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PHARMACOKINETIC PARAMETERS OF VALPROIC ACID AND CARBAMAZEPINE FROM ROUTINELY COLLECTED DATA: INFLUENCE OF PATIENT CHARACTERISTICS

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Individualising a drug dosage regimen is more appropriate if it is based on pharmacokinetics data derived from local populations. In this study, we estimated valproic acid (VPA) and carbamazepine (CBZ) clearances in the Malaysian population from routinely collected therapeutic drug monitoring (TDM) data. We also evaluated the effects of gender, age, weight and concurrent antiepileptic drug (AED) therapy on VPA and CBZ clearance. Data was collected retrospectively from TDM forms of adult patients. Apparent drug clearance was estimated based on the standard steady state clearance equation. Mann-Whitney and Kruskal-Wallis tests were used to evaluate gender and therapy differences, while Spearman's Rank correlation was used to determine the associations of age and weight with clearance. One hundred thirty-two samples for VPA and 67 for CBZ were included in the analysis. Patients' ages ranged from 15 to 72 years old. Mean VPA and CBZ clearances were found to be 0.36 l/kg/d and 1.60 l/kg/d, respectively. VPA clearance correlated positively but poorly with weight. Our results showed significant differences in (i) VPA clearance among male and female patients and (ii) VPA clearance between monotherapy and combination therapy. These findings provide a guide to initiate maintenance doses of VPA and CBZ in our local patients. Awareness of factors influencing drug clearance should help to optimise patients' dosing regimens.

Keywords: *Valproic acid, Carbamazepine, Clearance, Age, Weight, Gender*

INTRODUCTION

Variability in AED disposition between individuals when standard dosage regimens are administered may affect drug therapy. Various attempts have been made to describe the pharmacokinetic parameters of AEDs and to determine the influence of factors such as age, weight, gender, dose and concomitant medications. This has led to the integration of serum drug concentration (SDC) monitoring with

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clinical observation to provide a more optimal use of this group of drugs.

Few studies have examined the variability of antiepileptic drugs like VPA and CBZ in local patients. Such information is useful for optimising daily dosages of VPA and CBZ. Estimated doses of these drugs based on known patient variability would be more accurate and practical. This could reduce the potential for toxicity and decrease the need for repetitious drug assays. The overall well-being of the patient would be improved by better disease control or a reduction in toxicity.

In Malaysia, a TDM service was initiated in the early 1980s (Hassan 1990; Ismail 1990). The service was expanded to include the AEDs, digoxin and theophylline. More recently, hospitals in the country started to provide this service as part of routine drug monitoring in their patients (Matnor 1997; Othman, Abd Ghani and Aziz 1997; Manan, Mathews and Nordin 1997). Currently, almost all major hospitals in Malaysia provide TDM of AEDs. We believe that there is an abundance of data available from this routine SDC monitoring that may be useful for optimising drug therapy in patients with epilepsy in this country.

The primary objective of this study was to estimate VPA and CBZ clearances from these routinely collected data. The secondary objective was to evaluate the effects of gender, age, weight and concurrent AED therapy on VPA and CBZ clearances. Since these are data obtained under steady-state conditions, they would be very useful for physicians to estimate the initial maintenance dose of each drug and to predict changes in dosing regimen in patients taking combination AED therapy.

METHODS

We retrospectively analysed TDM data obtained from the Pharmacokinetics Laboratory of the Hospital Universiti Sains Malaysia (HUSM), Kelantan. Only data on adult patients receiving treatment with oral VPA or CBZ between January 2000 and December 2002 were included. The study was approved by the Director of HUSM.

To ensure that steady state conditions had been achieved, individual patients on monotherapy should have received same dose

for at least four weeks (Suzuki *et al*. 1991; Cloyd *et al*. 1993; Blanco-Serrano *et al*. 1999a, 1999b). Patients on combination therapy were required to receive the same drugs for at least two months (Sundqvist, Tomson and Lundkvist 1997; Blanco-Serrano *et al.* 1999a). Only TDM data with SDC measured at the end of dose interval (trough level) were included. Therapy compliance was accepted if a patient had two or more SDC analyses with coefficients of variation (CV) of less than 20% (Leppik, Cloyd and Sawchuk 1978; Blanco-Serrano *et al.* 1999a).

SDC data taken from patients during their hospitalisation were excluded. Patients with more than two AEDs were also excluded.

Pharmacokinetic Calculations

Drug clearance for individual patients was estimated based on the clearance equation at steady state (Liu and Delgado 1994; Sanchez-Alcaraz *et al*. 1998; Chan, Lee and Hue 2001):

$$CL = D/Css$$

where ,   CL = apparent clearance (l/kg/d)
             D = dosing rate (mg/kg/d)
             Css = steady state concentration (mg/l)

The bioavailabilities of both VPA and CBZ were assumed to be 100% (Liu and Delgado 1994; Gray, Botha and Miller 1998; Chan, Lee and Hue 2001). Individual values were used to estimate average population clearance rates. The influence of four covariates was analysed: gender, weight, age and concurrent administration of AEDs.

Statistical Analysis

Non-parametric calculations was used because the data was positively skewed. Mann-Whitney and Kruskal-Wallis tests were used to test for gender and therapy differences, while the Spearman's Rank correlation was used to determine the association between age and weight with clearance. Values of $p < 0.05$ were considered significant.

RESULTS AND DISCUSSION

One hundred thirty-two VPA SDC data points and 67 CBZ SDC data points from a total of 76 patients were included in the analysis. Table 1 summarizes clinical details for both groups. The doses of VPA used in this group of patients ranged from 6.25 to 66.67 mg/kg/day, corresponding to steady-state SDCs from 14.06 to 128.55 mg/l. Doses of CBZ ranged from 4.76 to 29.03 mg/kg/day, corresponding to steady-state SDCs between 3.38 mg/l and 13.82 mg/l.

The overall average VPA clearance in adult patients was found to be 0.36 l/kg/day. VPA is almost entirely eliminated from the body through hepatic metabolism, and less than 5% of the drug is eliminated through the renal system. The overall mean CBZ clearance in our adult patients was found to be 1.60 l/kg/d (Table 2). Like VPA, CBZ is also eliminated almost exclusively via a metabolic route, with less than 2% of the oral dose being excreted unchanged in the urine (Winter 1996). The overall mean clearance rate obtained in our study (1.60 l/kg/d) is consistent with rates reported by others (Liu and Delgado 1994; Chan, Lee and Hue 2001; Ismail and Ab Rahman 1993). We did not report the liver function data of the patients in our study because these tests are seldom documented on TDM forms.

Table 1: Demographics and treatment characteristics of the patients.

	VPA	CBZ
Observations (n)	132	67
Patients (n)	51	25
Race (Malay/Chinese)	50/1	25/0
Gender (Male/Female)	27/24	14/11
Weight (kg)	61.09 (28.2–98)	54.63 (28.2–80)
Age (year)	31.4 (15–72)	28.4 (15–51)
Dose (mg/kg/d)	20.41 (6.25–66.67)	13.82 (4.76–29.03)
Concentration (mg/l)	65.02 (14.06–128.55)	8.62 (3.38–13.82)
Monotherapy	90	43
CBZ (Yes/No)/VPA (Yes/No)	25/107	22/45
PHT (Yes/No)	12/120	2/65
PB (Yes/No)	5/127	–

Note: CBZ: carbamazepine; VPA: valproic acid; PHT: phenytoin; PB: phenobarbitone

Table 2: Apparent clearances of VPA and CBZ.

	VPA Clearance (l/kg/d) Mean (Range)	CBZ Clearance (l/kg/d) Mean (Range)
Average for all patients	0.36 (0.11–1.40)	1.60 (0.61–3.94)
Gender - Male	0.40 (0.16–1.29)	1.74 (0.80–3.94)
- Female	0.32 (0.11–1.40)	1.44 (0.61–2.38)
	p = 0.007	*p = 0.271*
Monotherapy	0.28 (0.11– 0.86)	1.65 (0.61 – 3.94)
Combination therapy		
+ CBZ or VPA	0.52 (0.18– 1.40)	1.54 (0.80 – 2.73)
+ PHT	0.60 (0.16– 1.29)	1.32 (1.23 – 1.40)
+ PB	0.46 (0.36– 0.63)	-
	** *p = 0.000*	** *p = 0.694*

Note: *Mann-Whitney test; **Kruskal-Wallis test

The influence of liver diseases on drug clearance is variable and unpredictable; most drug clearance will be affected only when liver impairment is severe. Therefore, conventional liver function tests are not regarded as accurate indicators of the status of liver metabolism (Wilkinson 1986). Nevertheless, in the absence of data on the status of liver functions in our patients, these findings should be treated with caution.

Male patients had a significantly higher rate of clearance of VPA compared with female patients (Mann-Whitney test, p = 0.007). Previous reports regarding the influence of gender on VPA clearance have been variable. Yukawa *et al.* (1997) reported that VPA clearance in female patients was 10% less than their male counterparts. Others found no significant difference in clearance between male and female subjects (Blanco-Serrano *et al.* 1999a, 1999b).

Similarly, studies examining the effect of gender on CBZ clearance produced conflicting results. CBZ is metabolised by cytochrome P450 enzymes, particularly CYP3A4. The majority of studies have reported that, for drugs metabolised by CYP3A4 isozymes, women have faster clearances than men (Schwartz 2003). However, our results show that gender has no effect on CBZ apparent clearance. Our results are consistent with data reported by others (Suzuki *et al.* 1991; Chan, Lee and Hue 2001; Delgado Iribarnegaray et al. 1997). In children, Liu and Delgado (1994) found that girls had lower total and intrinsic clearance rates than boys. They suggest that the lower clearance rate in girls is related to higher levels of oestrogen,

which can inhibit microsomal enzyme activities. A 1998 review suggests that no strong evidence links the effect of menstrual cycle on drug pharmacokinetics or pharmacodynamics (Kashuba and Nafziger 1998). Therefore, these conflicting results may be attributed to confounding factors like subject selection (e.g., ill patients vs. healthy subjects, age, social habits, race, concomitant administration of medications), route of administration, duration of study and sample size (Schwartz 2003).

VPA clearance correlated positively but poorly with weight ($r = 0.153$, $p = 0.039$). Earlier studies by Blanco-Serrano *et al.* (1999a, 1999b) suggested that VPA clearance correlates positively with body weight. We found no statistically significant correlations between VPA clearance and age ($r = -0.077$, $p = 0.189$). Similar findings have been reported by other groups (Blanco-Serrano *et al.* 1999b). Body weight may be a better indicator of physiological conditions and the metabolic capacities of the patient than age (Jiao *et al*. 2003). This is in contrast to paediatric patients; VPA clearance is relatively faster in younger children and declines with age (Blanco-Serrano *et al.* 1999a; Sanchez-Alcaraz *et al.* 1998). This high clearance rate is attributed to the hepatic metabolism (intrinsic clearance) of VPA rather than to changes in the free fraction (Cloyd *et al*. 1993).

We did not find significant correlations between CBZ clearance and age, or CBZ clearance and body weight. CBZ clearance rates have been found to be relatively higher in paediatric patients compared to adults (Gray, Botha and Miller 1998; Lanchote *et al.* 1995), suggesting that younger children may have a higher metabolic capacity for CBZ until they reach adulthood. Studies involving children or groups of patients spanning a wide range of age groups have shown that CBZ clearance significantly correlates with age and weight (Liu and Delgado 1994; Chan, Lee and Hue 2001; Gray, Botha and Miller 1998; Delgado Iribarnegaray *et al.* 1997). Our study focused exclusively on adults, suggesting that a relationship between clearance and age or weight may be less evident in adulthood. Similar observations among adult patients were reported by Ismail and Ab Rahman (1993).

VPA clearance is affected by the concurrent administration of other AEDs. We show that clearance rate is higher in patients on combination therapy with CBZ, PHT or PB than in those on VPA alone (Kruskal-Wallis, $p < 0.05$). This has been demonstrated in other

studies (Blanco-Serrano *et al.* 1999a, 1999b; Cloyd *et al.* 1993; Yukawa *et al.* 1997). CBZ, PHT and PB induce expression of metabolic enzymes. A possible mechanism is through the induction of drug metabolising enzymes in the liver by other AEDs resulting in increase intrinsic clearance (Cloyd *et al.* 1993).

The effects of co-administration with other AEDs on CBZ clearance are not consistent. Yukawa and Aoyama (1996) found that addition of VPA to CBZ results in a 7% increase in CBZ clearance. However, Delgado Iribarnegaray *et al.* (1997) found that VPA co-administration has no effect on CBZ clearance. Similarly, Gray, Botha and Miller (1998) showed concomitant VPA therapy results in clearance equivalent to monotherapy, but PHT co-administration increases CBZ clearance by a factor 1.4. Chan, Lee and Hue (2001) found that PHT has no effect on CBZ clearance, but PB increased CBZ clearance. Our study shows no difference in clearance rates between CBZ monotherapy and combination therapy with VPA. Data on co-administration with PHT and PB are insufficient to demonstrate an effect.

CONCLUSION

VPA and CBZ average clearance rates derived from local population data are useful to establish an initial maintenance dose of these drugs in adult patients. Furthermore, knowledge of SDCs and factors affecting drug clearance such as gender, weight and co-administered medications would further optimise dosage regimen in this group of patients.

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