Single and multiple dose pharmacokinetics of felbamate in the elderly

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Aims The objective of this study was to compare the pharmacokinetics, safety and tolerability of the antiepileptic drug felbamate in young and elderly healthy vounteers.
Methods The single and multiple dose pharmacokinetics of felbamate were examined in an open-label two-dose level parallel group study in 24 elderly (66 to 78-year-old) and 11 young (18 to 45-year-old) healthy volunteer subjects. Pharmacokinetics were determined from blood samples obtained over 120 h after administration of single 600 mg or 1200 mg doses, and after multiple doses of 600 mg or 1200 mg administered every 12 h. Safety and tolerability were assessed through laboratory tests, ECGs, vital signs and reported adverse events.
Results Single dose felbamate pharmacokinetic parameters differed between young and elderly subjects; compared with young subjects, elderly subjects had lower mean clearance (31.2 *vs* 25.1 ml min^{-1}; 90% CI −11.4 to −0.9; $P=0.02$) and a trend towards a greater half-life (18.6 *vs* 21.0 h; 90% CI −0.6 to 5.4; $P=0.11$). Mean AUC and C_{max} values were also higher in elderly subjects. No gender differences were noted for weight-adjusted pharmacokinetic variables. Felbamate was less well tolerated in elderly subjects compared with young subjects, as shown by higher rates of adverse event reporting and dropouts at the higher dose level. This may be due to age-related pharmacokinetic differences, to the rapid dose titration schedule used in this study, and/or to altered sensitivity to felbamate's pharmacodynamic effects.
Conclusions These findings imply that elderly subjects require lower initial dosing and slower dose titration of felbamate than non-elderly subjects.

Keywords: felbamate, pharmacokinetics, anti-epileptic drug, age

Introduction

Felbamate (2-phenyl-1, 3-propanediol dicarbamate) is a chemically unique orally active antiepileptic agent which has demonstrated anticonvulsant activity in patients with partial seizures with or without secondary generalization and Lennox-Gastaut syndrome [1, 2]. Pharmacokinetic studies in man have shown that following oral administration of [^{14}C] felbamate, greater than 90% of radioactivity is eliminated in urine indicating that felbamate is well absorbed [3]. Felbamate is eliminated by both renal excretion and hepatic metabolism, with formation of para- and 2-hydroxymetabolites (which are subsequently conjugated) and a monocarbamate metabolite [3]. Felbamate has a volume of distribution of $<1\,l\,kg^{-1}$, and does not bind extensively to plasma proteins [4].

Epidemiological studies on epilepsy have demonstrated that the incidence of seizures increases after 60 years of age [5], possibly as a result of increased vulnerability to disorders that induce seizures such as reduced haemostatic mechanisms, brain tumours, cerebrovascular accidents and infections. Because the tolerability, disposition or elimination of drugs may be altered in the elderly compared with younger subjects, it is important to evaluate the pharmacokinetics of new antiepileptic agents such as felbamate in this population.

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Methods

Thirty-five male and female subjects were enrolled into this open-label, single and multiple dose, parallel group study. Included were 24 elderly volunteers (mean age 71.3 years; range 66–78 years; mean weight 72.3 kg; range 51.0–91.9 kg; 12 females, 12 males), and 11 young volunteers (mean age 28.8 years; range 18–45 years; mean weight 70.2 kg; range 53.4–92.5 kg; four females, seven males). All subjects were determined to be in good health through medical history, physical examination and laboratory tests. This study was approved by a local ethics committee, and each subject provided written informed consent prior to participation.

The study duration was 14 days. All subjects received a single dose of felbamate on Day 1, followed by multiple blood sampling for pharmacokinetic assessment through to 120 h post dose (Day 6). Multiple doses of felbamate were administered from Days 6–14, and on the morning of Day 14, blood samples were obtained over 12 h for assessment of steady state pharmacokinetics. In the initial study design, subjects would receive felbamate 1200 mg single dose (Day 1), followed by 600 mg every 12 h on Days 6–7 and

1200 mg every 12 h on Days 8–14. However because of tolerability problems with this dose regimen, the protocol was amended to include a low dose group (Day 1: 600 mg; Days 6–7: 600 mg four times daily; Days 8–14: 600 mg every 12 h). Data presented here refer to these two groups as high and low-dose groups, respectively. Five subjects (four young, one elderly) in the high dose group participated in an extension of this study where they received felbamate 1200 mg every 8 h from Day 15–21, with pharmacokinetic sampling for 72 h subsequently.

Blood samples were collected into heparinized tubes immediately prior to treatment (0 h) on Days 1, 12, 13, 14 and 21 and at additional times following dosing on the days of pharmacokinetic evaluation. On Days 1 through 5 (post-single dose) blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, 72, 96 and 120 hr after dosing. On Days 14 and 21, blood samples were collected over 12 and 72 h, respectively, using the above sampling schedule. Plasma was separated by refrigerated centrifugation and was frozen to at least -20° C pending analysis for felbamate. Urine was collected at 4 h intervals on Days 1–5, 14 and 21 and was stored frozen to at least -20° C pending analysis. Plasma and urine samples were analyzed for felbamate by validated high performance liquid chromatographic methods [6]. The methods were validated with respect to linearity, specificity, limit of quantitation, precision and accuracy. Inter- and intraassay CVs were less than 5% and less than 3.8% respectively over the concentration range 0.1–50 $\mu g\,ml^{-1}$. The limits of quantitation (LOQ) were 0.1 $\mu g\,ml^{-1}$ in plasma and 1 $\mu g\,ml^{-1}$ in urine.

Physical examinations, ECGs, safety laboratory tests and recordings of vital signs were completed at screening, at various times during the study and at the completion of the multiple dose period. Throughout the study, the volunteers were continuously observed and questioned for the occurrence of adverse events.

Plasma concentrations above the LOQ were used for pharmacokinetic analysis using model independent methods [7]. The maximum plasma concentration (C_{max}) was the observed value. For single dose (Day 1) data, the terminal phase rate constant λ_z was calculated as the negative of the slope of the log-linear terminal portion of the plasma concentration-time curve using linear regression. The terminal phase half-life ($t_{1/2,z}$) was calculated as $0.693/\lambda_z$. The areas under the plasma concentration-time curve from time zero-to the final quantifiable concentration, AUC(0,t) (on day 1 only), and over the dosing interval τ, AUC(τ), were calculated using the linear trapezoidal rule ($\tau = 12$ h for multiple dosing). For single dose data, the value of AUC(0,t) was extrapolated to infinity by the equation: $AUC = AUC(0,t) + Ct/\lambda_z$, where Ct was the estimated concentration determined from linear regression at time t. Apparent total body clearance (CL/F) after single dosing was calculated as dose/AUC, and after multiple dosing as dose/AUC(τ). The apparent volume of distribution (V_z) was calculated from the single dose data as $(Dose/AUC)/\lambda_z$. Renal clearance (CLr) was calculated from the single dose data by the following equation: CLr = Ae/AUC, where Ae was the amount of felbamate excreted into the urine during a dosing interval. The effects of age and gender on pharmacokinetic variables were assessed by confidence interval analysis of between-group differences. Comparison of creatinine clearance values between groups was by two sample Student's t-test using a significance level of 0.05. Correlation of felbamate renal clearance and creatinine clearance was examined using Pearson's r statistic.

Results

Initial review of pharmacokinetic data from the elderly subjects grouped into 5-year cohorts (i.e. 66–70, 71–75, >75 years) demonstrated no age-related differences between groups (data not shown). Therefore, to maximize subject numbers in each group, the only comparisons for dose-independent variables (i.e. CL/F, V_z, CLr, $t_{1/2,z}$) are between young and elderly subjects. For dose-dependent variables (i.e. C_{max}, AUC), data from young and elderly subjects have been further divided into low- and high-dose groups.

Mean concentration-time profiles after single and multiple doses of high and low doses are shown in Figure 1, and mean (s.d.) pharmacokinetic parameters are presented in Table 1. Steady state was achieved for all subjects by Day 12 (data not shown). Statistically significant differences in the single dose pharmacokinetic parameters of felbamate were for noted for CL/F and CLr (both of which were approximately 20% lower in elderly compared with young subjects) and AUC (which was 20% higher in elderly compared with young subjects for the high dose group). Consistent but non-significant trends were noted for AUC (low dose group), C_{max} and $t_{1/2,z}$, with higher values in elderly subjects. In contrast, multiple dose pharmacokinetic parameters (C_{max}, AUC and CL/F) were generally similar in elderly and young subjects. Only five subjects were able to tolerate dose escalation to 3600 mg (four young male and one elderly male subjects). Mean (s.d.) C_{max} and AUCτ values for these five subjects were 100 (14) ng ml^{-1} and 745 (117) ng ml^{-1} h, respectively. Mean (s.d.) creatinine clearance values in young and elderly subjects were 82 (22) and 55 (15) ml min^{-1}, respectively ($P < 0.001$). Felbamate single dose renal clearance and creatinine clearance values were significantly correlated ($r^2 = 0.40$; $P < 0.001$).

Single dose clearance and $t_{1/2,z}$ data from all subjects were combined to examine the effects of gender on single dose pharmacokinetic parameters. Statistically significant differences were noted between males and females for CL/F and CLr (approximately 20–25% lower for females compared with males); however there were no gender differences for $t_{1/2,z}$ and bodyweight-adjusted CLr (Table 2).

There were no clinically relevant abnormalities or changes in the clinical laboratory tests, physical examinations, ECGs or vital signs in any subjects during the study. Overall, 30 of the 35 subjects (86%) reported at least one adverse event. The most frequently reported adverse events were headache (66%), nausea (66%), dizziness (51%), constipation (34%), somnolence (31%), ataxia (26%), insomnia (26%), impaired concentration (23%), dry mouth (17%), fatigue (17%), vomiting (14%), apathy (14%), confusion (11%), and pharyngitis (11%), and all were rated as mild to moderate in severity. The incidence of adverse events in the high dose group (21/21, 100%) was greater than that of the low dose group (9/14, 64%). The range of adverse events in the high

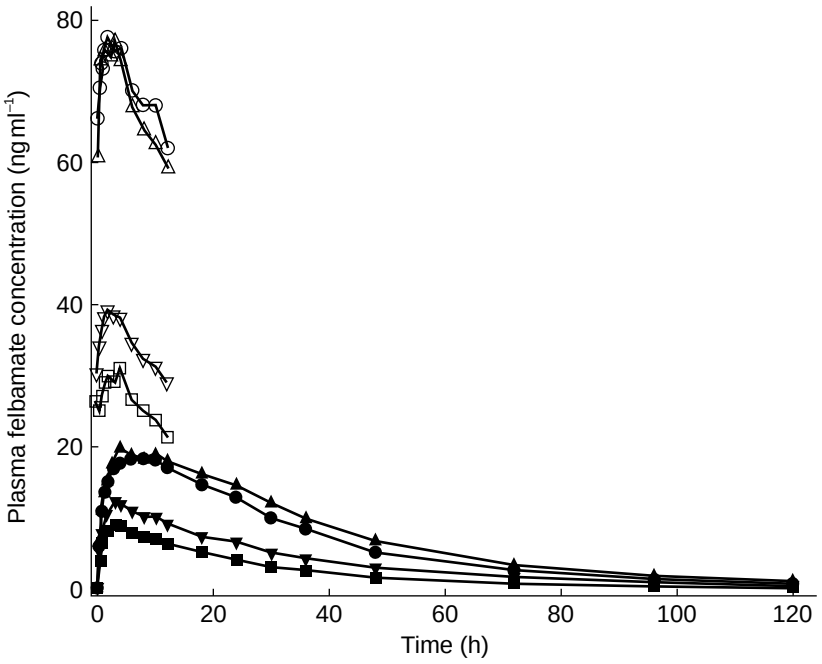

Figure 1 Mean plasma felbamate concentrations following single 600 mg doses in young (■) and elderly (▼) subjects; single 1200 mg doses in young (●) and elderly (▲) subjects; multiple doses of 600 mg every 12 h in young (□) and elderly (▽) subjects; and multiple doses of 1200 mg every 12 h in young (○) and elderly (△) subjects.

dose group was more extensive than those in the low dose group, although their nature (central nervous system and gastrointestinal in origin) was similar. In the low dose group the incidence of subjects reporting adverse events increased with increasing age; 33% in subjects aged 18–45 years, 50% in 66–70 year olds, 75% in 71–75 year olds, and 100% in subjects aged 76 years and over. The rate of adverse event reporting was slightly higher in females (4/6; 67%) compared with males (4/8; 50%) in the low dose group.

Overall, 16 of the 35 (46%) subjects discontinued prior to Day 14. Fifteen of the 16 subjects who discontinued were in the high dose group and all 15 were due to adverse events. Of these 15 discontinuations, there were 4/8 subjects (50%) aged between 18–45 years, 6/7 subjects (86%) aged 66–70 years, 4/5 subjects (80%) aged 71–75 years, and 1/1 (100%) aged 76 years and over (Table 3). In the high dose group, 10/10 females (100%) dropped out compared with 5/11 males (45%).

Discussion

Many drugs are less well tolerated in the elderly than in younger subjects. One reason for this may be age-related changes in pharmacokinetics as a result of changes in renal or hepatic function or body composition [8]. Age-related pharmacokinetic changes are most evident for compounds whose elimination is primarily by oxidative metabolism, but not for compounds eliminated by glucuronidation, sulphation or acetylation [8, 9]. Such changes are of particular importance for antiepileptic drugs (AEDs), where oxidative metabolism is an important route of elimination for certain older compounds (e.g. carbamazepine, phenytoin), and whose therapeutic indices are low. Altered pharmacokinetics have been reported in the elderly for most of the older AEDs [10]. For example, the elimination half-lives of phenytoin, valproate and carbamazepine are increased in elderly subjects compared with non-elderly adults; for the latter two drugs, the magnitude of this change has been estimated to be approximately 50% [10]. Similar effects have been seen for benzodiazepines which undergo oxidative metabolism (e.g. diazepam) [9]. In contrast, age-related pharmacokinetic changes have been shown to be relatively minor for the newer AEDs lamotrigine, vigabatrin and gabapentin [11–13], which are eliminated unchanged or which undergo primarily Phase 2 metabolism. The pattern of elimination of felbamate is not yet fully elucidated, but it is renally excreted unchanged and also undergoes some oxidative metabolism [3]. Thus age-related changes in these routes of elimination would account for the pharmacokinetic differences observed in elderly subjects in this study (e.g. reduced clearance, higher concentrations, longer $t_{1/2,z}$ compared with young subjects). Age-related pharmacokinetic differences were most evident during single dose assessment, but not during multiple dose assessment. The reason for this is unclear. To determine whether this might be an artifact of the high dropout rate in the elderly, as a result of differences in bioavailability affecting tolerability (i.e. subjects who had higher plasma concentrations would tend to drop out before multiple dose pharmacokinetic assessment, and thus reduce differences between age groups), mean single dose pharmacokinetic parameters were compared between elderly subjects who dropped out of the study and for those who remained. However these were similar between the two groups.

In addition to single dose pharmacokinetic differences, felbamate was less well tolerated in elderly subjects in this study compared with young subjects. Elderly subjects reported higher rates of adverse events and were more likely to drop out. Within the elderly subjects, there was a positive relationship between increasing age and incidence of adverse event reporting (for the low dose group) and with incidence of dropouts (for the high dose group). These observations may not only be associated with age-related pharmacokinetic differences, but may also indicate that the elderly are more sensitive to the pharmacodynamic effects of felbamate than younger subjects. Similar findings have been reported for a

Table 1 Mean (s.d.) pharmacokinetic parameters of felbamate in young and elderly subjects.

		Young subjects			*Elderly subjects*					
		Low dose	*High dose*	*Low+high dose*	*Low dose*	*High dose*	*Low+high dose*	*Difference (old–young)*	*90% CI*	P
Single dose	n★	2–3	8	10–11	9–10	12–13	21–23			
	C_{max} (ng ml^{-1})	8.9 (0.2)			12.7 (2.9)			5.2	−1.8–12.2	0.13
			19.6 (4.8)			22.0 (6.0)		2.4	−2.8–7.7	0.35
	AUC	244 (★★)			405 (120)			160.3	−5.1–325.7	0.06
	(ng ml^{-1} h)		711 (49)			854 (147)		143.3	29.5–257.1	0.02
	$t_{1/2,z}$ (h)			18.6 (3.2)			21.0 (4.3)	2.4	−0.6–5.4	0.11
	V_z (l)			50.0 (9.3)			45.4 (10.3)	−4.7	−12.2–2.9	0.22
	CL/F (ml min^{-1})			31.2 (2.1)			25.1 (5.3)	−6.1	−11.4–−0.9	0.02
	CLr (ml min^{-1})			11.6 (2.1)			9.2 (3.0)	−2.4	−4.5–−0.3	0.03
Multiple dose	n★	3	5–6	8–9	10	5	15			
	C_{max} (ng ml^{-1})	32.7 (3.2)			41.1 (7.0)			8.5	−1.0–17.9	0.07
			78.5 (16.4)			75.5 (11.9)		−3.0	−22.9–17.0	0.74
	AUCτ	318 (79)			414 (66)			96.1	−3.3–195.4	0.06
	(ng ml^{-1} h)		849 (140)			823 (132)		−25.7	−212.5–161.1	0.76
	CL/F (ml min^{-1})			27.0 (6.8)			24.7 (3.7)	−2.3	−6.7–2.1	0.30
	CLr (ml min^{-1})			10.0 (3.1)			10.1 (3.5)	0.1	−3.0–3.2	0.95

n★ = number of subjects for each pharmacokinetic parameter (values not available for all subjects). ★★not calculated; $n=2$.

Table 2 Effects of gender on mean (s.d.) felbamate pharmacokinetics.

		All males Low + high dose	*All females Low + high dose*	*Difference (F–M)*	*90% CI*	P
Single dose	n*	18–19	14–15			
	CL/F (ml min^{-1})	30.6 (7.4)	22.5 (4.5)	−8.06	−11.9–−4.3	0.001
	CL/F kg (ml min^{-1} kg^{-1})	0.39 (0.09)	0.33 (0.09)	−0.07	−0.12–−0.01	0.04
	CLr (ml min^{-1})	10.9 (3.1)	8.7 (2.4)	−2.2	−3.8–−0.5	0.03
	CLr/kg (ml min^{-1} kg^{-1})	0.14 (0.04)	0.13 (0.05)	−0.01	−0.04–0.02	0.54
	$t_{1/2,z}$ (h)	21.0 (3.7)	19.2 (4.5)	−1.8	−4.2–0.7	0.23

n* = number of subjects for each pharmacokinetic parameter (values not available for all subjects).

Table 3 Number of study dropouts—relationship with age and felbamate dose group.

Dose group	*Age group 18–45 years*	*66–70 years*	*71–75 years*	*> 76 years*	*All elderly*
High dose	4 (50%)	6/7 (86%)	4/5 (80%)	1/1 (100%)	11/13 (85%)
Low dose	0/3	1/4 (25%)	0/4	0/4	1/12 (8%)

range of other compounds including AEDs [8, 9, 14]. The exact mechanisms underlying this increased sensitivity is unknown but may include altered receptor sensitivity, changes in second messenger activity, or impairment of general homeostatic mechanisms [8]. It should also be noted that the rapid felbamate titration schedule in this study (doses were doubled over a 48 h period between Days 6 and 8) complicates this issue. The dose titration schedule used in this study was based on a schedule used in an early clinical study in patients with epilepsy [15]. More recent clinical studies as well as postmarketing experience have shown that the incidence of adverse events can be significantly reduced by using slower dose titration. Thus the rapid titration of felbamate in the present study may have contributed to the poor tolerability seen in the young high dose group, and the poor tolerability in elderly low and high dose groups. Design changes (introduction of the lower dose group) which occurred after the start of the study may have complicated the interpretation of some safety and pharmacokinetic findings. For example, the small numbers of young subjects in the low dose group complicates comparison of safety and dose-dependent pharmacokinetic data with low dose elderly subjects. However, this does not substantially detract from the main findings of the study, that there are age-related differences in felbamate pharmacokinetics and tolerability.

Although not a main objective of this study, these data also provide an opportunity to examine the effects of gender of felbamate's pharmacokinetics. CL/F and CLr adjusted for bodyweight are essentially similar between males and females (Table 2). However because females are lighter than males, they would tend to have higher felbamate concentrations during the study, which may account for the slightly higher rate of adverse event reporting in females administered low dose felbamate, and for the higher dropout rate in females administered high dose felbamate.

The mean pharmacokinetic parameters reported in this study are in close agreement with those reported in healthy volunteer studies after single 600 mg and 1200 mg doses [4] and multiple doses of 2400 mg day^{-1} [16]. As previously demonstrated [17] felbamate exhibits a linear relationship between dose and C_{max} or AUC over the dose range of 1200–3600 mg day^{-1}.

In conclusion, felbamate pharmacokinetics and tolerability are different in elderly compared with young subjects. The latter finding may be due to pharmacokinetic differences, or may also be due to increase sensitivity to the central effects of felbamate. Felbamate tolerability in the elderly may be enhanced if lower initial doses are used (e.g. 600 mg day^{-1}) combined with more cautious titration (e.g. increase by 600 mg at intervals no shorter than every 1–2 weeks) than the present recommendations for administration to non-elderly subjects.

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