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Pharmacokinetics of flupirtine in elderly volunteers and in patients with moderate renal impairment

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Summary: The pharmacokinetics of flupirtine after a single oral dose of 100 mg have been studied in patients with moderate renal impairment and in healthy elderly subjects aged 66–83 years. Mean elimination half-life of flupirtine was higher in elderly patients than in younger normal subjects, and this was associated with an increased maximum serum concentration and reduced clearance. The mean half-life in patients with renal impairment was higher than in normal subjects. There was no correlation between observed elimination half-life and degree of renal impairment, but the creatinine clearance of most patients fell in a narrow range between 43 and 60 ml/min. In the light of these results and until further information is available, it would be prudent to start treatment of patients who are elderly or have evidence of renal impairment with half the dose of flupirtine recommended for younger patients with normal renal function.

Introduction

Flupirtine is a centrally acting non-narcotic analgesic which has been shown to be effective in the management of postoperative and other painful conditions in which the primary requirement is for analgesia without sedation or anti-inflammatory effects.[1] Because this broad indication may include elderly patients, and patients with impaired renal function, it was considered necessary to study the influence of renal impairment and of old age on the pharmacokinetics of flupirtine. Two separate studies were therefore carried out, the first in patients with a moderate degree of renal impairment, and the second in elderly volunteers. All subjects gave written consent to participate in the studies, the protocols of which had been approved by the local Ethics Committees.

Methods

Renal impairment study

Twelve patients (10 males) were recruited, aged 50–70 years (median 55 years), weight 52–93 kg (median 73.9 kg), and creatinine clearance 44–99 ml/min (median 54.0 ml/min). No patient had evidence of major disease apart from their renal insufficiency, and none had any history of drug or alcohol dependence or abuse.

On the morning of the study the patients were given a light breakfast followed by a single oral dose of flupirtine maleate 100 mg. Blood samples were collected from an indwelling venous cannula before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 24 and 30 h after dosing. Heart rate and blood pressure were measured before and at 1 and 2 h after dosing. Patients were questioned at 6 h and 24 h about any possible adverse effects they had experienced.

Blood samples were separated and the serum deep-frozen until analysed. Serum flupirtine concentrations were measured using high performance liquid chromatography (HPLC) with fluorometric detection (excitation 323 nm, emission 370 nm cut-off filter) and using a flupirtine analogue (D9925) as internal standard. The limit of detection was 10 μg/l.

The pharmacokinetic analysis was carried out using the computer program STRIPE.[2]

Elderly volunteer study

Thirteen subjects (6 males) were recruited aged 66–83 years (median 69 years) and weight 51–80 kg

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(median 63 kg). All subjects were healthy on clinical history, physical examination and 12-lead ECG recording, and had normal values in haematological, biochemical and urinalysis screening tests.

The study lasted 12 days for each volunteer, with two main study days, day 1 and 11. On the morning of each study day the subjects were given a light breakfast followed by oral flupirtine maleate 100 mg with 100 ml water. Blood samples were collected from an indwelling venous cannula before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 12, 15 and 24 h after dosing. On days 11 and 12 samples were taken at these same times but additional samples were obtained at 28, 32 and 48 h. Samples were stored and analysed as in the first study.

The subjects received flupirtine maleate 100 mg three times daily on days 2–10, with a final dose of 100 mg on the morning of day 11. They reported to the Geriatric Unit every morning to collect their capsules.

Subjects were instructed to avoid xanthine-containing food or drinks during 12 h before the start of each main study until the last blood sample was obtained.

Tolerability was assessed by asking subjects to report all possible adverse effects experienced during the study.

Pharmacokinetic parameters were calculated as in the first study.

Results

Renal impairment study

Details of the group pharmacokinetic profiles are given in Table I. The mean half-lives of patients (9.8 h) was higher than that found in normal volunteers aged 18–35 years (6.5 h), and the range of values (6.5–13.5 h) indicates that no patients with renal impairment had a half-life lower than the normal mean. There appeared to be no correlation between observed elimination half-life and degree of renal impairment as assessed by creatinine clearance for the 12 patients (Figure 1). Figure 1 shows, however, that all but three of the patients had creatinine clearance between 43 and 60 ml/min.

There were no clinically or statistically significant changes in heart rate or blood pressure during the two hours following flupirtine administration. One patient complained of transient light-headedness at 90 min and transient headache at 5 h; another felt dizzy from 30 to 60 min after dosing; and a third complained of slight headache from 2.5 to 5 h after dosing.

Elderly volunteer study

Complete pharmacokinetic data were available from 7 subjects. Of the 6 whose data were not

Table I Mean pharmacokinetic parameters and their 95% confidence limits for flupirtine in normal and elderly subjects, and patients with mild renal impairment. Ranges are given in parentheses

Subjects	*Elimination* $t_{1/2}(h)$	*C max* (*μg/l*)	*T max** (*h*)	$AUC_{0-\infty}$ (*μg/l.h*)	*Apparent clearance* (*ml/min*)	*Apparent Vd(l)*
Normal†						
$n=91$	6.5	773	1.6	6,070	275	154
Renal impairment						
$n=12$	9.8	722	1.8	6,656	263	212
	8.7–10.9	615–829		5,827–7,389	229–297	285–239
	(6.5–13.5)	(461–1,108)	(0.5–3.0)	(5,655–8,810)	(183–442)	(118–294)
Elderly						
Day 1	14.0	1,116	1.8	10,346	161	195
$n=7$	11.2–16.8	985–1,347			134–210	124–224
	(3.7–27.6)	(977–1,675)	(0.5–2.5)	(6,085–14,848)	(112–273)	(73–289)
Day 12	18.6	1,977	2.0	9,991‡	147	216
$n=11$	14.8–22.4	1,622–2,332		8,434–11,548	135–169	186–246
	(12.2–37.9)	(1,443–3,605)	(1.0–4.0)	(7,418–17,274)	(79–237)	(165–272)

*Medians; †Data from ref. 4; ‡AUC_{0-8}.

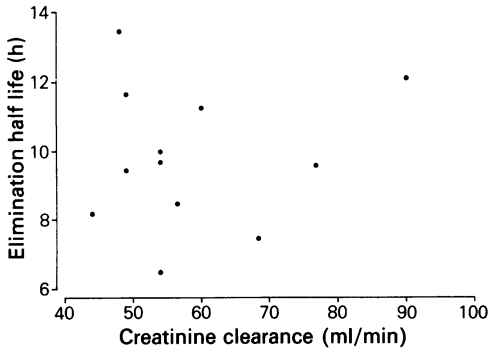

Figure 1 Relationship of elimination half-life (h) and creatinine in 12 patients with mild renal impairment.

included in the analysis, one was withdrawn during the study because of nausea, vomiting and dizziness, and another because he sprained a knee and could not continue in the study. In four subjects it was impossible to analyse drug levels on day 1 because of interfering peaks on the chromatographic recording; these subjects may have taken other medication during the few days before the study. Pharmacokinetic data for day 12 were available from 11 subjects. Details of the group pharmacokinetic profiles are given in Table I.

Of the 11 subjects who completed the treatment period, five complained of minor adverse effects: two complained of transient 'muzziness', two of transient lethargy, and one of transient faintness 24 h after taking the last dose in the study.

Discussion

The results of the two studies reported in this paper suggest that the mean elimination half-life of flupirtine is longer in elderly patients than in younger normal subjects or in younger patients with mild renal impairment. The prolonged half-life was associated with an increased maximum serum concentration (Cmax), particularly on day 12, and reduced apparent clearance. This is, perhaps, not surprising as glomerular filtration rate falls with increasing age even though plasma urea and creatinine concentrations may be within the normal range, as they were in the volunteer subjects used in this study. Furthermore, hepatic clearance of drugs tends to be reduced in the elderly and this might also have contributed to the prolonged half-life of flupirtine seen in these patients.

An early study of flupirtine excretion using a relatively non-specific analytical method suggested that its elimination half-life was about 10 h,[3] but more recent studies using the same HPLC method as in the present investigation have indicated that it may be about 7 h.[4] The mean elimination half-life in patients with mild renal impairment was 9.8 h, and although the range extended well into that of normal subjects, no patient with renal impairment had a half-life lower than the mean of normal subjects. Although no correlation was observed between the observed elimination half-life and creatinine clearance, all but three of 12 patients had creatinine clearance values between 43 and 60 ml/min. This is a narrow range, and it is perhaps not surprising that no correlation emerged. Further studies over a wider range of clearance values will provide more information on this. Until such further information is available it would be prudent to start treatment of patients who are elderly or have even mild degrees of renal impairment with half the dose of flupirtine recommended for younger patients with normal renal function. Doses should be given no more frequently than 12 hourly, and the dose increased according to the analgesic response and occurrence of adverse effects.

Flupirtine was generally well tolerated by both groups of subjects in these studies. Only minor transient adverse effects were noted in the single dose renal impairment study. In the 12 day study in the elderly one subject developed drug related side effects leading to her withdrawal from the study. Although five others experienced some side effects they were minor and transient.

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References

1. Galasko, C.S.B., Courtenay, P.M., Jane, M. & Stamp, T.C.B. Trial of oral flupirtine maleate in the treatment of pain after orthopaedic surgery. *Curr Med Res Opin* 1985, **9**: 594–601.
2. Johnston, A. & Woollard, R.C. STRIPE: an interactive computer programme for the analysis of drug pharmacokinetics. *J Pharmacol Methods* 1983, **9**: 193–200.
3. Hlavica, P. & Niebch, G. Investigations on the pharmacokinetics and biotransformation of the analgesic flupirtine in man. *Arzneimittelforschung* 1985, **35**: 67–74.
4. Data on file; Homburg Degussa.