The pharmacokinetics of sustained release tiaprofenic acid in elderly arthritic patients

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Tiaprofenic acid is a non-steroidal anti-inflammatory drug which is highly protein bound and excreted mainly by the kidneys. Previous pharmacokinetic studies with tiaprofenic acid in conventional formulations in elderly arthritic patients have shown no evidence of accumulation of this drug over periods of up to 12 weeks. A sustained release formulation of the drug was given to 14 elderly arthritic patients over 4 weeks and plasma profiles obtained at the beginning and end of treatment over a 24 h period. Area under the curve (AUC), maximum plasma concentration ($C_{\max}$) and plasma concentration at 24 h (C_{24}) were calculated and elimination half life ($t_{1/2}$) was estimated. AUCs to infinity at week 0 were compared with AUCs to infinity at week 4 as a measure of drug accumulation. No significant differences were found for any of these parameters between the beginning and end of treatment. The mean $t_{1/2}$ for both weeks was approximately 4.4 h. There was no evidence of any accumulation.

Keywords tiaprofenic acid arthritis elderly pharmacokinetics

Introduction

Tiaprofenic acid, 5-benzoyl-methyl-2-thiophene acetic acid (Surgam) is a non-steroidal anti-inflammatory and non-narcotic analgesic drug.

Previous pharmacokinetic studies (Pottier *et al.*, 1982) have shown that following oral administration of tiaprofenic acid there is rapid absorption from the gut and it is eliminated from the plasma with a half-life of approximately 2 h. It is highly bound to plasma albumin around 98%. About 60% of the dose is recovered in the urine, mainly as unchanged drug with less than 10% present as its metabolites.

Sustained released (S.R.) preparations modify the release rate of a drug and prolong its duration of action. Although we have already produced evidence that there is no significant accumulation of tiaprofenic acid in elderly patients taking conventional formulations of 200 mg three times daily for 1 week (Hosie & Hosie, 1987) and 300 mg twice daily over a period of 12 weeks (Hosie & Hosie, 1985), we felt it important to test these findings with the S.R. formulation with its differing disintegration pattern and its dosage regime

of 600 mg as a single dose as the dangers of drug toxicity in the elderly remain a significant clinical problem (Hamdy *et al.*, 1982; Stevenson & Hosie, 1985). We also wished to compare the $t_{1/2}$ of this preparation and dose with those previously ascertained in elderly arthritic patients—mean $t_{1/2}$ 2.05 h after 200 mg single dose (10 patients) (Hosie & Hosie, 1987) and 2.49 h after 300 mg single dose (12 patients) (Hosie & Hosie, 1985).

Methods

Patient selection

Fourteen patients, seven males and seven females, with an age range of 70–81 years (median 74.5 years) were studied in a single general practice centre. They all lived independently in the community and suffered from arthritis requiring treatment. The study protocol was approved by an independent ethics committee, and informed consent was obtained from all patients prior to

entry. Study exclusions were active peptic ulcer, hepatic enzymes greater than 50% of laboratory normal, serum creatinine greater than $160 \mu\text{mol l}^{-1}$, concurrent medication with anti-coagulants, immunosuppressives, oral hypoglycaemics or high dose steroids, hypersensitivity to tiaprofenic acid or propionic acid derivatives, and piroxicam therapy in the 4 weeks prior to entry to the study (due to its long half-life). No patients were on second line therapy, i.e. disease modifying agents in the treatment of rheumatoid arthritis.

Protocol

This was an open study lasting 4 weeks with a 3 day washout period using paracetamol alone up to 4 g daily. This was also the permitted escape analgesia throughout the study.

Plasma profiles of tiaprofenic acid were obtained on the first and last days of treatment when patients presented at 10.00 h having fasted since midnight. Under supervision they were given two 300 mg S.R. capsules of tiaprofenic acid with water. No food was allowed until 75 min after ingestion of this dose. Blood samples of 5 ml were taken via an indwelling intravenous catheter immediately prior to dosing and at intervals of 1, 2, 3, 4, 6, 7.5, 9, 10.5, 22, 23 and 24 h post dosing plus 48 h on day 28. Plasma was separated and stored deep frozen prior to subsequent assay in duplicate by a specific h.p.l.c. method (detection limit $0.5 \mu\text{g ml}^{-1}$) (Ward *et al.*, 1982).

During the 4 week study period patients took two 300 mg S.R. capsules every morning. Concomitant medication was noted and kept as constant as possible during the study period.

Statistical methods

The following pharmacokinetic parameters were calculated for each patient on days 1 and 28.

1. maximum plasma concentration, C_{max} ,
2. time to C_{max} , t_{max} ,
3. plasma concentration at 24 h, C_{24} ,
4. area under the plasma concentration time curve to 24 h, $\text{AUC}(24)$,
5. elimination half-life $t_{1/2}$

Also calculated by extrapolation of the linear regression of log concentration against time and by integration were the AUCs to infinity on days 1 and 28. These were compared to obtain a measure of drug accumulation. Comparisons of days 1 and 28 were made using the paired *t*-test for C_{max} , C_{24} , $\text{AUC}(24)$ and the test for accumulation. Mean differences between the days and their 95% confidence intervals were calculated.

For t_{max} and $t_{1/2}$ the Wilcoxon matched-pairs signed-ranks test was used to compare the values on the two test days.

Results

Initially 12 patients entered the study. However two patients deviated from the protocol on day 28 by taking their trial medication before attending the surgery on the test day. Two further patients were therefore recruited. One patient also deviated from the protocol by taking tiaprofenic acid in the 3 day washout period, thus her day 1 kinetics are really day 3 kinetics. All 14 patients entering the trial completed the 4 week study period and were included in the analysis where possible.

The mean or median values for the various parameters measured at days 1 and 28 are shown in Table 1. C_{max} on day 1 was 29.74 and on day 28, 30.35 ($\mu\text{g ml}^{-1}$). There was no significant difference between C_{max} on days 1 and 28 ($P = 0.77$).

For t_{max} the median values were 4.0 h on both days 1 and 28 with a range of 2–6 h on day 1 and 3–6 h on day 28.

There was no significant difference between t_{max} at days 1 and 28 ($P > 0.05$).

Neither was there a significant difference between C_{24} on day 1—1.16, and on day 28—1.25 $\mu\text{g ml}^{-1}$ ($P = 0.39$).

The AUC, calculated by the trapezoidal rule, showed no significant difference between the mean single dose AUC to 24 h on day 1, 244.75 and mean steady state AUC to 24 h on day 28, 253.12 $\mu\text{g ml}^{-1} \text{ h}$ ($P = 0.45$).

The AUC to infinity on day 1, 252.87 and AUC to infinity on day 28, 267.98 $\mu\text{g ml}^{-1} \text{ h}$ ($P = 0.20$) showed no significant difference and hence no significant accumulation.

For $t_{1/2}$ we have results only for the 11 patients who conformed to the protocol. The mean elimination half-life on both days 1 and 28 was 4.4 h and analysis showed no significant differences between the half-lives at days 1 and 28 ($P > 0.05$).

Discussion

A previous pharmacokinetic study of the standard tiaprofenic acid 300 mg twice daily dose taken for 3 months with four plasma kinetic profiles obtained during that time, showed persistent abnormally low plasma profiles for four male patients (Hosie & Hosie, 1985). The same four male patients also took part in this study and three of them again showed abnormally low

Table 1 Pharmacokinetic parameters, mean or median values with s.d. Number of subjects for each analysis in brackets

Parameter		Day 1	Day 28
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	Mean	29.74	30.35
	s.d.	± 8.82 (12)	± 7.07 (12)
$t_{\max}$ (h)	Median	4.0 (12)	4.0 (12)
	range	2–6	3–6
C_{24} ($\mu\text{g ml}^{-1}$)	Mean	1.16	1.25
	s.d.	± 0.75 (11)	± 0.80 (11)
AUC(24) ($\mu\text{g ml}^{-1} \text{ h}$)	Mean	244.75	253.12
	s.d.	± 71.82 (11)	± 77.69 (11)
AUC(∞)	Mean	252.87	267.98
	s.d.	± 76.33 (11)	± 83.58 (11)
$t_{1/2}$ (h)	Mean	4.4	4.4
	s.d.	± 0.63 (11)	± 0.69 (11)
$C_{\max}$	maximum plasma concentration		
$t_{\max}$	time of $C_{\max}$		
C_{24}	plasma concentration 24 h after the dose		
AUC(24)	area under the plasma concentration-time curve between 0–24 h		
AUC(∞)	area under the plasma concentration-time curve between $t = 0-\infty$		

plasma profiles. Further work is underway to elucidate this including estimation of protein binding.

In summary, 14 patients entered this 4 week open study of sustained release tiaprofenic acid, 600 mg as a single daily dose in the elderly. All patients completed the study with no serious adverse events reported. In this study we estimated $t_{1/2}$ to be 4.4 h on both study days.

With a highly protein bound drug excreted mainly by the kidney there is the possibility of accumulation of the drug with increasing age due to the age related decrease in renal function and decline in plasma albumin particularly marked in arthritic patients, with possible resultant increased free fraction of the drug.

In our study, however, of 14 elderly arthritic patients taking sustained release tiaprofenic acid 600 mg as a single daily dose, we found the mean plasma profiles obtained on days 1 and 28 were very similar and analysis of the pharmacokinetic parameters showed no significant differences between days 1 and 28.

Therefore we could show no significant accumulation of the drug during a 4 week treatment period in elderly arthritic patients.

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