg)	Range of daily dose (mg)	Cmin (mg/l)	Cmax (mg/l)	Cmax/Cmin ratio
All patients (n=319)	881,5±21,8	150-2000	6,7±0,1	7,9±0,15	1,21±0,013
Patients achieved TC range (n=252)	922,2±23,0	200-2000	6,9±0,1	8,1±0,1	1,18±0,01
Patients not achieved TC range (n=20)	517,5±85,0	150-2000	2,4±0,2	3,0±0,2	1,29±0,10
Patients with over-TC range (n=4)	1250,0 ±170,8	800-1600	13,5±0,2	15,1±0,7	1,11±0,047

It is important to note that the immediate-release drug forms of CBZ were used in significantly lower doses (about 1.5 times) than sustain-release formulations, the average Cmin and Cmax was significantly lower, respectively (Table 5). As a result, the rate of TC range achievement was also significantly higher when using sustain-release forms of CBZ, particularly for residual Cmin. Among patients who achieved TC range of CBZ was 75.9% at monotherapy and 86.3% in combinations. Mean daily doses, levels Cmin and Cmax of CBZ at combined therapy with other AEDs was significantly higher than at monotherapy, as the result of drug interactions, but this did not affect the frequency of achievement of the TC range (Table 6).

Table 5: Comparison dosages, concentrations and rates of achievement TC range in CBZ treated patients with different drug forms

Rates/levels	Sustain-released drug forms (n=208)	Immediate-release drug forms (n=111)
Cmin (mg/l)	7,2±0,16	5,87±0,22**
Cmax (mg/l)	8,3±0,18	7,14±0,26**
Mean dose (mg/day)	994,7±26,6	669,4±28,9**
Patients achieving TC range Cmin	90,4%	74,8%**
Patients with sub-TC range Cmin	8,2%	24,3%**
Patients with over-TC range Cmin	1,4%	0,9%
Patients achieving TC range Cmax	88,0%	83,8%
Patients with sub-TC range Cmax	3,4%	11,7%**
Patients with over-TC range Cmax	8,7%	4,5%*
Note: * p<0.05, ** p<0.001 between groups of patients.		

Note: * p<0.05, ** p<0.001 between groups of patients.

Table 6: Comparison dosages and concentrations in patients receiving CBZ monotherapy or in combined with other AEDs

Groups of patients	Mean daily dose (mg)	Cmin (mg/l)	Cmax (mg/l)	Patients achieved TC range (%)
Patients received monotherapy (n=224)	797,3±26,4	6,1±0,26	7,3±0,2	75,9%
Patients received combined therapy with VPA (n=95)	1019,1±28,9*	6,5±0,2	7,6±0,2	86,3%
Patients received combined therapy with other AEDs (n=186)	1080,0±30,3**	8,0±0,2**	9,4±0,2**	86%

Note: * p<0.05 and ** p<0.001 between groups of monotherapy and combined therapy.

The proportion of patients who have not reached TC range Cmin and Cmax in CBZ group was 6.3% (20 patients), and sub-TC range Cmin occurred in 44 patients (13.8%). The vast majority (88.6%) of patients with sub-TC range CBZ daily doses were in the range 150-600 mg/day, which is initial dose, and only in one case - 2000 mg/day. However, mentioning that dosage ranges for patients with sub-TC and TC range of CBZ closely overlap, making concentrations unpredictable and creating problems with dosage choose. In this group, the vast majority

of patients received monotherapy, predominantly immediate-acting drug forms. In patients with sub-TC range CBZ Cmax/Cmin ratio was slightly higher in comparison with patients who achieved TC range (1.29 versus 1.18, respectively), indicating on plasma concentration instability.

Analyzing the individual performance of patients with sub-TC range CBZ we revealed 4 cases: in 1 woman received 600 mg/day there was no accumulation of the drug in blood (Cmin and Cmax=0); 1 woman had sub-TC range despite using dose 2000 mg/day (Cmin=3.0 mg/l, Cmax=3.9 mg/l); 2 men received CBZ 400 mg/day had very low concentrations (Cmin=0.7 and 1.1 mg/l, Cmax=1.6 and 1.5 mg/l, respectively). These cases were characterized by paradoxically low concentrations of CBZ related to the therapeutic doses that could be explained by pharmacogenetic disorders of metabolism (primarily CYP3A4 and CYP3A5) [11].

One pharmacogenetic study conducted in China in 84 patients with epilepsy, revealed the influence of CYP3A5 polymorphism in CBZ metabolism. Thus, it was found that 20.8% were CYP3A5'1 allele carriers (genotype AA or AG) and had a lower concentrations of CBZ taking a significantly higher dose than CYP3A5'3 allele carriers (genotype GG) (512.5 versus 441mg/day) [11]. Similar results were shown by other authors in different populations, revealingthe role of genetic polymorphism of CYP3A5 for CBZ [12, 13].

The number of over-TC range cases in patients taking CBZ, was 4 women (1.25%); dosage range was 800-1600 mg day (mean 1250 mg/day) as monotherapy. However, an over-TC of the Cmax level occurred in 23 patients, amounted 13.2 mg/l; only in 2 patients concentration exceeded toxic (more than 15 mg/l). The dosage range in all over-TC range cases was 750-1600 mg/day (mean 1193 mg/day), but the vast majority of over-TC patients (82.6%) received daily doses above 1000 mg; 10 patients used a combination of two AEDs (clonazepam, levetiracetam, lamictal, topamax). Thus, the range of dosages for over-TC patients completely fit in a dose range of patients with TC range of CBZ, which makes doses unpredictable for toxicity.

TDM results were further analyzed based on the average therapeutic doses of CBZ that used in clinical practice. Typically, the initial dose of CBZ is 600 mg/day, titrated after that depending on the clinical efficacy and amounting about 1000-2000 mg/day. We choice three daily dosage ranges: initial doses less than 600 mg/day (mean dose 485.3 mg/day) (n=112), middle therapeutic doses 601-1200 mg/day (mean dose 955.4 mg/day) (n=158), high doses 1201 mg/day and more (mean dose 1549 mg/day) (n=49). Mean concentrations in initial doses were: Cmin=4.9±0.18 mg/l, Cmax=5.96±0.19 mg/l. The achievement of TC range for CBZ was observed in 64.3% of patients using initial doses (less than 600 mg/day), and increased to 87% if taking higher doses (600 mg/day or more). The detailed analysis of the results of TDM in different ranges of dosages of CBZ presented that the highest rate of TC range achievement was observed in the middle dosage range (601-1200 mg/day) – 89.2%, which were used in 50% of patients (mean concentrations Cmin=7.4±1.16 mg/l, Cmax=8.6±0.18 mg/l). Mean concentrations in CBZ doses more than 1200 mg/day were: Cmin=8.6±0.3 mg/l and Cmax=10.0±0.35 mg/l; the achievement of TC range was observed in 79.6%. With the increasing of CBZ dose, increased the frequency of over-TC: at doses less than 600 mg/day over-TC range was no cases, whereas at doses of 600 and 1200 mg/day, their frequency has reached 1.3% and 4.1%, respectively, the frequency over-TC range Cmax - 8.8% and 18.4%, respectively.

Thus, the results TDM of CBZ in real clinical practice showed that it is difficult to predict the frequency of TC range achievement when administering CBZ drug. Despite the higher frequency of TC range achievement comparing to VPA, CBZ dosage ranges that provide therapeutic, sub-TC and over-TC practically coincide and have very wide range (200-2000 mg). Therefore, the number of cases failing to achieve TC range was 2.5 times less, and number of over-TC - 10 times greater in comparison with VPA use. Furthermore, using combined therapy with other AEDs was essential for CBZ due to pharmacokinetic interactions.

Discussion

The results of this study reflect the actual practice of AEDs use in epileptic patients and are important for practical application of TDM. Well known that in 20-25% epilepsy patients fail to achieve clinical efficacy; adverse effects on nervous system and other toxic effects (e.g. hepatotoxicity) are often occur [14]. TDM is an important tool for personalized approach to antiepileptic pharmacotherapy due to the concentration-dependent efficacy and safety/toxicity. TDM allows to objectifying therapeutic drug concentrations to control safety, and identify complementary cases such as inefficiency of therapy and pharmacogenetic problems, requiring medication changing. Thus, pharmacogenetic disorders of AEDs currently being actively studied, because it is thought to be important factor of pharmacokinetic inter-patient variability (especially drug clearance); impetus for such studies was population pharmacokinetic data of AEDs [10].

Despite the importance of TDM for AEDs, there are only few publications on the results of studies of concentrations of these drugs in real clinical practice. Basic pharmacokinetic studies were carried out in 1980-90 years with a scientific purpose and allowed to build population pharmacokinetic models, and to determine the TC range of AEDs [1,3]. However, currently there is a large amount of modern drug formulations of VPA and CBZ with modified release that optimize the pharmacotherapy of patients with epilepsy. An important question is how they improve outcomes and provide TC range in actual practice.

Among the recent publications related to the year 2000, we managed to find a few publications from Asian countries. Thus, the results of Asian study at the National Laboratory of Nepal (2008), planned to evaluate TDM of AEDs in 417 epilepsy patients (adults and children) in real practice, the frequency of a TC range achievement was 79.3% when taking CBZ and 62% with VPA (TC range 50-100 mg/l), what agrees with our study results [15]. However, cases of over-TC range observed in 4.9% of patients in CBZ group, while in VPA group - significantly higher (18%) than in our study. A narrower TC range of VPA can explain these differences: in our study, the upper limit of VPA concentration was higher (150 mg/l), in accordance with Russian national population AEDs studies [16]. Furthermore, some foreign researchers also use similar TC range [17,18]. If we use a range of 50-100 mg/l, the frequency of TC range achievement with VPA would be only 49% at mean dose of 1274 mg/day; and the frequency of over-TC range would increase to 17.6%, as in Asian study. It is known that in Asian population genetic polymorphism of metabolizing hepatic enzymes is more common (such as cytochrome P450), which could be responsible for the higher frequency of VPA overdose.

In a number of other Asian studies on TDM for AEDs in actual practice had similar results in TC range achievement: 74% for CBZ 73% for CBZ and 45% for VPA 50% for CBZ and 40% for VPA [19-21]. However, the average doses of VPA were not more than 500 mg/day, which is almost 2 times less than in our practice.

Carrying TDM of AEDs in real clinical practice is relevant method to manage the effectiveness and safety of epileptic patient's treatment. Raising specialists awareness about the results of TDM in real practice is essential important for pharmacotherapy optimization and promotes rational use of TDM.

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