Interaction of Phenytoin and Primidone

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Summary

The ratio of derived phenobarbitone to unmetabolized primidone in the serum was significantly higher in 50 epileptic patients on a combination of primidone and phenytoin than in 12 patients on primidone alone, though the dose and serum levels of primidone were similar in the two groups. Out of 253 patients attending a seizure clinic 47% were taking a combination of these two anticonvulsants. The effect of phenytoin on the metabolism of primidone may have clinical implications in view of the frequency of their combined use.

Introduction

Since many epileptic patients receive anticonvulsant drugs for most of their lives it is not surprising that recently an increasing number of interactions between different anticonvulsants and between anticonvulsants and non-anticonvulsant drugs have been recognized.¹ While monitoring serum anticonvulsant levels in epileptic patients we saw several cases in which phenytoin had had an apparent influence on primidone metabolism. Primidone exerts its anticonvulsant effect at least in part by its oxidation *in vivo* to phenobarbitone.²

Fig. 1 shows the course of a patient who presented with primidone intoxication on a daily dose of 1500 mg. After reducing this to 750 mg/day both the primidone and the derived phenobarbitone levels fell considerably and signs of toxicity disappeared. To prevent any possible exacerbation of seizures phenytoin was increased from 100 to 300 mg/day; as a result serum phenytoin rose sharply and, remarkably, there was a further increase in the serum phenobarbitone despite a continuing decrease in the serum primidone. When the dose of phenytoin was reduced to 200 mg/day the fall in serum phenytoin was again accompanied by a corresponding change in serum phenobarbitone. The fluctuating serum phenytoin levels, caused by varying the dose, seemed to influence the derived phenobarbitone level without affecting that of the unmetabolized primidone.

As a result of this and similar cases, we decided to examine the relation of phenobarbitone to primidone levels in patients on primidone alone and on both primidone and phenytoin.

Patients and Methods

All patients were attending the King's-Maudsley seizure clinic. Group 1 consisted of 12 patients, nine women and three men, aged 17-53 years (mean 31.4 years) taking primidone. Group 2 consisted of 50 patients, 21 women and 29 men, aged 18-64 years (mean

33.6 years) taking primidone and phenytoin. A few patients in each group were on other anticonvulsant or psychotropic drugs—carbamazepine, ethosuximide, diazepam, amphetamine—but no patient was receiving phenobarbitone.

Serum for anticonvulsant determinations was drawn during a routine clinic visit between 10 a.m. and 12 noon. Serum phenytoin, phenobarbitone, and primidone were determined by the on-column methylation technique of Kupferberg³ using a Hewlett-Packard series 5750 research gas chromatograph.

FIG. 1—Interaction of primidone and phenytoin in 50-year-old man (see text).
Conversion: Traditional to SI Units—Phenobarbitone: 1 mg/l $\approx$ 4.31 μ mol/l. Primidone: 1 mg/l $\approx$ 4.58 μ mol/l. Phenytoin: 1 mg/l $\approx$ 3.96 μ mol/l.

FIG. 2—Relation of serum phenobarbitone:primidone ratio to serum phenytoin in all patients.

Results

There was no significant difference in the daily dose or serum level of primidone in the two groups, but there was a significant increase in the phenobarbitone:primidone ratio in group 2 (student's *t* test, $P < 0.02$) as a result of relatively higher serum phenobarbitone levels (table 1). In group 2 the correlation between serum phenytoin and the phenobarbitone:primidone ratio was 0.23, which was just short of significance ($P > 0.05$). On combining the data in groups 1 and 2, however, there was a significant correlation ($r = 0.34$, $P < 0.01$). The regression was calculated as phenobarbitone:primidone = $1.73 + 0.38$ (phenytoin) (fig. 2).

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TABLE I—Comparison of Groups 1 and 2. Values are Means $\pm$ S.D.

	No. of Patients	Primidone Dose (mg/kg)	Serum Primidone (μ mol/l)	Serum Pheno-barbitone (μ mol/l)	Pheno-barbitone: Primidone
Group 1	12	12.6 $\pm$ 1.9	54.1 $\pm$ 6.9	83.5 $\pm$ 15.9	1.57 $\pm$ 0.17
Group 2	50	12.2 $\pm$ 0.6	52.2 $\pm$ 2.8	101.6 $\pm$ 6.0	2.20 $\pm$ 0.12*

*P < 0.02.

Conversion: SI to Traditional Units

Primidone: 1 μ mol/l $\approx$ 0.218 mg/l.Phenobarbitone: 1 μ mol/l $\approx$ 0.232 mg/l.

Discussion

Our data suggest that phenytoin has an effect on the metabolism of primidone which results in relatively higher levels of phenobarbitone derived from primidone. This effect is related partly to the serum level of phenytoin. There was no apparent influence on the unmetabolized primidone levels. Similar findings have recently been reported by Fincham *et al.*,⁴ who, however, found no relation between the phenobarbitone: primidone ratio and serum phenytoin.

Fincham *et al.*⁴ suggest that phenytoin induces the liver enzyme system responsible for the oxidation of primidone to phenobarbitone, but there are other possible explanations. Despite great interest in the effects of phenobarbitone on phenytoin metabolism¹ there has been little study of the effect of phenytoin on phenobarbitone. Both clinically⁵ and experimentally⁶ phenytoin may raise serum levels of phenobarbitone. Rizzo *et al.*⁶ suggested that phenytoin may competitively inhibit the metabolism of phenobarbitone or impair its renal excretion. Such mechanisms might also explain the effect of phenytoin on phenobarbitone derived from primidone.

The combination of phenytoin and primidone is commonly encountered in clinical practice; at King's-Maudsley seizure clinic a combination of phenytoin and primidone, sometimes in association with other drugs, was being taken by 119 (47%)

out of 253 patients. This was at least twice as common as any other anticonvulsant combination (table II). Thus we suspect that the interaction of phenytoin and primidone may be important clinically in relation to both seizure control and toxicity.

TABLE II—Anticonvulsant Drugs Taken by 253 Patients Attending King's-Maudsley Seizure Clinic

	No. (%) of Patients		No. (%) of Patients
Phenobarbitone	4 (1.6)	Primidone, phenytoin, and other drugs	42 (16.6)
Phenobarbitone and other drugs*	4 (1.6)	Primidone, phenytoin, and phenobarbitone	13 (5.1)
Primidone	8 (3.2)	Primidone, phenytoin, phenobarbitone, and other drugs	6 (2.4)
Primidone and other drugs	14 (5.5)	Phenobarbitone and primidone	4 (1.6)
Phenytoin	26 (10.3)	Phenobarbitone, primidone, and other drugs	4 (1.6)
Phenytoin and other drugs	18 (7.1)	Other drugs	4 (1.6)
Phenobarbitone and phenytoin	28 (11.1)		
Phenobarbitone, phenytoin, and other drugs	20 (7.9)		
Primidone and phenytoin	58 (22.9)		

*Other drugs included ethosuximide, carbamazepine, diazepam, sulthiame, and pheneturide.

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Cardiac Tamponade and Central Venous Catheters

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Summary

An analysis of the reports on 16 patients who developed cardiac tamponade, complicating the use of central venous catheters, showed that 14 died. The two survivors were treated by removal of the catheter and needle aspiration of the pericardial fluid. Some patients complained of warning symptoms such as nausea, pain, and dyspnoea, and the combination of tachycardia, hypotension, and raised venous pressure was common. We suggest that awareness of the hazard, radiographic visualization of the catheter tip, and expeditious treatment would reduce the mortality.

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Introduction

Wherever it lies, the tip of an intravenous catheter may perforate the vein wall. Perforation is particularly hazardous when the central veins are catheterized and may lead to hydromediastinum, hydrothorax, or, more catastrophically, cardiac tamponade. In some cases—for example, during cardiac catheterization—it is necessary to pass the tip of the catheter into the heart itself and tamponade is an accepted complication, but for most purposes of central venous monitoring and feeding a more peripheral site can be accepted. Nevertheless, cardiac tamponade continues to be reported. From reported observations and our own experience of a case, which is described below, we suggest precautions to prevent tamponade and describe how to recognize it clinically and institute emergency treatment.

Case History

A 35-year-old man presented with a severe dumping syndrome and diarrhoea after truncal vagotomy and pyloroplasty. Conservative measures were of no avail and two reversed jejunal loops were interposed, one between the stomach and duodenum and the other 100 cm distal to the ligament of Treitz. Gastric aspiration produced large volumes of fluid postoperatively and barium-meal examination on the