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Original article

Influence of age and co-medication on the steady-state pharmacokinetics of valproic acid in Tunisian patients with epilepsy

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ABSTRACT

Aim. – Valproic acid (VPA) is a widely prescribed broad-spectrum antiepileptic drug. However, the use of VPA is complicated in clinical practice by its remarkably wide variability of pharmacokinetics. The objective of this study was to investigate the effects of demographic factors and associated therapies on steady-state plasma VPA concentrations in patients with epilepsy.

Methods. – This retrospective cohort study was carried out using the routine therapeutic drug monitoring (TDM) database. Stepwise logistic regression analysis was used to compare serum VPA levels in 78 epilepsy patients treated with VPA in association with at least one other drug that could have interacted with CYP2C9, CYP2C19 or UGT enzymes.

Results. – The frequency of subtherapeutic serum VPA levels was significantly increased with younger age ($P < 0.02$), the number of co-medications ($P < 0.007$) and use of enzyme-inducing co-medications ($P < 0.02$). No significant correlations between VPA dose and trough plasma concentrations were found, as the latter did not increase in proportion to the dose.

Conclusion. – Routine monitoring of VPA serum levels would be extremely useful in epilepsy patients in the pediatric age group and in those who require associated enzyme-inducing medications.

1. Introduction

Valproic acid (VPA) has wide anticonvulsive effects, and still serves as the drug of choice in the treatment of epilepsy due to its broad therapeutic spectrum. However, VPA has a narrow therapeutic range for the treatment of epilepsy (50–100 mg/L), and shows considerable individual variability in both its pharmacokinetics and pharmacodynamics. Therefore, its plasma concentrations need to be monitored to guide dose adjustments during the course of therapy.

VPA undergoes extensive metabolism, with <5% of the dose excreted unchanged in urine. Its biotransformation involves three major metabolic pathways: glucuronidation

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catalyzed by uridine diphosphate glucuronosyltransferases (UGTs); mitochondrial β-oxidation; and microsomal omega (ω1) oxidation and ω oxidation catalyzed by various cytochrome P450 (CYP) enzymes [1]. Approximately 20–70% of a dose of VPA is excreted in the urine as glucuronide conjugates [2], while CYP-catalyzed metabolism of VPA accounts for about 10% of the administered dose, mainly mediated by CYP2C9 and CYP2C19 [3]. Therefore, the metabolism of VPA can be altered by other drugs, including both antiepileptic drugs (AEDs) and non-AEDs. However, the most important interactions affecting VPA pharmacokinetics are those resulting from either induction or inhibition of its metabolism [4].

There are only a few studies investigating the factors affecting the pharmacokinetic of VPA [3,5–7]. Thus, the present study has used data from routine therapeutic drug monitoring (TDM) to investigate the effects of demographic factors and associated therapies on steady-state plasma VPA concentrations in epilepsy patients.

2. Materials and methods

2.1. Study design, setting and patients

This observational, single-center, retrospective study was carried out using the routine TDM database, which includes the following variables: sociodemographic information (age, gender, weight, specialty of the prescriber); information about the VPA prescription (daily dose, duration of therapy, clinical indication of prescription, time of blood collection, serum drug concentration values); and other drugs concomitantly administered with VPA.

For purposes of the present study, the TDM database was also used to identify patients who fulfilled the following inclusion criteria: (i) use of VPA in combination with at least one other drug in patients with epilepsy; (ii) availability of serum VPA concentration values at steady state for the period between January 2014 and June 2015; and (iii) availability of information on patient's body weight, dose of VPA, duration of therapy, time of blood collection and clinical indication for VPA prescription. In cases of multiple serum-level determinations of the same drug, only the last determination was considered for evaluation to avoid multiple inclusion of the same patient.

As the biotransformation of VPA is catalyzed in part by CYP2C9, CYP2C19 and UGT, it was hypothesized that the concomitant administration of drugs that inhibit or induce the metabolic pathway of VPA may be complicated in clinical practice by the remarkably wide variability of VPA pharmacokinetics. For this reason, all observed co-administered drugs with VPA were listed and then categorized according to their metabolic interactions with CYP2C9, CYP2C19 or UGT enzymes (Table 1) [8–13]. Patients were considered exposed to enzyme inducers or inhibitors if they received at least one drug able to induce or inhibit any of the three enzymes. Taking into account the time course of drug interactions, co-medication with enzyme inducers was defined as when the duration of association with VPA was >2 weeks [14,15]. Patients co-medicated with drugs not interacting with CYP2C9, CYP2C19 or UGT enzymes were excluded.

2.2. Blood-sampling and drug assays

Blood samples for determination of serum VPA levels were collected at steady state (at least 6 days after the last dose change) and before the morning dose. All concentrations were measured as part of the routine patients' care by fluorescence polarization immunoassay (AxSYM, Abbott Diagnostics, Abbott Park, IL, USA). The normal range of VPA steady-state plasma concentrations is 50–100 mg/L [16].

2.3. Statistical analysis

Patients were divided into three groups according to their VPA plasma levels: subtherapeutic (<50 mg/L); supratherapeutic (>100 mg/L); and normal (50–100 mg/L). Continuous variables (age, body weight, transformed daily dose (mg/kg/day),

Table 1 – Metabolic pathways of drugs co-administered with valproic acid (VPA) in epilepsy patients.

Drugs	References	Cytochrome P450 isoenzymes		Conjugation
		CYP2C9	CYP2C19	UGT
Carbamazepine (n = 16)	[8,9,12,13]	Substrate, inducer		Inducer
Phenobarbital (n = 13)	[8,9,12,13]	Substrate, inducer	Substrate, inducer	Inducer
Lamotrigine (n = 3)	[8,10,12]			Substrate
Fluoxetine (n = 3)	[8,12,13]	Substrate, inhibitor	Substrate, inhibitor	
Clobazam (n = 10)	[8,12,13]		Substrate	
Diazepam (n = 2)	[8,12,13]	Substrate	Substrate	
Clopidogrel (n = 5)	[12,13]	Substrate, inhibitor	Substrate	
Amiodarone (n = 2)	[8,12,13]	Inhibitor		
Isoniazid (n = 3)	[12,13]		Inhibitor	
Rifampicin (n = 3)	[11–13]	Inducer	Inducer	Inducer
Sulfamethoxazole (n = 1)	[12,13]	Substrate		
Fluconazole (n = 4)	[8,12,13]	Inhibitor	Inhibitor	
Metronidazole (n = 4)	[12,13]	Inhibitor		
Omeprazole (n = 4)	[8,12,13]	Substrate	Substrate	

CYP: cytochrome P450; UGT: uridine diphosphate glucuronosyltransferase.