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PHARMACOKINETICS AND DISPOSITION

Impact of age, gender and *CYP2C9/2C19* genotypes on dose-adjusted steady-state serum concentrations of valproic acid—a large-scale study based on naturalistic therapeutic drug monitoring data

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Abstract
Purpose Valproic acid (VPA) has an extensive interindividual pharmacokinetic variability. Published data regarding the impact of gender, age, and *CYP2C9/2C19* genetics on VPA variability are conflicting, and the purpose of present study is to clarify the effect of these factors on dose-adjusted steady-state serum VPA concentration (C:D ratio) in a large, naturalistic patient material.
Methods In patients who had been subjected to *cytochrome P450* (*CYP*) genotyping and therapeutic drug monitoring of VPA, information about serum concentrations, dose, gender, age, and *CYP2C9/2C19* genotypes was retrospectively collected from a routine TDM database during the period 2008-2012. The effects of age, gender, and *CYP2C9/CYP2C19* genotypes on C:D ratios of VPA were investigated by multivariate analyses (mixed model) including sampling time as covariate.
Results In total, 857 serum concentrations from 252 patients were included. A significant gender effect was observed with a 1.3-fold higher estimated C:D ratio in females than in males, i.e., geometric means 0.34 vs. 0.27 μM/mg/day, respectively ($p < 0.001$). A similar and significant difference in estimated geometric means was found between patients >65 vs. ≤65 years, i.e., 0.36 vs. 0.26 μM/mg/day ($p < 0.001$), respectively. Finally, no association between the various *CYP2C9/2C19* variant genotypes and C:D ratio of VPA was observed ($p > 0.1$).
Conclusion The present study shows that age and gender significantly influence VPA serum concentration. In order to obtain similar drug exposure, our findings suggest that older female patients would generally require 30–50 % lower dosing of VPA compared to younger males. Moreover, we conclude that *CYP2C9/2C19* genotype is not relevant for variability in VPA exposure.

Keywords Valproic acid · Pharmacokinetics · Elderly · Gender · *CYP2C9* · *CYP2C19* · Pharmacogenetics

Introduction

Valproic acid (VPA), an anticonvulsant drug, has been shown to be effective for treatment of acute mania and bipolar disorders [1, 2]. VPA exhibits an extensive interindividual pharmacokinetic variability [3], but factors determining this variability are poorly understood.

The metabolism of VPA is complex resulting in approximately 50 known metabolites [4]. The major metabolic pathways of VPA comprise glucuronidation, mitochondrial β-oxidation, while CYP-mediated oxidation is a minor route [5–9]. Factors of potential importance for individual differences in VPA metabolism include age, gender, and genetic polymorphisms. According to the FDA-approved product label [10], intrinsic clearance of VPA is reduced in older compared with younger patients. However, several publications have reported no effect of age on total VPA serum concentration [11–13]. The FDA states that dose-adjustment is not required based on gender, but published data are conflicting regarding impact of gender on VPA pharmacokinetics as well. Moreover, inconsistent with the secondary role of CYP-mediated metabolism,

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some studies have reported an effect *CYP2C9/CYP2C19* genotype on pharmacokinetic variability of VPA [14, 15].

Overall, it is a high degree of uncertainty with respect to the actual clinical relevance of the above-mentioned variables for individual dose requirements of VPA, probably due to the fact that most previous studies were limited by small sample size and single dose administration. The purpose of the present study was therefore to clarify the impact of age and gender, as well as *CYP2C9*/*2C19* genotypes, on steady-state dose-adjusted serum concentration of VPA in a large, naturalistic patient material using multivariate statistical analysis.

Methods

Study design

The study was based on data available from a therapeutic drug monitoring (TDM) service at Center for Psychopharmacology, Diakonhjemmet Hospital, Norway. Serum VPA concentrations from *CYP*-genotyped patients were collected retrospectively during January 2008 to December 2012. As the samples were analyzed at a TDM service for psychotropic drugs, use of VPA among the included patients was probably mainly on psychiatric treatment indications rather than epilepsy.

Determination of *CYP* genotypes and serum VPA concentrations had been performed by request of physicians as a part of clinical routine. Information about the determined serum concentrations, the respective patients' *CYP2C9* and *CYP2C19* genotypes, age, gender, possible co-medication, dosage, and sampling time (i.e., time interval between last drug intake and sample withdrawal) was recorded from the TDM files. When multiple serum concentration analyses of VPA had been performed for the same patient, all measurements were considered for inclusion.

Serum concentration measurements were included in the study if (1) serum samples had been withdrawn 10–26 h after the last dose intake, (2) requisition forms provided information about dosage, (3) serum concentrations were considered likely to be at steady-state, (4) no recorded co-administration of carbamazepine, phenobarbital or phenytoin, and (5) measured serum concentrations were above the lower limit of quantification. Consideration of steady-state conditions was based on information available on the requisition forms.

The study was approved by the Regional Committee for Medical and Health Research Ethics.

VPA serum analysis

Serum VPA concentrations were determined by an UPLC MS/MS method developed at Center for Psychopharmacology, Diakonhjemmet Hospital, Norway. Briefly, samples were prepared with protein precipitation using cold acetonitrile containing imipramine (internal standard). Chromatographic separation was performed by an Acquity UPLC BEG shield RP18 column (1.7 μm 1.0 × 100 mm; Waters) using gradient elution at 40 °C with a mix of ammonium acetate buffer (pH = 4.8) and acetonitrile (18–45 %) as mobile phase. The retention times were 2.89 and 2.86 min for VPA and imipramine, respectively. Detection with multiple reaction monitoring was performed at the following transitions: *m/z* 143 → 143 for VPA and *m/z* 281 → 86 for imipramine.

Reference standards were obtained from Sigma (St. Louis, MO, USA). Calibration curves were prepared in the concentration intervals 200–800 μM (i.e., 28.8-115.4 μg/mL in mass units). The lower limits of quantification, defined as signal-to-noise ratio of 10, was 15 μM (2.2 μg/mL) for VPA. The coefficient of variation was less than 7 % for VPA serum concentration measurements. The conversion factor of VPA molar-to-mass unit was 0.144 (1 μmol/L = 0.144 μg/mL).

CYP2C9/2C19 genotyping

CYP2C9 and *CYP2C19* was performed by TaqMan-based SNP assays detecting the variant alleles *CYP2C19*2*,**3*,**4*, **17*, and *CYP2C9 *2*, **3* (detailed procedures described elsewhere [16–18]). For *CYP2C9*, the patients were categorized either as carriers or non-carriers of reduced-function variant alleles (i.e., presence or non-presence of *2C9 *2* and/or **3*). For *CYP2C19*, patients were categorized into three subgroups, i.e., (1) homozygous carriers of the increased-function variant allele *2C19*17*, (2) carriers of a lack-of-function variant allele (*2C19* *2,*3, and/or *4), or (3) homozygous wild-type carriers (*2C19*1/*1*). Since lack-of-function *2C19* variant alleles override the effect of *2C19*17* [18], patients with a combined genotype were classified into subgroup (2).

Measures and statistics

The effects of gender, age, *CYP2C9*-, and *CYP2C19* genotype on C:D ratios (μM/mg/day) were evaluated by linear mixed model analyses. Similar analyses were used to evaluate the effects of the same variables on absolute (unadjusted) serum concentration and daily dose of VPA. The application of mixed model analyses as multivariate test instead of multiple linear regression enabled weighting for different number of serum concentration measurements/observations available from each of the included patients (i.e., all data utilized so that each patients' importance in the statistical analysis could be weighted according to their respective number of measurements). Sampling time was included as covariate in the mixed model analyses evaluating the effects on dose-adjusted and absolute serum concentrations. The definition of elderly, >65 years according the World Health Organization [19], was used as cut-off value in the mixed model analysis. To support the age cut-off at 65 years, a simple plot of individual

C:D ratios in sectioned age groups (10 years per group) were plotted and compared.

Prior to the mixed model analyses, the respective outcome variables C:D ratio, absolute serum concentration and daily dose of VPA were logarithmically transformed. After analyses, group estimates were transformed back to original scale and presented as geometric mean values with 95 % confidence intervals. Statistical significance was considered as $p < 0.05$. SPSS Software version 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses, while GraphPad Prism version 4 (GraphPad Software Inc., La Jolla, CA, USA) was used for graphical presentations.

Results

In total, 261 patients with available *CYP2C9*/*CYP2C19* genotypes and measured VPA serum concentration were identified in the TDM database. Seventy-three samples from thirteen patients were excluded from the study not meeting the inclusion criteria. Among the included patients ($n = 252$), 141 had more than one serum concentration measurements. In total, 857 serum concentrations were included for statistical analysis. About 90 % of the serum samples had been withdrawn within 10–16 h after the last dose intake for analysis of VPA concentration.

The characteristics of the patient population are summarized in Table 1. Among the included patients, 39 of the patients (10.9 %), representing 94 serum concentration measurements, were patients >65 years, whereas 213 patients (763 measurements) were grouped below or equal 65 years. Furthermore, 113 patients were males and 139 patients were females. In supplementary Fig. 1, simple plots of individual C:D ratios in age-sectioned subgroups in males and females are shown.

In the whole population, the range of individual C:D ratio was >60-fold (0.02-1.2 μM/mg/day). The mixed model analyses are summarized in Table 2. A significant effect on age was evident with an estimated 41 % higher mean C:D ratio of VPA in patients >65 years compared to patients ≤65 years ($p < 0.001$). Similarly, female patients had a significantly 26 % higher mean C:D ratio compared to male patients ($p < 0.001$). The observed higher C:D ratio of VPA in patients >65 years was reflected by a significantly lower prescribed mean daily dosage compared to patients ≤65 years. Correspondingly, the estimated mean absolute serum concentration of VPA was significantly lower in patients >65 years compared to patients ≤65 years, i.e., 317 vs. 364 μM ($p < 0.05$). With respect to gender, daily dose, but not absolute mean VPA serum concentration, was significantly lower in females compared to males. The interaction variable between gender and age (age*gender) was not significant ($p = 0.313$) in the mixed model analysis. Neither *CYP2C9* nor *CYP2C19* genotype had any significant effect on C:D ratios or absolute serum concentrations of VPA ($p > 0.1$), but carriers of reduced-function *CYP2C9* variant alleles were prescribed

Table 1 Characteristics of the study population

Patient and valproic acid data	
Male/female, *n*	113/139
Mean age, years (range)	45.1 (16–89)
Number of patients, *n* (age ≤65/>65)	252 (213/39)
Number of serum VPA conc. measurements	857
Mean sampling time, h (range)	13.5 (10–26)
Mean daily VPA dose, mg (range)	1553 (84–5400)
Mean s-VPA concentration, μM (range)	414.0 (15–1476)
CYP2C9 genotype	Number of patients, *n* (%)
*CYP2C9*1/*1*	181 (71.8)
*CYP2C9*1/*3*	23(9.1)
*CYP2C9*3/*3*	0
*CYP2C9*1/*2*	45 (17.9)
*CYP2C9*2/*2*	2 (0.8)
*CYP2C9*2/*3*	1 (0.4)
CYP2C19 genotype	Number of patients, *n* (%)
*CYP2C19*1/*1*	95 (37.8)
*CYP2C19*1/*2*	57 (22.7)
*CYP2C19*2/*2*	9 (3.5)
*CYP2C19*2/*17*	17 (6.8)
*CYP2C19*1/*17*	65 (25.9)
*CYP2C19*17/*17*	8 (3.2)

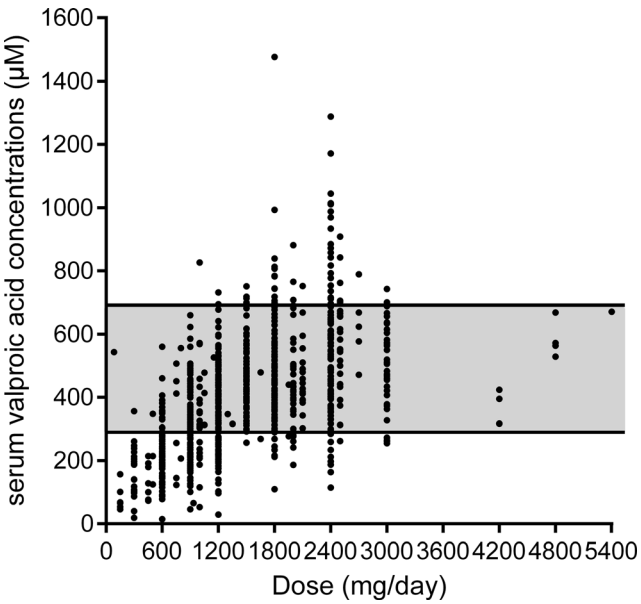

Fig. 1 Distribution of individually measured serum concentration (μM) of valproic acid (VPA) at different prescribed daily doses (mg/day). The shaded area indicates the therapeutic reference range of VPA (300–700 μM). The conversion factor of VPA molar-to-mass unit is 0.144 (1 μmol/L = 0.144 μg/mL)

Table 2 Estimated effects of gender, age, and *CYP2C9/2C19* genotypes on dose-adjusted serum concentration, absolute (unadjusted) serum concentration, and daily doses of valproic acid in patients using mixed model analyses. Data are presented as estimated geometric means in the respective subgroups with 95 % confidence intervals

Variables	Dose-adjusted serum concentration (μM/mg/d)[a]	*p* value	Absolute serum concentration (μM)[a]	*p* value	Drug dosage (mg/d)[a]	*p* value
Gender						
Males	0.27 (0.26–0.29)	–	328 (305–353)	–	1191 (1101–1288)	–
Females	0.34 (0.32–0.36)	<0.001[†]	352 (329–376)	0.06	998 (929–1072)	<0.001[†]
Age						
Patients ≤65 years	0.26 (0.25–0.27)	–	364 (348–381)	–	1387 (1322–1456)	–
Patients >65 years	0.36 (0.33–0.39)	<0.001[‡]	317 (284–353)	<0.05[‡]	857 (763–961)	<0.001[‡]
CYP2C9						
Wildtype *(*1/*1)*	0.30 (0.28–0.31)	–	352 (331–373)	–	1161 (1090–1239)	–
Carriers of **2 and/or *3*	0.31 (0.29–0.34)	0.16	328 (301–358)	0.12	1023 (933–1121)	<0.01[#]
CYP2C19						
Wildtype *(*1/*1)*	0.30 (0.28–0.32)	–	335 (311–361)	–	1079 (997–1166)	–
Carriers of **2*	0.32 (0.30–0.34)	0.15	357 (329–388)	0.13	1107 (1013–1208)	0.57
Carriers of **17/*17*	0.30 (0.28–0.32)	0.52	327 (302–355)	0.6	1086 (997–1184)	0.87

[a] Data are presented as geometric mean (95 % confidence interval)

[†] Significantly different from control group (male)

[‡] Significantly different from control group (patients ≤65 years)

#Significantly different from control group (*CYP2C9* wildtype)

The model is adjusted for sampling time at 13.5 h. The conversion factor of VPA molar-to-mass unit is 0.144 (1 μmol/L = 0.144 μg/mL)

significantly lower doses than the homozygous wild-type subgroup ($p < 0.01$, Table 2).

Figure 1 shows the variability in absolute serum VPA concentrations at different prescribed daily doses. Among the 274 serum VPA concentrations outside the therapeutic reference range (i.e., 300–700 μM), 17.5 % of serum VPA concentrations were above the upper reference limit and these originated mainly from females (85 %). Of the remaining serum VPA concentrations outside the therapeutic reference range, who were below the reference limit, 53 % originated from females. The average prescribed dosage was approximately 1550 mg/day ranged from 84 to 5400 mg/day.

Discussion

In the literature, it is a high degree of uncertainty regarding the clinical impact of aging, gender, and *CYP2C9/2C19* genotype on pharmacokinetic variability of VPA [11–15, 20–23]. In the present study, which included substantially more patients than the previous ones, we found that gender and age >65 years are associated with significantly higher C:D ratios of VPA compared to males and younger patients, respectively. According to the quantitative model estimates of subgroup C:D ratios, our findings suggest that female patients >65 years would generally require 30–50 % lower daily dose of VPA to achieve therapeutic serum concentrations compared with younger male patients. While the product label of VPA recommends lower dosing in elderly, no recommendation is provided regarding gender. Thus, the current study contributes with new knowledge and possible clinical relevance regarding gender-dependent dose requirements of VPA.

The mechanism(s) of why females obtain higher VPA levels per dose than males is not obvious. Glucuronidation is regarded as the major metabolic pathway of VPA, and in vitro studies have reported involvement of multiple UGT isoforms (UGT1A3, 1A4, 1A6, 1A8, 1A9, 1A10, 2B7, and 2B15) in VPA glucuronidation [6, 24–26]. Although there is evidence that females generally exhibit less UGT activity than males [27, 28], the literature is equivocal on this point, and little is known about gender-specific impact on individual UGT enzymes. Alternative explanations for the gender-related variability in steady-state trough C:D ratio includes differences in bodyweight/distribution, bioavailability, and/or drug compliance. For instance, Ibarra et al. have showed increased reabsorbed fraction and bioavailability of VPA doses in females compared to males [14], hence indicating gender differences in hepatobiliary output, which emerge as higher bioavailability of VPA in females than males. Although not reported among VPA users, studies have indicated that females have better compliance than males, which potentially could be a non-biological factor of relevance for higher C:D ratios in

the former subgroups. Regardless of reason for the gender difference in C:D ratio, a clinically important observation was that females—despite receiving lower doses than males—obtained similar absolute VPA concentrations as males and were over-represented among the cases where the measured serum concentration was above the therapeutic reference range. This suggests that females might be at increased risk of adverse effects if doses are not individualized.

In our analysis, we used 65 years as a cut-off according to the World Health Organization's definition of "elderly" [19]. However, the physiology of aging is complex, and defining an age limit in pharmacological research is complicated since biological age is not correlated with chronological age. Despite this complexity, it appeared that use of 65 years was reasonable in this study based on simple assessment of age-dependent changes in C:D ratios of VPA (supplementary Figure 1). In our study, the elderly patients obtained significantly have higher C:D ratio and were prescribed lower daily dosage than younger patients. Although, the intrinsic clearance is reduced by 40 % in elderly compared to younger patients [10], previous studies have reported contradictory findings on the impact of aging on VPA concentration, but the present analysis suggests that patients >65 years achieve approximately 40 % higher total serum concentration of VPA than younger patients. Moreover, the free fraction of VPA has been reported to be significantly higher in older vs. younger subjects [11], which means that overall active (free) concentration of VPA per dose is possibly even more increased in the elderly that indicated from total serum concentration estimates in our study. Additionally, pharmacodynamic sensitivity is believed to be increased in older patients due to various age-related changes in receptors, neurotransmitters and second-messenger systems in the brain [29–31]. Therefore, it is important to be aware of a potentially increased vulnerability of side effects and toxicity of VPA in patients >65 years.

Despite the limited CYP-mediated metabolism of VPA in vitro, it has been published conflicting data regarding the impact of *CYP2C9* /*2C19* genotypes on VPA pharmacokinetics [20–22]. Our findings provide strong evidence that *CYP2C9/2C19* genetics have little or no impact on VPA dose requirements. Based on this finding, a surprising observation was that the daily VPA dosage in our patients was significantly lower in carriers of reduced-function *CYP2C9* variant alleles than on homozygous wild-type carriers. The reason is difficult to outline, but a possible explanation might be that physicians generally dose patients who have reduced metabolism of an enzyme less intensive than others—regardless of drug type.

The use of TDM data for research purpose is associated with methodological limitations. In the data material, steady-state conditions were interpreted from information on requisition forms and not objectively confirmed. Moreover, co-prescription of interacting drugs, except from phenytoin, phenobarbital, and carbamazepine, was not systematically identified. With respect to gender, information about use of oral contraceptives would have been of particular relevance to possess, since they may affect glucuronidation rate [32, 33]. Moreover, lacking information on drug compliance is a limitation of the study, and it could not be excluded that increased C:D ratios in females reflect better compliance compared with males [34]. Other methodological limitations include unknown bodyweight and somatic comorbidity, as well as variable time between last dose intake and serum sampling. However, compared with many other studies, many variables of potential relevance for VPA pharmacokinetics were available in the present investigation. The inclusion of a high number of patients and observations, combined with multivariate data analysis, represents a strength of the study and likely outweigh many of the mentioned limitations.

Conclusion

The present study shows that age and gender significantly influence VPA serum concentration. In order to obtain similar drug exposure, our findings suggest that older female patients would generally require 30–50 % lower dosing of VPA compared to younger males. Finally, we conclude that *CYP2C9*/*2C19* genotype, in line with the respective enzymes' secondary importance in VPA metabolism, is not of clinical importance for the variability in VPA pharmacokinetics.

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Authors' contributions RLS, TH, HR, and EM have designed the study. RLS and EM have performed the research. RLS and TH have analyzed the data, and RLS has written the paper. All authors have revised the paper critically and approved it for submission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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