

Valproic Acid and Plasma Levels of Primidone and Derived Phenobarbital

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SUMMARY: Five patients were studied to determine whether kinetic interaction occurs between valproic acid and primidone. During concurrent administration of primidone and valproic acid no significant interaction was observed. Primidone and derived phenobarbital levels did not change significantly. No adjustment of primidone dose was required when valproic acid was used as adjunctive therapy.

RÉSUMÉ: Nous avons étudié chez 5 patientes les interactions cinétiques possibles entre l'acide valproïque et la primidone. Lors d'administration simultanée des 2 produits nous n'avons observé aucune interaction significative. Les niveaux de primidone et de phénobarbital, qui en découle, n'ont pas changé significativement. Il ne fut pas nécessaire d'ajuster les doses de primidone quand l'acide valproïque était employé comme thérapeutique adjuvante.

Kinetic interactions have been reported between valproic acid (VPA) and phenytoin (DPH) (Bardy et al., 1976; Bruni, et al., 1979a; Bruni et al., 1979b; Wilder et al., 1978), phenobarbital (PB) (Patsalos and Lascelles, 1977; Wilder et al., 1978), and trimethedione (TMD) (Gram et al., 1980). The most frequent clinical interaction is the elevation of plasma PB concentrations when VPA is co-administered. This interaction has been shown to be due to inhibition of PB metabolism by VPA with a decrease in the conversion of PB to its major metabolite hydroxyphenylphenobarbital (HPPB) (Bruni et al., 1980). A significant portion of primidone (PD) is metabolized to phenobarbital and with co-administration of VPA a rise in the derived PB plasma concentration would also be expected. However, there is little information to support this possibility. In a study by Wilder and associates it was suggested that derived PB concentrations did not rise significantly when VPA was co-administered (Wilder et al., 1978). However, the patients treated with this drug combination were too few to make a valid conclusion and they were not studied in detail.

A study was designed to determine whether the co-administration of valproic acid would lead to significant changes in plasma primidone and derived phenobarbital concentrations.

MATERIALS AND METHODS

Five adult patients (3 males and 2 females) with complex partial seizures (mean age 27 years) had been treated with primidone therapy for a minimum of five months. Daily doses ranged from 500 mgs to 1000 mgs (6.6 Mg/kg to 19.2 Mg/kg) and were maintained during the period of study. Determinations of plasma PD and PB

concentrations were performed monthly. Plasma samples were drawn 10 to 12 hours after the last dose of PD. Because of the long half-life of PB it was thought that these differences in sampling time would not result in significant differences in PB levels. The mean plasma concentrations for PD and PB were determined from the values obtained in the previous four months when the patients were assumed to be in steady state conditions.

Valproic acid therapy was started in gradually increasing doses to a daily dose range of 1250 mg to 2500 mg (28.8 Mg/kg to 34.7 Mg/kg). The primidone dose was unchanged. After six weeks of valproic acid therapy plasma VPA, PD, and PB were monitored bimonthly for an additional eight weeks under conditions of plasma sampling similar to those prior to initiation of VPA therapy. The data are presented in table I. The paired student t test was used for statistical analysis.

RESULTS

After the co-administration of VPA no consistent or significant change was observed in the PD or PB plasma concentrations despite VPA plasma concentrations that are known to inhibit PB metabolism. No excessive sedation was reported by the patients when VPA was instituted. Mild transient nausea was noted in four of the patients. In two patients this occurred within minutes of dose ingestion, however in two patients nausea was delayed for one and two hours respectively.

DISCUSSION

Elevation of plasma PB occurs in the majority of patients when they are concurrently treated with PB and VPA. This often requires a reduction

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TABLE I

Changes In Primidone and Derived Phenobarbital Levels During Co-administration of Valproic Acid

Patient	Primidone Dose		Plasma Concentrations (Mcg/Ml)				Valproic Acid Conc. (Mcg/Ml)
	Mg/Day	Mg/kg	PRE-VPA	PB	PD +VPA	PB	
1	500	6.6	6.0 ± 1.8 (SD)	21.8 ± 3.6	5.8 ± 2.1	20.4 ± 2.9	52.3 ± 8.2
2	750	12.5	9.8 ± 2.1	20.9 ± 2.5	8.3 ± 2.0	17.5 ± 4.0	68.4 ± 6.6
3	750	15.0	12.4 ± 1.5	18.9 ± 3.0	14.5 ± 1.9	22.0 ± 1.8	64.5 ± 4.2
4	750	13.6	7.2 ± 2.3	28.3 ± 4.1	8.9 ± 1.6	27.0 ± 3.7	89.9 ± 9.4
5	1000	19.2	14.3 ± 1.9	25.8 ± 3.5	14.8 ± 1.4	23.2 ± 3.2	74.8 ± 7.2

of the PB dose to prevent sedation. Surprisingly, the levels of PD and derived PB did not change significantly and no alteration in the dose of PD was required where VPA was added.

It can be hypothesized that this lack of kinetic interaction is the result of a double interaction: a decreased conversion of PD to PB tending to reduce PB plasma concentrations and inhibition of PB metabolism tending to raise plasma PB concentrations. It is possible that these two opposing effects are of a similar magnitude and have a "cancelling effect". Higher plasma concentrations of PD are not observed possibly because of a compensatory increase in its renal excretion. If the opposing effects are not of similar magnitude elevation of PB levels may occur and anticonvulsant drug monitoring is recommended when the two drugs are used concurrently.

Two patients experienced delayed nausea upon initiation of VPA therapy. This had been the experience of a number of patients (Bruni, unpublished data) and may be related to peak VPA plasma levels which are generally observed 1 to 4 hours after dosing (Bruni and Wilder, 1979). It is possible that the nausea in these patients is a result of a central effect of VPA rather than direct gastric irritation.

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