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Coadministration of Phenytoin and Felbamate: Evidence of Additional Phenytoin Dose-Reduction Requirements Based on Pharmacokinetics and Tolerability with Increasing Doses of Felbamate

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Summary: *Purpose:* This open-label study investigated the pharmacokinetic interaction of phenytoin (PHT) and felbamate (FBM).

Methods: Ten subjects with epilepsy receiving PHT monotherapy were administered increasing doses of FBM (1,200, 1,800, 2,400–3,600 mg/day) at 2-week intervals. PHT doses were reduced by 20% on an individual basis when evidence of clinically significant intolerance was present. With intolerance, the PHT dose was reduced before the next incremental FBM dose. Blood samples were analyzed for FBM, PHT, and PHT metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH).

Results: Total PHT plasma concentrations increased with coadministered FBM. PHT C_{max} increased from 15.9 μg/ml at baseline to 20.9 μg/ml after 1,200 mg/day FBM and to 26.8 μg/ml after 1,800 mg/day FBM. Four subjects required a 20% PHT dose reduction after 1,800 mg/day FBM and six after the administration of 2,400 mg/day FBM. All subjects required further 20% PHT reductions before 3,600 mg/day FBM. FBM C_{max} and AUC_{τ} were reduced, and apparent clearance increased compared with data from FBM monotherapy.

Conclusions: With the initiation of FBM therapy in subjects receiving PHT, the PHT dosage should be reduced by 20%. Further PHT dose reductions are likely to be necessary if the FBM dose is increased. The requirements for reductions in dose might be predicted by clinical signs of PHT intolerance. **Key Words:** Felbamate—Phenytoin—Coadministration—Dose adjustments.

Chemically unrelated to other anticonvulsants, felbamate (FBM; 2-phenyl-1,3-propanediol dicarbamate; Felbatol) possesses activity in nearly all major seizure types (1,2). FBM is approved by the Food and Drug Administration as an adjunct therapy or monotherapy in the treatment of partial seizures in adults, with and without secondary generalization, and as adjunct therapy in the partial and generalized seizures associated with Lennox–Gastaut syndrome in children. Recent postmarketing experience revealed incidents of aplastic anemia (3) and hepatic failure. FBM labeling has been revised to reflect these events, and presently the anticonvulsant is indicated only in those patients in whom alternative treatments fail and whose epilepsy is so severe that the risk of aplastic anemia or hepatic failure or both is deemed acceptable in light of benefits conferred by its use. This study was completed before the first reported instance of aplastic anemia and before the suggestion of a link between FBM and hepatic failure.

FBM elimination involves approximately equal parts of hepatic metabolism and renal clearance of unchanged FBM (4,5). FBM induction of metabolism [carbamazepine (CBZ)(6,7)], [valproate (VPA), phenobarbital (PB)(8–10)] of hepatic microsomal enzyme systems may explain the pharmacokinetic changes occurring with other anticonvulsants (AEDs). Limited clinical data are available on the pharmacokinetic interaction of FBM and phenytoin (PHT). PHT, however, may hold the most

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troublesome consequences for clinicians because of its low therapeutic index and dose-dependent nonlinear pharmacokinetics. A doubling of plasma PHT concentrations has been reported in patients coadministered 1,600 mg/day FBM (11).

This study sought to examine the pharmacokinetics of FBM, PHT, and HPPH after FBM–PHT coadministration in subjects with epilepsy. Subject tolerability and trough PHT concentrations were used to determine when dose adjustments were required.

MATERIALS AND METHODS

Subjects

This study was IRB approved (UMDNJ–Robert Wood Johnson University Hospital Institutional Review Board), and all subjects signed a study specific informed consent before the initiation of study procedures.

Ten subjects (five male and five female subjects) with epilepsy [complex partial seizures with or without generalization receiving stable PHT monotherapy (Dilantin Kapseals; Parke-Davis); 200–500 mg/day b.i.d. or t.i.d. dosing regimens for ≥3 weeks] participated in this open-label study. PHT was dispensed into polypropylene vials, and its use monitored by MEMS closures. Subjects ranged in age from 19 to 50 years. All subjects weighed within 25% of their desirable weight (range, 98–188 pounds) for height and frame size (1983 Metropolitan Life Tables). Female subjects were required to be practicing adequate birth control or be surgically incapable of pregnancy. None of the subjects had histories or indications of barbiturate use, alcohol abuse, and liver or kidney dysfunction.

Study design

This was a five-period, open-label study of ~11 weeks in duration. The study was designed to examine the clinical tolerability and pharmacokinetic characteristics of FBM and PHT during coadministration. A 3-week baseline period (Period 1) of PHT monotherapy, preceded the administration of FBM. FBM, 1,200 mg/day (400 mg t.i.d.), was coadministered with PHT (Period 2) for 2 weeks. Subsequent periods (3, 4, and 5), each lasting 2 weeks, scheduled 600 mg/day increases in FBM doses. Before starting successive periods of the study, PHT dose decreases of 20% were allowed if significant adverse experiences were noted. The decision to reduce the PHT dose was based on both the subject's report of the tolerability of the combination and trough PHT concentrations. Because the study design included PHT dose reductions based primarily on tolerability, some subjects entered periods without dose reductions. All subjects had PHT dose reductions before administration of 3,600 mg/day FBM.

Pharmacokinetic parameter estimates

To ensure steady state, trough plasma samples were collected for 2 or 3 days before serial blood draws on each period's last day. On the last day of each study period, subjects fasted for ≥10 h, and venous blood samples were taken before the dose (0 h), 0.5, 1, 2, 3, 4, 6, 8, and 12 h after the morning drug doses. Samples were shipped frozen to Wallace Laboratories, Cranbury, NJ, U.S.A., for analysis of PHT, HPPH, and FBM. SmithKline Beecham Laboratories (Norristown, PA, U.S.A.) determined trough PHT levels (taken before 0-h blood collection).

The following pharmacokinetic parameter estimates were determined by using plasma concentration-versus-time data. C_{max}, (the maximum observed plasma concentration), T_{max} (the time to C_{max}), 0-h (trough) plasma concentrations (C_{trough}). The linear trapezoidal was used to calculate the area under the curve during the dosing interval (AUC_τ). The average plasma concentration at steady state (C_{ss}) was calculated by dividing the AUC_τ by the dosing interval. Apparent clearance [CL/kg was calculated by dividing the dose (in milligrams) by AUC_τ, further divided by the unit body weight]. Pharmacokinetic parameter estimates were made by using SAS (Cary, NC, U.S.A.). The percentage of FBM and PHT protein binding were calculated by the formula:

$$\text{Percentage bound} = 100 - [AUC_\tau \text{ (free)}/AUC_\tau \text{ (total)}] \times 100$$

Safety

Safety of the subjects was monitored at baseline and during the course of the study by vital signs, clinical laboratory tests (clinical chemistry, hematology, and urinalysis as well as assessments of compliance and seizure frequency). Trough PHT concentrations were monitored at each weekly visit. Due to the open-label design and small sample size, reported seizure activity with PHT monotherapy and during FBM–PHT coadministration was recorded but not statistically compared.

All but one subject (subject 11) elected to continue in a long-term, follow-on FBM protocol after completion of this study, with further appropriate reductions in PHT dose.

Analytic methods

A validated isocratic liquid chromatographic method with a protein-free ultrafiltrate of plasma was developed for human plasma. Chromatographic conditions include a 4.6 × 150-mm Spherisorb ODS2, 3 μm high-performance liquid chromatography (HPLC) column. A phosphate buffer–acetonitrile–methanol mobile phase (700:160:140) was used with an ultraviolet absorbance detector (210 nm). Analyses of standards indicated linearity of FBM, PHT, and 5-(4-hydroxyphenyl)-phenyl-

hydantoin (HPPH) over the ranges 0.991–200, 0.195–100, and 0.049–25 μg/ml, respectively. Details of the assay have been described elsewhere (12).

RESULTS

All 10 subjects completed the initial 1,200 mg/day FBM with PHT coadministration period. Six subjects tolerated the AED combination well, and no changes were made to PHT dosage when the FBM dose was increased to 1,800 mg/day. These subjects had a dose reduction before 2,400 mg/day FBM. The remaining four subjects (group B), tolerated the 1,200 mg/day FBM dose less well and had the PHT dose reduced ~20% before receiving 1,800 mg/day FBM.

The changes in PHT dose with each incremental FBM dose increase were based primarily on the subjects' reported tolerance to the preceding dose regimen. Trough PHT concentrations were evaluated for associations with clinical toxicity. The grouping of subjects (groups A and B) was determined at the time of the first PHT dose reduction and was based on a separation of subjects who required PHT dose reduction and was made solely for the purpose of pharmacokinetic comparisons. The demographic characteristics of the groups appeared similar. Thus it is not possible to predict the tolerability of the combination. However, signs of intolerance related to the combination therapy, when occurring, resolved within 1–2 days of PHT dose reduction.

Phenytoin pharmacokinetics

PHT plasma protein binding was unaffected by FBM daily doses of ≤3,600 mg/day. The percentage (mean ± SD) PHT binding was 92.36 ± 0.42 (n = 10) during PHT monotherapy and 93.49 ± 0.22 (n = 3) when coadministered with 3,600 mg/day FBM.

All subjects had estimates of PHT pharmacokinetic parameters performed after 2 weeks of PHT (no dose adjustment) and 1,200 mg/day FBM. The changes in total PHT C_{max} and apparent clearance (CL/kg) during PHT monotherapy are shown in Fig. 1. The total PHT (all subjects) C_{max} was 17.6 ± 5.0 μg/ml with PHT monotherapy and increased to 22.9 ± 5.5 μg/ml after coadministration with 1,200 mg/day FBM (30% increase). The mean apparent PHT clearance was 19.7 ± 10.4 with PHT monotherapy and decreased to 15.4 ± 7.2 (ml/h)/kg during FBM–PHT coadministration.

Based on the subjects' reported tolerance and the degree of seizure control with the combined therapy, subjects either continued with their original PHT dose or had their PHT dose reduced 20% before the second FBM dose increase to 1,800 mg/day. Combination therapy was well tolerated, and the FBM dose was increased to 1,800 mg/day (600 mg, t.i.d.) without any PHT dose adjust-

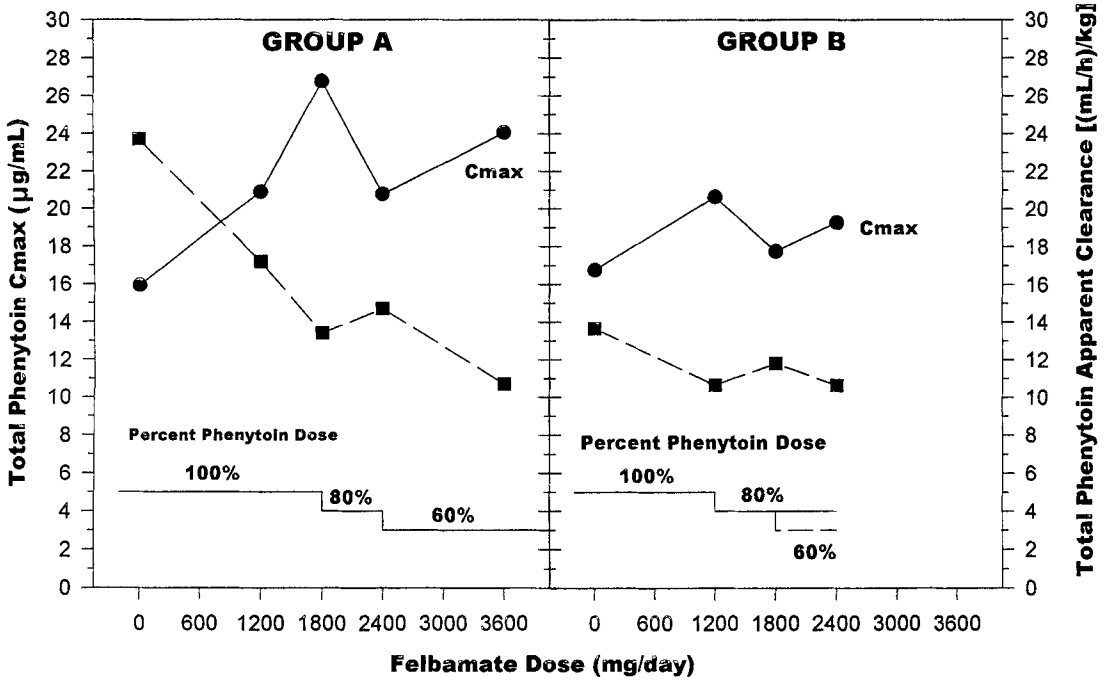

FIG. 1. Total phenytoin (PHT) C_{max} and apparent clearance during monotherapy and during felbamate (FBM) coadministration (groups A and B). Subjects who received 1,200 and 1,800 mg/day FBM but required a PHT dose reduction before 2,400 mg/day FBM were designated group A (n = 6). Subjects requiring a dose reduction before 1,800 mg/kg FBM were designated group B (n = 4). The mean total PHT C_{max} (circles) and apparent clearance (squares) are shown in relation to changes in FBM (X-axis) and PHT dose (solid line). The dotted line represents two subjects (group B) who required an additional PHT dose reduction. None of the group B subjects completed the final period of the study (3,600 mg/day FBM), although only one discontinued FBM.

ment in group A. The next PHT dose reduction in this group occurred before the 2,400 mg/day FBM regimen. Some patients required a PHT dose reduction after the 1,200 mg/day FBM regimen (group B).

Phenytoin pharmacokinetic parameter estimates among groups

The effect of increased doses of FBM on PHT C_{max} is shown in Fig. 1 and Tables 1 and 2. At baseline the mean total PHT concentration was 15.9 μg/ml (group A). C_{max} increased to 20.9 μg/ml with coadministration of 1,200 mg/day FBM and 26.8 μg/ml with 1,800 mg/day FBM. After a PHT dose reduction of 20% and an FBM increase in dose to 2,400 mg/day, C_{max} was increased to 20.8 μg/ml. After 3,600 mg/day FBM, the mean C_{max} was 24.1 μg/ml. PHT C_{trough}, AUC_τ, and C_{ss} also increased proportionately with increasing FBM doses and were reduced after PHT dose reduction. The apparent clearance (CL/kg) of PHT was consistently reduced with increasing FBM dose regimens (Table 1).

In the group of subjects in whom the clinical signs of intolerability from the PHT–FBM combination (group B) were apparent after 1,200 mg/day FBM, a PHT dose reduction before the initiation of 1,800 mg/day FBM was implemented. The same pharmacokinetic pattern observed in group A is evident with the dose reduction of PHT in group B (Table 2).

Free phenytoin pharmacokinetics

Free PHT accounted for <10% of the total plasma PHT concentrations. As the FBM dose increased from 0 to 400 to 600 mg, t.i.d., the C_{max} for free PHT increased from 1.16 to 1.51 to 1.88 μg/ml in group A. The AUC_τ increased from 8.8 to 11.3 to 14.3 μg/h/ml, respectively. C_{trough} and C_{ss} also increased with increasing FBM doses (data not shown). Clearance of free PHT decreased from 306 to 232 and 183 μml/h/kg. Similar results were noted in group B (data not shown).

HPPH Pharmacokinetics

The HPPH C_{max} was 0.15 ± 0.05 μg/ml with monotherapy and decreased 20% during coadministration of 1,200 mg/day FBM to 0.12 ± 0.05 μg/ml (mean of all subjects). In group A, when the FBM dose was increased from 0 to 1,200 to 1,800 mg/day, the C_{max} for HPPH decreased from 0.14, to 0.12, to 0.12 μg/ml, respectively (Table 1). Subjects in group B provided similar results (Table 2). There were also proportionate decreases in HPPH C_{trough}, C_{ss}, and AUC_τ. Concentrations continued to decline with increasing FBM doses and even when PHT doses were reduced. Measurements of free plasma HPPH often yielded values below the limits of detection of the assay. This precluded additional evaluation.

Felbamate pharmacokinetic parameter estimates

FBM plasma protein binding was unchanged. During coadministration of FBM with PHT, the percentage bound fraction ranged from 34.11 ± 2.05 (n = 10) to 35.83 ± 1.36 (n = 3). These values are similar to those previously reported during FBM monotherapy.

Total plasma FBM pharmacokinetic parameter estimates indicated a dose-related increase in C_{max}, C_{ss}, C_{trough}, and AUC_τ with increasing FBM dose in the presence of PHT. However, these pharmacokinetic parameters were reduced after PHT coadministration compared with values observed in subjects receiving FBM monotherapy. Apparent clearance and T_{max} were unaffected by FBM dose or changes in the PHT dose regimen (Table 3). However, C_{max}, C_{ss}, and AUC_τ were reduced and apparent clearance increased after PHT coadministration compared with reported values in subjects receiving FBM monotherapy (13,14; see Discussion).

Safety

Based on the experience of this study, FBM coadministration with unadjusted PHT doses often led to clinically significant reports of intolerance. The most com-

TABLE 1. *Plasma total phenytoin and HPPH pharmacokinetic parameters in group A*

	Felbamate dose (mg/day)				
	0	1,200	1,800	2,400	3,600
PHT dose (mg/day)	397 ± 73 (6)	397 ± 73 (6)	397 ± 73 (6)	332 ± 73 (6)	353 ± 68 (3)
Total phenytoin pharmacokinetic parameters (mean ± SD)					
C_{max} (μg/ml)	15.9 ± 4.1	20.9 ± 5.4	26.8 ± 6.7	20.8 ± 4.5	24.1 ± 4.3
CL/kg (ml/h)/kg	23.7 ± 14.1	17.2 ± 8.0	13.4 ± 6.0	14.7 ± 5.9	10.7 ± 3.3
C_{ss} (μg/ml)	14.5 ± 4.0	19.1 ± 4.7	24.4 ± 5.3	19.6 ± 3.9	22.8 ± 4.2
C_{trough} (μg/ml)	14.9 ± 4.6	20.7 ± 5.5	25.4 ± 6.7	20.8 ± 4.7	24.6 ± 4.0
AUC_τ (μg/h/ml)	116.1 ± 32.0	153.1 ± 37.2	195.0 ± 42.2	156.9 ± 31.9	182.4 ± 33.7
Total HPPH pharmacokinetic parameters (mean ± SD)					
C_{max} (μg/ml)	0.14 ± 0.07	0.12 ± 0.06	0.12 ± 0.06	0.10 ± 0.04	0.12 ± 0.04
C_{ss} (μg/ml)	0.13 ± 0.06	0.11 ± 0.05	0.11 ± 0.06	0.09 ± 0.04	0.11 ± 0.04
C_{trough} (μg/ml)	0.13 ± 0.07	0.12 ± 0.05	0.12 ± 0.05	0.10 ± 0.04	0.11 ± 0.04
AUC_τ (μg/h/ml)	1.03 ± 0.52	0.89 ± 0.43	0.89 ± 0.46	0.73 ± 0.33	0.89 ± 0.33

Group A, phenytoin dose was reduced 20% before increasing felbamate dose to 800 mg/t.i.d. (2,400 mg/day).

TABLE 2. *Plasma total phenytoin and HPPH pharmacokinetic parameter estimates in group B*

	Felbamate dose (t.i.d.)				
	0 mg	1,200 mg	1,800 mg	2,400 mg	3,600 mg
PHT dose (mg/day)	273 ± 56 (4)	273 ± 56 (4)	205 ± 41 (4)	180 ± 28 (2)	—
Total phenytoin pharmacokinetic parameters (mean ± SD)					
C_{max} (μg/ml)	16.8 ± 4.8	20.7 ± 3.2	17.8 ± 5.8	19.3 ± 5.1	—
CL/kg (ml/h)/kg	13.7 ± 3.3	10.7 ± 4.3	11.8 ± 4.8	10.6 ± 3.3	—
C_{ss} (μg/ml)	15.4 ± 4.7	19.7 ± 3.8	16.3 ± 5.8	17.6 ± 4.2	—
C_{trough} (μg/ml)	16.2 ± 4.7	19.8 ± 3.4	18.0 ± 5.8	17.6 ± 5.9	—
AUC_{τ} (μg/h/ml)	123.3 ± 37.3	157.9 ± 30.5	130.4 ± 46.5	105.6 ± 25.4	—
Total HPPH pharmacokinetic parameters (mean ± SD)					
C_{max} (μg/ml)	0.17 ± 0.03	0.15 ± 0.03	0.13 ± 0.04	0.10 ± 0.02	—
C_{ss} (μg/ml)	0.16 ± 0.03	0.14 ± 0.03	0.12 ± 0.03	0.10 ± 0.02	—
C_{trough} (μg/ml)	0.16 ± 0.04	0.14 ± 0.03	0.12 ± 0.04	0.08 ± 0.002	—
AUC_{τ} (μg/h/ml)	1.25 ± 0.24	1.08 ± 0.24	0.99 ± 0.27	0.56 ± 0.11	—

No subject in group B completed period 5 (3,600 mg/day felbamate). Phenytoin doses were reduced before 1,800 mg/day felbamate in all subjects, and in two subjects, reduced again, before the 2,400 mg/day felbamate dose increment.

mon adverse events (number of occurrences/number of subjects reporting) included abnormal thinking (15/eight), nausea (10/seven), diplopia (nine/three), fatigue (eight/five), and somnolence (eight/five). In general, adverse events dissipated with decreases in PHT dose but often returned with increasing FBM doses (and corresponding increases in plasma PHT). Some adverse events resulted in subjects terminating the study. However, with the exception of one subject, all chose to continue in an open-label FBM study in which further PHT dose reductions often lead to discontinuation of PHT therapy.

DISCUSSION

Because the plasma protein binding of neither PHT nor FBM was altered during coadministration, the most likely explanation for increasing PHT plasma concentrations involves the inhibition of cytochrome P-450 (CYP) isoforms. In vitro studies indicated that FBM inhibited CYP2C19 in human liver microsomes with a K_i of 54 μg/ml (within the range of therapeutic plasma concentrations) but had no effects on the seven other major isoforms tested including CYP2C9 (4).

PHT hydrolysis to HPPH is reportedly mediated by hepatic isoform CYP2C9 (15). However, there have been problems with this assumption. Zhou et al. (16) examined PHT hydroxylation in the oral mucosa of subjects with gingival hyperplasia. PHT added to tissue incubates resulted in marked variability in the degree of hydroxylation, and there was no apparent correlation with the extent of HPPH formation and CYP2C9 activity. This could suggest that metabolism of PHT is mediated by isoforms other than CYP2C9.

Based on studies of predicted versus reported AED drug–drug interactions, Levy (17) suggested that CYP2C9 is involved in PHT conversion to HPPH but that an alternate CYP2C19 pathway of PHT metabolism is affected by FBM. In subjects with a genetic CYP2C19 deficiency, the PHT K_m was generally unchanged, whereas the V_{max} for PHT metabolism was significantly

TABLE 3. *Felbamate pharmacokinetic parameter estimates in groups A and B during phenytoin coadministration*

		Felbamate dose (mg/day)			
	Group	1,200	1,800	2,400	3,600
C_{max} (μg/ml)	A	20.7 ± 4.4	30.6 ± 5.5	37.7 ± 8.5	54.0 ± 6.9
	B	25.6 ± 1.7	36.1 ± 2.1	57.8 ± 1.9	—
T_{max} (h)	A	1.5 ± 0.8	2.0 ± 1.1	1.3 ± 0.5	1.3 ± 0.6
	B	2.0 ± 1.4	2.0 ± 0.8	2.5 ± 0.7	—
CL/kg (ml/h)/kg	A	57.9 ± 6.3	57.2 ± 7.7	61.4 ± 4.7	54.4 ± 6.6
	B	45.7 ± 16.2	47.2 ± 19.3	54.8 ± 10.5	—
C_{ss} (μg/ml)	A	18.0 ± 3.6	27.6 ± 5.5	34.1 ± 7.2	49.8 ± 3.8
	B	23.3 ± 2.6	35.3 ± 4.3	52.8 ± 2.2	—
C_{trough} (μg/ml)	A	14.3 ± 2.7	22.3 ± 4.9	28.6 ± 5.4	43.8 ± 6
	B	19.1 ± 3.7	29.9 ± 4.8	45.3 ± 6.4	—
AUC_{τ} (μg/h/ml)	A	108.2 ± 21.7	165.8 ± 33.1	204.5 ± 43.4	298.8 ± 18.8
	B	139.8 ± 15.6	211.9 ± 25.8	316.7 ± 13.0	—

Values represent the mean ± SD.

reduced (18). This deficiency in PHT hydroxylation was associated with toxic PHT plasma concentrations despite therapeutic dose regimens (19,20). The fact that PHT plasma concentrations increase 25–35% with FBM coadministration lends support to the CYP2C19 alternate metabolic pathway hypothesis, particularly because HPPH concentrations were for the most part decreased or unchanged despite increasing plasma PHT concentrations. Clearly, further clarification of the contribution and extent of the two isoforms involved in PHT metabolism is required.

Because PHT toxicity can occur with plasma concentrations within or slightly exceeding the therapeutic range for most subjects, knowledge of dose adjustments required for continued seizure control and maintaining therapeutic/nontoxic plasma concentrations of PHT on an individual basis is of import. The coadministration of FBM at doses of 1,800 and 2,400 mg/day required ~20% decreases in PHT dose to maintain pre-FBM plasma PHT concentrations. FBM titration to doses of 3,600 mg/day required overall PHT dose reductions on average of 40% (range, 20–72%) based on tolerability.

FBM pharmacokinetic parameters were affected by PHT coadministration when compared with those of subjects receiving FBM monotherapy (14). FBM C_{max} and AUC_{τ} displayed linearity over the dose range of 400–6,000 mg/day when administered as monotherapy (13, 14,21). Although linearity was observed with respect to dose in this study, comparisons of C_{max} values obtained in FBM monotherapy subjects at 1,200, 2,400, and 3,600 mg/day FBM indicates that the coadministration of PHT resulted in 60, 58, and 56% reductions, respectively. The reductions in C_{max} are related to the increased FBM clearance resulting from PHT coadministration.

The mean apparent clearance values in group A of 57.9, 61.4, and 54.4 (ml/h)/kg for the 1,200, 2,400, and 3,600 mg/day FBM regimens correspond to reported values of 26.8, 28.5, and 30.1 (ml/h)/kg reported when the same doses are administered as monotherapy (14). These findings are also consistent with PHT-induced induction of the microsomal enzymes. FBM clearance has been reported to decrease and approach monotherapy values after the discontinuation of PHT coadministration (22). However, FBM has a wide therapeutic window with seizure control being reported in the range of 50–100 μg/ml with minimal side effects reported (23). Thus reductions in PHT daily dose and the normalization of FBM clearance would be of less concern clinically than corresponding increases in PHT plasma concentrations after FBM coadministration.

In summary, PHT doses should be reduced with FBM coadministration because PHT pharmacokinetic parameters change markedly with addition of FBM. Similar reductions should be addressed with any increase in FBM dose. Although our study described patients placed into arbitrary groups for purposes of pharmacokinetic analyses, each patient was technically considered as an individual in regard to decisions based on intolerance, trough PHT concentrations, and adequacy of seizure control. Plasma PHT concentrations should be frequently monitored as well as signs of intolerance and changes in seizure frequency when increasing the FBM daily dose regimen.

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