The Pharmacokinetics of Single and Multiple Doses of Tiaprofenic Acid in Elderly Patients with Arthritis

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Summary. We have studied the single dose and steady-state pharmacokinetic of tiaprofenic acid in ten elderly arthritic patients living in the community (5 men and 5 women) taking 200 mg tid for 8 days.

The mean area under the plasma concentration-time curves to 8 h (AUC (0-8)) did not alter significantly from day 1 to day 8 (77.25 to 79.61 µg·ml⁻¹·h). The mean terminal phase half-life (t½) was 2.05 h and 2.25 h on Days 1 and 8 respectively in patients in whom the calculations were possible (7 patients on Day 1 and 6 patients on Day 8). The median observed time of maximum concentration (tₘₐₓ) and the mean observed maximum plasma concentration (Cₘₐₓ) of 100 min and 21.3 µg·ml⁻¹ respectively on Day 1 were not significantly different from the values obtained on Day 8 (tₘₐₓ 120 min; Cₘₐₓ 20.7 µg·ml⁻¹). The kinetic data suggest that there should be no significant accumulation of tiaprofenic acid in elderly ambulant people suffering from arthritis.

Key words: tiaprofenic acid, arthritis; pharmacokinetics, elderly

Tiaprofenic acid, 5-benzoyl-methyl-2-thiophene acetic acid (Surgam), is a non-steroidal anti-inflammatory and non-narcotic analgesic drug. In clinical studies it has been shown to be effective in the treatment of rheumatoid arthritis, osteoarthritis, and non-articular rheumatic conditions [1, 2, 3, 4, 5].

Previous pharmacokinetic studies [6] have shown that following oral administration of tiaprofenic acid there is rapid absorption from the gut and elimination from the plasma with a t½ of approximately 2 h. It is about 98% bound to plasma albumin. About 60% of the dose is recovered in the urine, mainly as unchanged drug with less than 10% present as its metabolites.

As non-steroidal anti-inflammatory drugs are widely prescribed in the elderly population, and in view of possible problems with accumulation of such drugs in the elderly [7, 8] it was felt important to establish the pharmacokinetics of tiaprofenic acid in elderly patients with arthritis, and to determine whether any accumulation occurred during treatment with tiaprofenic acid in a dose of 200 mg tid for 1 week.

Methods

We studied 10 patients (5 men and 5 women) in a single general practice. Their ages ranged from 69 to 78 years (median 73 years), their body weights ranged from 48 to 87 kg (mean 66 kg), and all suffered from osteoarthritis requiring treatment. Being elderly most of the patients suffered from other diseases, and six of the ten were receiving concomitant medication which remained constant throughout.

Study exclusions were peptic ulceration, severe hepatic or renal disease, hypersensitivity to propionic acid derivatives, or treatment with anticoagulants, immunosuppressive drugs, oral hypoglycaemic drugs, gold salts, penicillamine, or steroids.

This was an open study lasting 8 days, with a 3-day washout period using paracetamol alone up to 4 g daily. This was also the escape analgesia throughout the study.

Written informed consent was obtained from all patients before entry and the study protocol was approved by an independent ethics committee.

Plasma profiles of tiaprofenic acid were obtained on the first and last days of treatment. The patients came at 9 a.m. having fasted since midnight. Under
supervision they were given a single 200 mg dose of tiaprofenic acid with 200 ml of water. Blood samples of 10 ml were taken immediately before dosing and at 20, 40, 60, 80, and 100 min, and 2, 4, and 8 h after dosing. No food was allowed until 2 h after dosing, when patients were allowed a light breakfast. A salad lunch was provided immediately after the 4 h blood sample had been taken. After the 8 h blood sample a second dose of tiaprofenic acid 200 mg was given and treatment was continued until day 7 in a dosage of 200 mg tid.

The blood samples were centrifuged and the plasma separated and stored at -20 °C for subsequent assay by high performance liquid chromatography [9].

Calculations

The following pharmacokinetic variables were determined:

a) Area under the plasma concentration versus time curve (AUC). This was calculated by the linear trapezoidal rule for the period 0-8 h.

b) Observed maximum plasma concentration (Cmax).

c) Observed time of maximum plasma concentration (tmax).

d) Terminal phase half-life (t½). This was calculated for each patient by the use of linear regression of log plasma concentration against time, starting with the sampling point after the maximum concentration. An accurate t½ could not be calculated when the observed tmax occurred at 4 h or at 8 h and we therefore have t½ results for only 7 patients on day 1 and 6 patients on day 8.

For AUC, Cmax, and t½ statistical comparisons were made using Student's paired t-test to determine the significance of within-patient differences for Day 1 and Day 8 results. Confidence intervals of the differences between the two test days were also calculated. For the observed time of maximum plasma concentrations, the Wilcoxon rank test was used to compare within-patient differences for Days 1 and 8.

Results

All ten patients completed the 8-day treatment period, and no adverse reactions were reported. Routine biochemistry, haematology, and urinalysis revealed no significant differences in the values obtained from Days 1 and 8. The mean derived values of the pharmacokinetic variables are presented in Table 1 and the plasma concentration versus time profiles in Fig. 1.

As only a limited number of sampling times was available it was not always possible to characterise