Single-dose pharmacokinetics of felbamate in patients with renal dysfunction

P. Glue,¹ W. Sulowicz,³ R. Colucci,¹ C. Banfield,¹ S. Pai,² C. Lin² & M. B. Affrime¹

Departments of¹Clinical Pharmacology and ²Drug Metabolism and Pharmacokinetics, Schering-Plough Research Institute, Kenilworth, New Jersey, USA, and ³Chair and Department of Nephrology, Jagellonian University, Krakow, Poland.

Aims The purpose of this study was to evaluate the effects of renal impairment on the single-dose pharmacokinetics of the antiepileptic felbamate.

Methods Twelve subjects with three levels of renal dysfunction (creatinine clearance >30–80, >10–30 or 5–10 ml min⁻¹) and four controls with normal renal function (creatinine clearance >80 ml min⁻¹ were studied). Plasma and urine samples were obtained for 144 h following administration of a single 1200 mg dose.

Results Compared with controls, apparent total body clearance, renal clearance and urinary excretion of felbamate were decreased, and half-life, C_{max} and AUC values were increased in subjects with renal dysfunction. The magnitude of these changes was associated with the degree of renal dysfunction. Nonrenal clearance and apparent volume of distribution values were also lower in renal dysfunction subjects, but there was no association between the extent of these changes and degree of renal dysfunction. Renal clearance of felbamate accounted for approximately 30% of apparent total body clearance in the control group and from 9–22% in the renal failure patients. Renal clearance of felbamate was significantly correlated with creatinine clearance ($r^2=0.75$; $P<0.001$).

Conclusions These data suggest that initial dosage and titration of felbamate may require adjustment in patients with renal dysfunction.

Keywords: felbamate, renal dysfunction, pharmacokinetics

Introduction

Felbamate (2-phenyl-1,3-propanediol dicarbamate) is a chemically unique antiepileptic agent which has demonstrated efficacy in the treatment of Lennox-Gastaut Syndrome and partial onset seizures [1, 2]. Studies in man indicate that felbamate is well absorbed (>90%), has a volume of distribution of approximately 0.81 kg⁻¹, and that binding to plasma proteins is <25% [3, 4]. Estimates of half-life vary from 14 to 23 h [3]. It is eliminated by both renal excretion and hepatic metabolism [3, 4], with the proportion cleared renally being approximately 30% [5]. Felbamate metabolites, including 2-hydroxy, parahydroxy and dicarbamate metabolites, are also renally excreted [4]. Because felbamate may be used in patients with renal dysfunction, it is important to evaluate the effects of renal impairment on the pharmacokinetics of felbamate. The purpose of this study was to describe the pharmacokinetics of felbamate in control subjects and in patients with varying degrees of renal dysfunction.

Methods

Sixteen adult male volunteers (mean age 45.3 years, range 29–61; mean weight 77.3 kg, range 61–106) participated in this study. They were divided into four groups of four subjects based on creatinine clearance (CL_{cr}) values obtained

from 24 h urine collections performed during screening: controls (Group 1) were required to have CL_{cr} values greater than 80 ml min⁻¹; patients with chronic renal failure (Groups 2, 3 and 4) were required to have CL_{cr} values of >30–80 ml min⁻¹, >10–30 ml min⁻¹, and >5–10 ml min⁻¹ respectively. All subjects in Group 1 (controls) had no significant medical history, were in good health and were drug free for at least 2 weeks prior to the study start. Subjects in Groups 2–4 had no other medical conditions than those associated with their chronic renal failure, had stable chronic renal failure, were otherwise in good health, and were maintained on established medication during the study (with the exception of calcium carbonate and aluminium hydroxide, which were not permitted for 12 h prior to dosing). The reasons for renal dysfunction in Groups 2–4 included glomerulonephritis (seven subjects), nephrolithiasis with or without pyelonephritis (four subjects), and unknown (one subject). All subjects provided written informed consent prior to entry in the study and ethical approval was granted by an Ethics Committee. Volunteers were observed during the study for adverse events, and vital signs and safety laboratory tests were also monitored.

This was an open label single dose pharmacokinetic study. Following administration of felbamate 1200 mg, pharmacokinetic assessment was carried out up to 144 h postdose. Blood samples were collected prior to morning dosing (0 h), and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 60, 72, 96, 120 and 144 h post dose. Twenty-four hour block urine samples were collected simultaneously. Plasma and urine samples were used for determination of felbamate

Correspondence Dr Paul Glue, Schering Plough Research Institute, Clinical Pharmacology—Clinical Research, 2015 Galloping Hill Road, K15-44455, Kenilworth, NJ 07033-0539, USA.

concentrations, which were measured by h.p.l.c.-u.v. (limit of quantification $0.1 \mu\text{g ml}^{-1}$) [4]. Inter- and intra-assay coefficients of variation for felbamate were $<14\%$ in both sets of samples. Plasma concentrations were used for pharmacokinetic analyses using model independent methods [6]. The maximum plasma concentrations (C_{max}) were the observed values. The area under the plasma concentration-time curve from time zero to 144 h [$\text{AUC}(0, 144 \text{ h})$] was calculated using the linear trapezoidal rule. AUC extrapolated to infinity (AUC) was calculated as the sum of AUC to the final measurable sample plus the estimated concentration at the final timepoint (C_t) divided by the elimination rate constant (λ_z). Apparent total body clearance (CL/F) was calculated from the ratio of dose to AUC, and apparent volume of distribution (V_z/F) by the ratio of CL/F to λ_z . Half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. Renal clearance (CL_R) was calculated as the ratio of the amount of felbamate excreted in the urine from zero to 144 h [$\text{Ae}(0-144 \text{ h})$] to plasma $\text{AUC}(0, 144 \text{ h})$.

Results

All subjects completed the study. Felbamate was generally well tolerated, with seven subjects reporting a total of eight treatment-related adverse events, including six reports of mild-moderate headache, and single reports of dizziness and dyspepsia. Pharmacokinetic parameters for all four Groups are summarized in Table 1, and mean plasma concentration-time curves are shown in Figure 1. The small number of subjects in each group precluded formal statistical analysis, however the results demonstrate changes in the pharmacokinetics of felbamate in relation to degree of renal function, as measured by CL_{cr} . Compared with controls, mean concentration-time profiles, C_{max} , AUC and $t_{1/2}$ values were greater for subjects with renal dysfunction; CL/F , CL_R and $\text{Ae}(0, 144 \text{ h})$ values were reduced. The only variables which did not demonstrate progressive changes as renal function diminished relative to controls were nonrenal clearance (CL/F minus CL_R), which was approximately 30–35% lower in subjects with renal dysfunction, and apparent volume of distribution, which was approximately 11–17% lower.

Figure 1 Mean plasma concentration-time profiles of felbamate in control subjects (Group 1, $\text{CL}_{\text{cr}} > 80 \text{ ml min}^{-1}$ —●) and subjects with renal dysfunction (Groups 2–4; $\text{CL}_{\text{cr}} > 30\text{--}80 \text{ ml min}^{-1}$ —■; $\text{CL}_{\text{cr}} > 10\text{--}30 \text{ ml min}^{-1}$ —▲; $\text{CL}_{\text{cr}} 5\text{--}10 \text{ ml/min}$ —▼).

Felbamate CL_R was significantly correlated with CL_{cr} ($r^2 = 0.75$; $P < 0.001$).

Discussion

As might be predicted for a drug which undergoes renal clearance, felbamate's pharmacokinetic profile is altered in patients with renal dysfunction. Impaired renal function is associated with higher plasma felbamate concentrations, a longer half-life, and reduced drug clearance. The reduction in CL_R accounts for the progressive decline in CL/F values with diminishing renal function. An unexpected finding is the consistent 30–35% reduction in nonrenal clearance in Groups 2–4 relative to the control subjects (Group 1), suggesting that the pharmacokinetic changes observed in

Table 1 Mean (%CV) pharmacokinetic parameters of felbamate in control subjects (Group 1) and patients with renal dysfunction (Groups 2–4).

	Group			
	1	2	3	4
Required CL_{cr} (ml min^{-1})	>80	$>30\text{--}80$	$>10\text{--}30$	$5\text{--}10$
Actual CL (ml min^{-1})	97.5 (20)	44.8 (25)	18.8 (41)	9.0 (16)
[range]	[87–127]	[35–58]	[12–28]	[7–10]
C_{max} ($\mu\text{g ml}^{-1}$)	14.2 (9)	17.8 (15)	17.5 (16)	20.8 (13)
AUC ($\mu\text{g ml}^{-1} \text{ h}$)	526 (20)	856 (7)	906 (5)	1119 (19)
$t_{1/2}$ (h)	19.2 (16)	27.1 (17)	28.2 (20)	33.9 (9)
CL/F ($\text{ml min}^{-1} \text{ kg}^{-1}$)	0.500 (14)	0.310 (13)	0.285 (16)	0.253 (15)
CL_R ($\text{ml min}^{-1} \text{ kg}^{-1}$)	0.145 (37)	0.068 (43)	0.035 (18)	0.023 (12)
Nonrenal CL ($\text{ml min}^{-1} \text{ kg}^{-1}$)	0.355 (20)	0.242 (19)	0.250 (18)	0.229 (16)
V_z/F (l kg^{-1})	0.822 (18)	0.716 (16)	0.682 (20)	0.734 (7)
$\text{Ae}(0, 144 \text{ h})$ (%dose)	29.1 (33)	21.2 (40)	12.0 (20)	8.74 (12)

All values mean (%CV); $n = 4$.

this study are not only due to changes in the renal elimination of felbamate. Factors which might contribute to this include changes in the absorption of felbamate, or changes in its extrahepatic or hepatic metabolism [7].

The possibility that the absorption of felbamate is reduced in patients with renal dysfunction cannot be addressed in this study. However some factors which might potentially affect absorption can be excluded: for example, no patients reported nausea, vomiting or diarrhoea prior to or following dosing, and phosphate binding agents were withheld for 12 h prior to dosing.

Many of the drug-metabolizing enzymes found in the liver are also present in the kidneys, mainly in the renal cortex [8], and these are involved in oxidative, reductive, hydrolytic and conjugative reactions [9]. It has been estimated that the kidney may have 15% of the metabolic activity of the liver [10]. Thus, some of the observed reduction in the non-renal clearance of felbamate may be due to reduced activity of renal drug-metabolizing enzymes, as a reflection of the extent of renal disease. Finally, changes in hepatic drug metabolism have been reported in patients with renal failure for other compounds (e.g. metoclopramide, propranolol, bufuralol, erythromycin) [11], although the exact mechanism for these changes has not been determined. There are no common pharmacokinetic factors which would predict which drugs are susceptible to this effect, although it is possible that compounds which are CYP2D6 substrates are more likely to be inhibited than CYP3A4 substrates [11]. Preliminary *in vitro* data suggest that felbamate is metabolized by CYP3A4 and CYP2E1 (data on file, Schering-Plough Research Institute); the relative importance of these isozymes in its metabolism is yet undetermined. The clinical implication of these findings is that felbamate treatment of patients with renal dysfunction may require lower initial doses and more cautious titration than is currently advised for patients with normal renal function.

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