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Pharmacokinetic interaction studies between felbamate and vigabatrin

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To assess the possible occurrence of pharmacokinetic interactions between the antiepileptic agents felbamate and vigabatrin, two randomized, double-blind, placebo-controlled, crossover studies were conducted in healthy male volunteers. In Study I, 18 subjects received oral vigabatrin 1000 mg every 12 h for two 8 day periods with felbamate 1200 mg every 12 h or placebo. In Study II, 18 other volunteers were administered oral felbamate 1200 mg every 12 h for two 8 day periods with vigabatrin 1000 mg every 12 h or placebo. On the eighth day of each treatment period, blood and urine samples were collected over 12 h for determination of the active S(+)- and inactive R(−)-vigabatrin enantiomer concentrations (Study I) or felbamate concentrations (Study II). In Study I, the pharmacokinetic parameters of R(−)-vigabatrin were similar during co-administration with felbamate or placebo. Felbamate produced a 13% increase in AUC(0,12 h) and an 8% increase in urinary excretion of S(+)-vigabatrin. Although these changes were statistically significant, their magnitude was small. In Study II, the pharmacokinetic parameters of felbamate were similar during concurrent administration with vigabatrin or placebo. These data indicate that there are no clinically relevant pharmacokinetic interactions between felbamate and vigabatrin in man.

Keywords felbamate vigabatrin pharmacokinetics

Introduction

Felbamate (2-phenyl-1,3-propanediol dicarbamate) is a chemically unique antiepileptic agent. It is eliminated by both renal excretion and hepatic metabolism [1]. Studies in man indicate that felbamate is well absorbed (> 90%), has a small volume of distribution (< 1 l kg^{-1}) and binds only moderately to plasma proteins (< 25%) [1, 2]. Pharmacokinetic interactions have been reported between felbamate and other antiepileptic drugs. Felbamate reduces the clearance of phenytoin, phenobarbitone and valproate, and increases the clearance of carbamazepine, while its own clearance is increased by phenytoin, carbamazepine and phenobarbitone [3–6]. Several of these interactions may be a result of altered activity of hepatic drug metabolizing enzymes.

Vigabatrin (γ-vinyl GABA; 4-amino-hex-5-enoic acid), a synthetic derivative of the neurotransmitter GABA, exists as a racemic mixture of the active S(+) and inactive R(−)-enantiomers [7]. Vigabatrin is eliminated renally unchanged, does not influence cytochrome P450 enzyme activity, nor does it bind to plasma proteins [7]. The only reported drug interaction involving vigabatrin is a reduction of phenytoin plasma concentrations but the mechanism for this is still uncertain [8].

Although interactions between felbamate and vigabatrin would appear to be unlikely, and the therapeutic indices of both drugs are high, it is important to determine the presence of any pharmacokinetic interactions because of the likely coadministration of these two drugs in the treatment of epilepsy. This paper describes two studies investigating possible interactions; Study I: the effects of felbamate on the pharmacokinetics of vigabatrin; and Study II: the effects of vigabatrin on the pharmacokinetics of felbamate.

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Methods

Eighteen healthy male volunteers between the age of 19 and 33 years and weighing between 65 and 83 kg participated in Study I. A further 18 healthy male subjects aged between 19 and 34 years and weighing between 60 and 91 kg were enrolled in Study II. All 36 volunteers were non smokers and Caucasian. They were drug free for at least 2 weeks prior to the study and received no other drugs during the study. All subjects were in good health based on medical history, physical examination, electrocardiogram and routine clinical chemistry tests. All volunteers provided written informed consent prior to entry to the study and approval was granted by an Ethics Committee. Volunteers were observed during the study for adverse events, vital signs and clinical chemistry tests were also monitored.

Both studies used balanced, randomized, placebo-controlled, double-blind designs. In Study I, all 18 volunteers received vigabatrin (2 g day^{-1}) on an open basis during two treatment periods of 8 days each, and were also assigned to receive double-blind felbamate during one treatment period and placebo during the other. Felbamate was titrated from 1200 mg day^{-1} (Day 1) to 2400 mg day^{-1} (Days 2–8). Both drugs were administered twice daily except on Day 8, where subjects were dosed in the morning only. The two treatment periods were separated by a 14 day washout period. In Study II, felbamate was administered on an open basis during both treatment periods with double-blind vigabatrin or placebo. The same doses, dosing schedules and washout period were used as described for Study I.

For both studies, pharmacokinetic assessment was carried out over 12 h on Day 8 of each treatment period. Blood samples were collected prior to morning dosing (0 h), and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h post dose. Single urine samples (0–12 h) were collected simultaneously. Samples were assayed for vigabatrin enantiomers (Study I) or felbamate (Study II). Additional blood samples to measure trough plasma concentrations were collected on Days 6 and 7 of each treatment period in both studies.

S(+)- and R(−)-vigabatrin plasma and urinary concentrations were determined by a chiral GCMS method (plasma limit of quantification (LOQ) 0.5 μg ml^{-1}; urine LOQ 5 μg ml^{-1}) [9]. Felbamate plasma and urinary concentrations were determined by h.p.l.c. u.v. (LOQ 0.1 μg ml^{-1}) [4]. Inter- and intra-assay coefficients of variation were < 14% for all analyses. Pharmacokinetic parameters were calculated using model independent methods [10]. The maximum plasma concentrations (C_{max}) were the observed values. The area under the plasma concentration-time curve from time zero to 12 h [AUC(0,12 h)] was calculated using the linear trapezoidal rule. Renal clearance (CL_R) was calculated as the ratio of the amount excreted in the urine from zero to 12 h [*Ae*(0,12 h)] to plasma AUC(0,12 h). Log-transformed plasma pharmacokinetic parameters and non-log transformed urinary excretion data were compared using crossover ANOVAs. Steady-state conditions were assessed by comparing trough values using a repeated measures ANOVA. With 18 subjects, there was 80% power to detect a 7–8% difference from the R(−)- and S(+)-vigabatrin AUC reference means (Study 1), and an 11% difference from the felbamate AUC reference mean (Study 2).

Results

Study I: Effects of felbamate on the pharmacokinetics of vigabatrin

Although 18 subjects were enrolled and completed Study I, pharmacokinetic analyses were performed on only 16 subjects because two volunteers showed quantifiable plasma felbamate concentrations while receiving vigabatrin plus placebo treatment. Steady state was achieved by Day 6 for S(+)- and R(−)-vigabatrin (Table 1) and felbamate (data not shown). Felbamate did not affect the C_{max} or renal clearance of S(+)-vigabatrin. However, AUC(0,12 h) increased by approximately 13% (P = 0.001), and the amount excreted in the urine over 12 h increased by approximately 8% (P = 0.04) compared with placebo treatment. Coadministration of felbamate did not affect the C_{max}, AUC(0,12 h), or the urine recovery of the R(−)-enantiomer of vigabatrin (Table 1; Figure 1a and b). Five subjects (28%) reported adverse event(s) during this study, which included headache, nausea, vomiting, diarrhoea, somnolence and dizziness. These were mild to moderate in severity and resolved spontaneously. Headache was the most frequent adverse event reported.

Study II: Effects of vigabatrin on the pharmacokinetics of felbamate

All 18 subjects were included in the pharmacokinetic analysis of Study II. Steady state was achieved for S(+)- and R(−)-vigabatrin by Day 6 (data not shown) and for felbamate by Day 7 (Table 1). Coadministration of vigabatrin did not affect the C_{max}, AUC(0,12 h) renal clearance or the urine recovery of felbamate compared with placebo (Table 1; Figure 1c). Three subjects (17%) reported adverse event(s) including headache, nausea, abdominal discomfort and vomiting, which were mild to moderate in severity and resolved spontaneously. Headache was the most frequent complaint.

Discussion

The main finding of these studies is that there are no clinically relevant pharmacokinetic interactions between felbamate and vigabatrin. In Study I, felbamate had no effects on the pharmacokinetics

Table 1 Mean (s.d.) pharmacokinetic parameters of R(−)- and S(+)-vigabatrin enantiomers and felbamate in Studies 1 and 2

	Study 1				*Study 2*	
	R(−)-vigabatrin		*S(+)-vigabatrin*		*Felbamate*	
	V + F	*V + P*	*V + F*	*V + P*	*F + V*	*F + P*
Day 6 C_{min} (μg ml^{-1})	1.78 (0.36)	1.72 (0.46)	2.09 (0.23)	1.66 (0.28)	43.9 (7.9)	48.0 (11.5)
Day 7 C_{min} (μg ml^{-1})	1.86 (0.43)	1.78 (0.39)	2.16 (0.35)	1.69 (0.27)	48.7 (8.8)	51.9 (11.9)
Day 8 C_{min} (μg ml^{-1})	1.85 (0.37)	1.92 (0.52)	2.14 (0.36)	1.64 (0.33)	50.5 (11.6)	51.0 (11.7)
C_{max} (μg ml^{-1})	18.2 (4.4)	19.3 (4.2)	10.3 (1.9)	9.9 (1.5)	65.9 (9.2)	65.9 (13.8)
PE	94		103		101	
CI	82–107		94–112		97–105	
AUC(0,12 h) (μg ml^{-1} h)	66.7 (12.0)	68.0 (10.9)	53.0 (7.4)*	47.0 (6.1)*	636 (95)	663 (126)
PE	98		113		96	
CI	93–102		108–118		92–101	
Ae(0, 12 h) (mg)	456 (87)	463 (60)	369 (63)**	339 (47)**	442 (146)	399 (140)
CL_R (ml min^{-1} kg^{-1})	1.59 (0.30)	1.59 (0.22)	1.61 (0.29)	1.68 (0.29)	0.17 (0.07)	0.15 (0.07)

*Day 8 V + F *vs* V + P, $P = 0.001$.
**Day 8 V + F *vs* V + P, $P = 0.04$.
V: vigabatrin; F: felbamate; P: placebo; PE: point estimate; CI: 90% confidence interval (expressed as a percentage of experimental treatment to placebo).

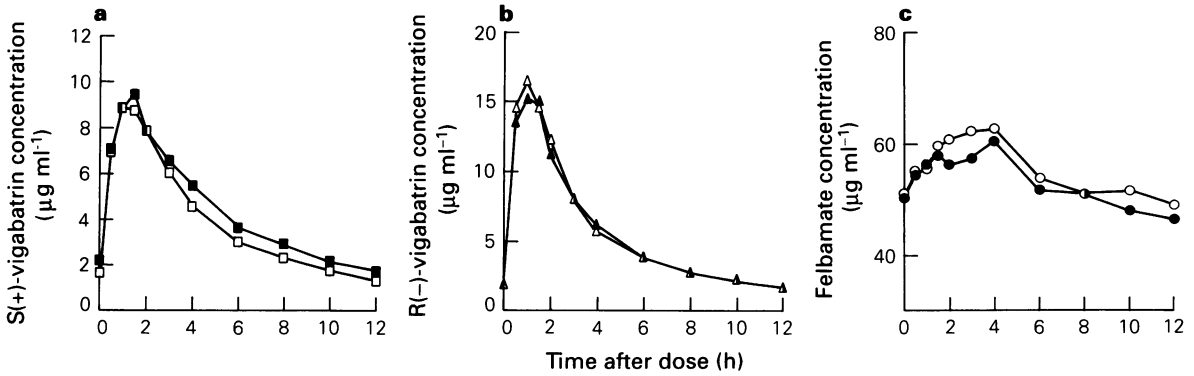

Figure 1 a) Effects of felbamate (■) or placebo (□) on mean plasma S(+)-vigabatrin concentrations ($n = 16$); b) effects of felbamate (▲) or placebo (△) on mean plasma R(−)-vigabatrin concentrations; c) effects of vigabatrin (●) or placebo (○) on mean plasma felbamate concentrations ($n = 18$).

of the R(−)-enantiomer. However, statistically significant changes were observed in two pharmacokinetic parameters of S(+)-vigabatrin (AUC(0,12 h) and urinary excretion) following coadministration of felbamate. These increases were small (13 and 8%, respectively) and are unlikely to be of clinical relevance. The results of Study II indicated that vigabatrin had no effect on the pharmacokinetics of felbamate. The pharmacokinetic measurements for felbamate and vigabatrin enantiomers are in accord with those reported previously [6, 11]. The absence of clinically relevant pharmacokinetic interactions in these two studies suggests that coadministration of felbamate and vigabatrin in patients should be uncomplicated.

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