INVESTIGATION OF PHENOBARBITAL-CARBAMAZEPINE-VALPROIC ACID INTERACTIONS USING POPULATION PHARMACOKINETIC ANALYSIS FOR OPTIMISATION OF ANTIEPILEPTIC DRUG THERAPY: AN OVERVIEW

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SUMMARY

Antiepileptic drugs are associated with a wide range of drug interactions. Although monotherapy with antiepileptic drugs is preferred, patients with multiple seizure types or refractory disease generally require various combinations of antiepileptic drugs. Pharmacokinetic interactions between antiepileptic drugs represent a major complication of epilepsy treatment with polytherapy. It is important to be aware of possible interactions, so as to anticipate clinical effects and to reduce the risk of both toxicity and seizures worsening when a drug is added to, or withdrawn from, the patient's antiepileptic drug regimen. This report is an overview of the drug-drug interactions between antiepileptic drugs (phenobarbital ↔ carbamazepine, carbamazepine ↔ valproic acid and phenobarbital ↔ valproic acid) by population pharmacokinetic analysis.

KEY WORDS

phenobarbital, carbamazepine, valproic acid, clearance, population pharmacokinetic analysis

1. INTRODUCTION

Knowledge of the potential pharmacokinetic interactions between antiepileptic drugs is essential in designing a safe and effective therapeutic regimen for patients with epilepsy. Pharmacokinetic interactions between antiepileptic drugs arise most frequently as a consequence of drug-induced changes in hepatic metabolism, and less frequently from changes in plasma protein binding. Phenobarbital, carbamazepine and valproic acid are the major drugs used to treat epilepsy. Phenobarbital and carbamazepine are potent inducers of the cytochrome P-450, epoxide hydrase and urine disphosphate glucuronosyltransferase enzyme systems. Valproic acid inhibits to different extents many hepatic enzyme system activities involved in drug metabolism and is able to significantly displace drugs from plasma albumin. This report outlines the latest drug-drug interaction studies by population pharmacokinetic analysis, which can be used to guide dosage adjustment of established antiepileptic drugs.

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2. PHENOBARBITAL

Phenobarbital is the oldest and one of the most widely used of the modern antiepileptic drugs. It has been suggested that the therapeutic serum concentration range for this drug is 10-40 μg/ml for epileptic seizures /1,2/. Optimal use of phenobarbital in pediatric patients requires information regarding the drug's pharmacokinetics.

Phenobarbital has the potential to interact with any drug that is metabolized by the mixed-function oxidative system. The effect of carbamazepine on phenobarbital disposition is variable. Cereghino *et al.* /3/ showed no effect of carbamazepine on phenobarbital concentrations in adults. Guelen and van der Kleijn /4/ showed that concomitant administration of phenobarbital and carbamazepine resulted in a 15% decrease of phenobarbital clearance in children. The effect of valproic acid on phenobarbital disposition is probably one of the clinically most important interactions /5/, as it occurs predictably in the majority of patients taking these two drugs together. The mechanism by which valproic acid causes phenobarbital accumulation is thought to involve inhibition of phenobarbital metabolism /6/. Valproic acid inhibits both p-hydroxylation /7/ and N-glucosidation /8/ of phenobarbital and significantly reduces its total clearance /9/. Subsequent clinical trials confirmed that serum phenobarbital levels rose when valproic acid therapy was initiated. The increases have usually ranged from 15-70%, but have sometimes been much higher /10/.

In our study, the effects of drug-drug interactions on phenobarbital disposition were examined through a retrospective analysis of serum concentration data from 349 pediatric and adult epileptic patients (age range 0.4-33.3 years) /11/. Patients received phenobarbital as monotherapy or in combination with either carbamazepine or valproic acid. The final regression model for clearance by a nonlinear mixed-effect model (NONMEM) approach was:

$$CL\ (l/h) = 0.0523 \cdot \text{body weight}^{0.433} \cdot CO$$

where CO is a scaling factor for concomitant medication with a value of 1 for patients on phenobarbital monotherapy, $46.4^{(-1/\text{body weight})}$ for those receiving concomitant carbamazepine, and 0.642 for those receiving concomitant valproic acid. The regression analysis for clearance showed that total body weight and concomitant medication were important prediction factors of phenobarbital clearance. The effects of carbamazepine on phenobarbital clearance were maximal in

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early childhood (about 54%), and decreased in a weight-related fashion in children, with minimal changes observed in adults (Fig. 1). Concomitant administration of phenobarbital and valproic acid resulted in a 35.8% decrease of phenobarbital clearance.

Botha *et al.* /12/ similarly showed by a NONMEM approach that concomitant administration of phenobarbital and carbamazepine or phenytoin resulted in a 13% decrease of phenobarbital clearance for South African children. Concomitant administration of phenobarbital and valproic acid led to a decrease in phenobarbital clearance of 38%.

$$CL\ (l/h) = [Exp(0.0288 \bullet body\ weight(kg) - 2.53)] \bullet CO$$

where Exp is the natural logarithm base, and CO is a scaling factor for concomitant medication with a value of 1 for patients on phenobarbital monotherapy, 0.87 for those receiving concomitant carbamazepine or phenytoin, and 0.62 for those receiving concomitant valproic acid.

A method that would provide correct predictions about whether a drug concentration is subtherapeutic, therapeutic, or toxic with a given dosage regimen would be valuable. It may be possible to predict phenobarbital clearance using the weight-related and drug-drug interaction factors from these studies. Using this clearance value, steady-state concentrations can be calculated for a given dosage rate. Figure 2 shows the dosages needed to achieve steady-state serum phenobarbital concentrations of 15 μg/ml in patients with or without carbamazepine or valproic acid cotherapy /11/.

3. CARBAMAZEPINE

Carbamazepine is currently considered the drug of choice for the treatment of partial seizures, generalized tonic-clonic seizures, and other minor or partial seizure disorders. Carbamazepine is also approved as the drug of choice for treatment of the pain associated with trigeminal neuralgia. It is well known that carbamazepine dosage adjustment in clinical practice is difficult because of the lack of a good relationship between dose and the desired effect, enzymatic induction, its narrow therapeutic range reported to be 4-12 μg/ml in epileptic seizures, and variation in the pharmacokinetic characteristics of the drug /13-15/.

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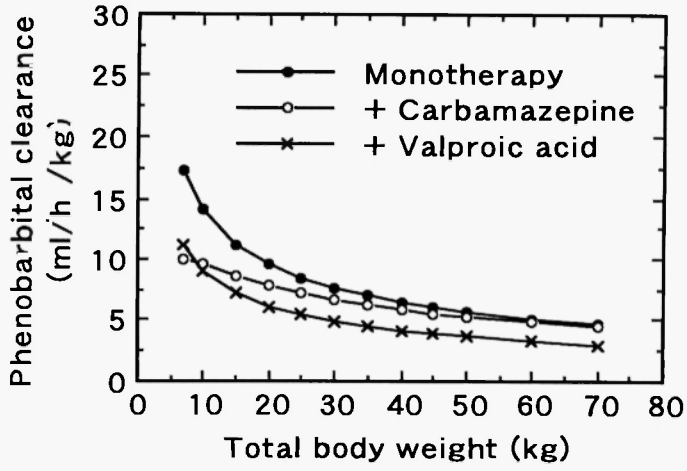

Fig. 1: Effects of total body weight and co-medication on phenobarbital clearance.

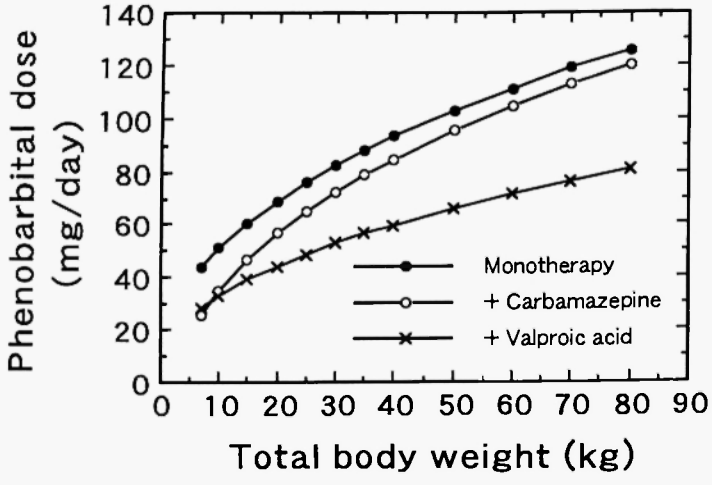

Fig. 2: Phenobarbital dose needed to achieve a serum concentration of 15 μg/ml in patients with or without carbamazepine or valproic acid cotherapy.

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Several studies have noted the induction of carbamazepine clearance by the concomitant administration of other antiepileptic drugs /16-20/. The concomitant use of enzyme-inducing antiepileptics, such as phenytoin, phenobarbital, and primidone, decreases average serum carbamazepine concentrations. Drug interactions with carbamazepine include its increased enzymatic biotransformation by phenobarbital, phenytoin and primidone. There are a number of conflicting reports on the effect of valproic acid on carbamazepine disposition. Both increases and decreases in carbamazepine concentrations have been observed following the addition of valproic acid /19/. In addition, elevation of carbamazepine epoxide concentration has been reported after the addition of valproic acid /21/. The mechanism seems to be inhibition of carbamazepine-10,11-epoxide conversion to carbamazepine-10,11-trans-diol /20/ and carbamazepine-10,11-trans-diol glucuronidation /22/. Since the interaction between valproic acid and carbamazepine may involve both displacement from protein binding and metabolic inhibition, carbamazepine concentrations may increase, decrease, or remain unchanged when the drugs are coadministered, depending on which effect prevails. Thus, evaluation and management of such variability is needed to optimize therapy for each patient individually.

Delgado Iribarnegaray *et al.* /23/ showed by a NONMEM approach that total body weight, daily dose, age and concomitant phenobarbital were important prediction factors for carbamazepine clearance. They showed that concomitant administration of carbamazepine and phenobarbital resulted in a 28.9% increase of carbamazepine clearance for children with epilepsy.

$$CL\ (l/h) = [0.0122 \cdot \text{body weight(kg)} + 0.0467 \cdot \text{daily dose(mg/kg)}] \cdot \text{age(yr)}^{0.331} \cdot 1.289^{PB}$$

where PB is an indicator variable that has a value of unity if the patient is treated with phenobarbital, and zero otherwise. In our study, concomitant administration of carbamazepine and phenobarbital showed an increase in carbamazepine clearance of 16% /24/.

$$CL\ (l/h) = 0.0649 \cdot \text{body weight(kg)}^{0.664} \cdot \text{daily dose(mg/kg)}^{0.465} \cdot 1.07^{VPA} \cdot 1.16^{PB} \cdot 1.27^{POLY}$$

where VPA is an indicator variable that has a value of unity if the patient is treated with valproic acid, zero otherwise, and POLY is an

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indicator variable that has a value of unity if the patient is treated with more than two antiepileptic drugs, and zero otherwise.

Additionally, Gray *et al.* /25/ proposed

$$CL\ (l/h) = [0.7 \bullet [\text{body weight(kg)}]^{0.4}] \bullet CO,$$

where CO is a scaling factor for concomitant medication with a value of 1 for patients on carbamazepine monotherapy or concomitant valproate, and 1.4 for those receiving concomitant inducers (phenobarbital and/or phenytoin). Graves *et al.* /26/ also proposed

$$CL\ (l/h) = [0.0134 \bullet \text{body weight(kg)} + 3.58] \bullet CO,$$

where CO is a scaling factor for concomitant medication with a value of 1 for patients on carbamazepine monotherapy, 1.42 for those receiving concomitant phenytoin only, 1.17 for those receiving phenobarbital or felbamate, and 1.62 for those receiving phenytoin and phenobarbital or felbamate. Optimizing carbamazepine therapy for patients receiving enzyme-inducing antiepileptic drugs is more difficult because of the significantly greater interpatient variability in clearance observed among patients receiving these drugs.

In our study, concomitant administration of carbamazepine and valproic acid showed an increase in carbamazepine clearance of 7%; however, this is in contrast with the results of Delgado Iribarnegaray *et al.* /23/, Gray *et al.* /25/ and Graves *et al.* /26/, who reported that valproic acid did not significantly affect its clearance. It might be possible to predict carbamazepine clearance for any patient by use of the weight-related, daily dose-related and drug-drug interaction factors from our study. Figure 3 shows the dosages needed to achieve steady-state serum carbamazepine concentrations of 8 μg/ml in patients with or without valproic acid or phenobarbital cotherapy /24/.

4. VALPROIC ACID

Valproic acid is a branched-chained fatty acid, unrelated structurally to any other antiepileptic drug. It has a broad spectrum of activity against both convulsive and nonconvulsive generalized epilepsies. It has been suggested that the therapeutic serum concentration range for this drug is 50-100 μg/ml for epileptic seizures /27/. Optimal use of valproic acid in pediatric patients requires information regarding the drug's pharmacokinetics.

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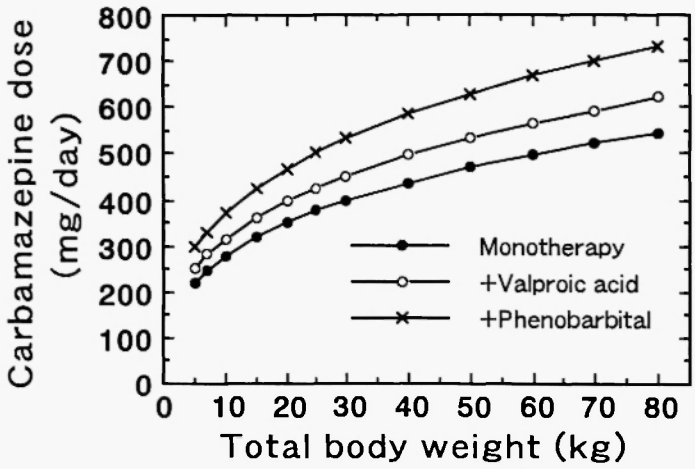

Fig. 3: Carbamazepine dose needed to achieve a serum concentration of 8 μg/ml in patients with or without phenobarbital or valproic acid cotherapy.

Valproic acid is often administered with other antiepileptic drugs, a practice that can lead to clinically significant pharmacological interactions. Concomitant administration of such enzyme-inducing antiepileptic drugs as carbamazepine, phenobarbital, primidone, or phenytoin will markedly accelerate the metabolic conversion of valproic acid, particularly in children /28-33/.

In our study, the effects of total body weight, daily dose, gender and drug-drug interactions on valproic acid clearance were examined through a retrospective analysis of serum concentration data from pediatric and adult epileptic patients /34/. Patients received valproic acid as monotherapy or in combination with either of the antiepileptic drugs carbamazepine or phenobarbital. The final regression model for clearance by a NONMEM approach was:

$$CL\ (l/h) = 0.0156 \cdot \text{body weight(kg)}^{0.748} \cdot \text{daily dose(mg/kg)}^{0.183} \cdot 0.898^{GEN} \cdot CO^{PB} \cdot CO^{CBZ}$$

where CO^{PB} equals 1.10 if the patient is treated with phenobarbital, a value of unity otherwise; CO^{CBZ} equals 0.769•daily dose (mg/ kg)$^{0.179}$ if the patient is treated with carbamazepine, a value of unity otherwise, and GEN is an indicator variable that has a value of unity if the patient

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is a female, zero otherwise. Concomitant administration of valproic acid and phenobarbital resulted in a 10% increase in valproic acid clearance. Valproic acid clearance increased 16-49% when varying the valproic acid daily dose from 10-40 mg/kg in the presence of carbamazepine. The clearance in female patients was approximately 10% less than that in male patients.

Botha *et al.* /35/ suggested that total body weight and concomitant carbamazepine are important prediction factors of valproic acid clearance:

$$CL\ (l/h) = Exp[0.022 \bullet body\ weight(kg) - 1.38]$$

for monotherapy, where Exp = the natural logarithm base. They showed that carbamazepine produced an increase of 61% in valproic acid clearance. Serrano *et al.* /36/ also showed that concomitant administration of carbamazepine elicits an increase in valproic acid clearance of 35.9% in epileptic children on valproic acid monotherapy or valproic acid plus concomitant carbamazepine:

$$CL\ (l/h) = 0.012 \bullet body\ weight(kg)^{0.715} \bullet daily\ dose(mg/kg)^{0.306} \bullet 1.359^{CBZ},$$

where CBZ is an indicator variable that has a value of unity if the patient is treated with carbamazepine, zero otherwise. The clearance of valproic acid is profoundly affected by the concurrent administration of other antiepileptic drugs /37/. The mechanism(s) by which valproic acid interacts with other antiepileptic drugs has not been definitely established /10,38,39/. However, the induction of drug metabolizing enzymes in the liver by other antiepileptic drugs is the most likely explanation /40/. These results also show that the clearance of valproic acid is clearly larger when valproic acid is given in combination with carbamazepine or phenobarbital than when valproic acid is given alone. The additional influence of phenobarbital was relatively slight (10%) /34/. Sackellares *et al.* /41/ found, in children, that phenobarbital reduced the valproate level:dose ratio by 45%. May and Rambeck /42/ found that the concentration of valproic acid was lower when the drug was given in combination with phenobarbital (76.3%) than when given alone (100%). A similar effect has been noted with carbamazepine (66.2%). Carbamazepine has been reported to increase the metabolic clearance and decrease the plasma concentration of valproic acid /32,33,43,44/. The specific metabolic pathways induced by carbamazepine include glucuronidation, ω

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oxidation, and ω-1 oxidation /45/. In our study, the concomitant administration of carbamazepine gave a higher induction of clearance with an increasing daily dose of valproic acid than when it was given with phenobarbital.

Clinically important drug interactions between valproic acid and carbamazepine or phenobarbital may occur not only when they are added but also when they are withdrawn from therapy. Withdrawal of carbamazepine or phenobarbital alters valproic acid concentrations to a lesser degree, the average increase being 50% and 67%, respectively /46/. For example, increased valproate serum concentrations were reported in six patients following carbamazepine discontinuation, associated with signs of valproate toxicity in one of the patients /47/.

A method that would provide correct predictions about whether a drug concentration is subtherapeutic, therapeutic, or toxic in a given dosage regimen would be valuable. It might be possible to predict valproic acid clearance for any patient by use of the weight-related, daily dose-related, gender and drug-drug interaction factors from our study. Figure 4 shows the dosages needed to achieve steady-state

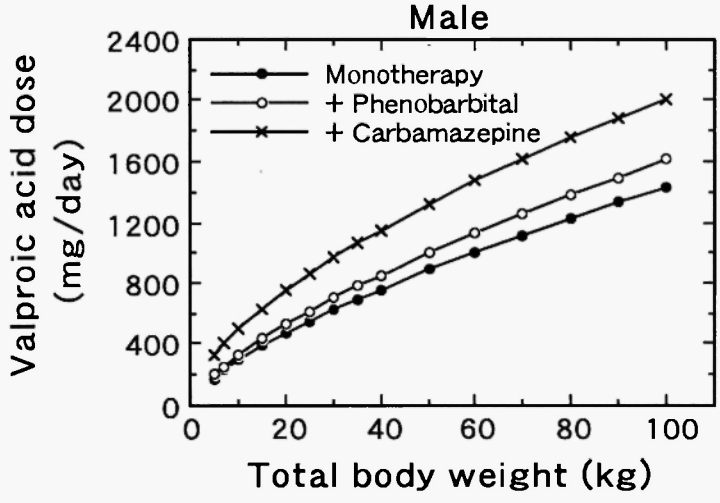

Fig. 4: Valproic acid dose needed to achieve a serum concentration of 75 μg/ml in patients with or without phenobarbital or carbamazepine cotherapy.

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serum valproic acid concentrations of 75 μg/ml in patients with or without carbamazepine or phenobarbital cotherapy /34/.

5. THERAPEUTIC IMPLICATIONS

Drug interactions in patients receiving antiepileptic drugs are a common complication of therapy. Interpatient variability in drug disposition and response is commonly observed in therapeutics, and thus evaluation and management of such variability form the basis for individualized pharmacotherapy. If the mathematical approach to determining drug doses were accurate and practical, the use of calculated doses could reduce the potential for toxicity and decrease the need for repetitive drug assays. In this article, a mathematical relationship between drug clearance and individual patient characteristics, such as drug interaction with concomitant drug(s), body weight, daily drug dose, age and gender, was discussed by population pharmacokinetic analysis. These estimated clearances could provide predictions about whether a drug concentration is subtherapeutic, therapeutic, or toxic in a given dosage regimen, and may be acceptable for individualized dosage adjustment. Moreover, this report shows the feasibility of using sparse data, collected during routine clinical care, to estimate population parameters and to detect drug-drug interactions through the use of population approach techniques. These techniques permit the identification of the most important factors contributing to interindividual variability in drug kinetics.

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