Naproxen kinetics in synovial fluid of patients with osteoarthritis

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1 The kinetics of naproxen in synovial fluid were studied in 407 osteoarthritic outpatients with knee effusion requiring aspiration, following a single 1100 mg oral dose of naproxen sodium.

2 The drug concentration-time profiles were described by a biexponential function. Naproxen entered synovial fluid rapidly, reaching a maximum concentration of 36 mg l^{-1} (C_{max}) at 7.5 h. The first order input rate constant (k_{0s}) was 0.41 ± 0.15 h^{-1} with a lag time (t_{lag}) of 0.24 ± 0.36 h.

3 Elimination from the fluid was slow ($t_{1/2} = 31 \pm 12$ h) and appreciable drug concentrations were still measurable (27 mg l^{-1}) after 24 h.

4 During once daily dosing of naproxen sodium, naproxen should accumulate in synovial fluid, a steady-state being achieved within a week of treatment. The predicted accumulation ratio based on trough concentration was 2.4.

Keywords naproxen synovial fluid pharmacokinetics osteoarthritic patients

Introduction

The time-course of non-steroidal anti-inflammatory drugs (NSAID) in synovial fluid may be relevant to the treatment of inflammatory disease (Wallis & Simkin, 1983). However, although the synovial fluid is accessible, it is difficult to take serial synovial fluid samples from patients. Few pharmacokinetic data for NSAIDs based on this sampling site are available.

Naproxen concentrations in synovial fluid have been reported following oral dosing with either naproxen (Jalava *et al.*, 1977; Katona *et al.*, 1980) or naproxen sodium (Dougados *et al.*, 1985, 1986). These studies showed rapid penetration of the drug into the joint followed by a slow elimination. The mean synovial elimination half-life based on a small number of patients was 24 and 26 h following 500 and 1000 mg single doses of naproxen, respectively (Katona *et al.*, 1980). However, these studies were based on too few data to permit the assessment of the synovial drug concentration-time curve.

The aim of the present study was to assess the synovial kinetics of naproxen in synovial fluid from a large number of osteoarthritic patients following a single-dose of 1100 mg naproxen sodium.

Methods

Patients and protocol

Four hundred and seven patients, mean ($\pm$ s.d.) age 59.0 ± 9.7 years (range 22–87 years), with active osteoarthritis of the knee gave their informed consent to participate in the study. All were outpatients of rheumatological clinics. They

were free of renal and liver impairment and had knee effusions requiring aspiration. The patients did not receive intra-articular corticotherapy for at least 4 weeks or other NSAIDs for at least 3 days before the study.

The patients were given a single 1100 mg oral dose of naproxen sodium (Apranax 550®, Laboratoires Syntex France, Puteaux, France). A single synovial fluid sample was obtained between 1 and 30 h post dosing. The samples were stored frozen at $-20°$C and dispatched in dry ice to Laboratoires Cerba for subsequent analysis (Cergy Pontoise, France).

Analytical method

After the addition of an internal standard (methyl-paraben) and the removal of proteins by aceto-nitrile/phosphate buffer, the synovial fluid was diluted with the mobile phase and total naproxen was assayed by reverse phase high performance liquid chromatography with u.v. detection.

The chromatographic system consisted of a 25 cm column packed with C 18 Nucleosil (5 μ) and a mixture of acetonitrile/0.025 м NaH_2PO_4 pH = 4.4 50/50 v/v as the mobile phase. The column effluent was monitored at 230 nm. The lower limit of measurement was 0.5 mg l^{-1} and the between-day coefficient of variation averaged 6.95% for a concentration range of 10 to 50 mg l^{-1}. The calibration plot was linear between 1 and 100 mg l^{-1}.

Pharmacokinetics

All of the concentration-time data were described by the following biexponential function:

$$C_s(t) = A. [e^{-k_{s0}(t-t_{lag})} - e^{-k_{0s}(t-t_{lag})}]$$

where k_{0s} and k_{s0} = first order rate constants describing respectively the input (output) of the drug into (from) the synovial fluid and t_{lag} = lag time.

Since we had only a single measurement per patient, it was not possible to estimate the different sources of variability (inter- and intra-individual and residual variabilities). Mean parameter estimates were obtained by fitting the model to the pooled data ('naive pooled data' approach (Sheiner, 1984)), using an iterative nonlinear least square algorithm. The standard deviations of the parameter estimates were obtained from the Fisher information matrix (Boxenbaum et al.,1974). Since the inter-individual variability in the data was likely to be considerably higher than the experimental varia-

bility, the data were not weighted in the fitting procedure. An estimation of the residual variance (variance not explained by the model) following model adjustment (comprising essentially inter-individual variance) was obtained from:

$$\sigma^2_{res} = \frac{S}{n-p}$$

where S = sum of squared deviations between measured and model-predicted levels, n = number of levels measured and p = number of model parameters.

The model was used to predict the multiple-dose kinetic profile of naproxen in synovial fluid following once daily dosing of naproxen sodium. Based on model predictions, the accumulation ratio was computed as the ratio of the 24 h level at steady-state (trough level) to the 24 h level following the first dose. Parameter estimation and model predictions were performed using a package of interactive computer programmes (Iliadis, 1985; Iliadis et al., 1986).

Results

A biexponential function adequately described the observed drug concentration-time profile (Figure 1). Pharmacokinetic parameter estimates (± s.d.) are given in Table 1.

Naproxen entered the synovial fluid rapidly (k_{0s} = 0.41 ± 0.15 h^{-1} and t_{lag} = 0.24 ± 0.36 h); the model predicted C_{max} of 36 mg l^{-1} was achieved 7.5 h post dosing, but as soon as 2 h post dosing the synovial drug concentration was 22 mg l^{-1}. Elimination was slow, the estimated $t_{1/2}$ being 31 ± 12 h. At 24 h post-dose the synovial levels remained high (27 mg l^{-1}).

The standard deviation of the residual variability was estimated to be 15 mg l^{-1}. This absolute standard deviation would lead to a 40–50% coefficient of variation for synovial drug concentrations over most of the profile (between about 3 to 24 h post-dose). The maximum coefficient of variation was 128% at the first hour.

Owing to the long elimination half-life, a once daily dosage regimen should result in an accumulation of naproxen in the synovial fluid, steady-state being achieved within a week. The predicted accumulation ratio based on trough levels was 2.4. The maintenance regimen of 550 mg daily would achieve at steady-state, a mean drug concentration of 40 mg l^{-1} with a very flat kinetic profile, the predicted minimum and maximum steady-state synovial drug concentrations being 32 and 46 mg l^{-1}, respectively.
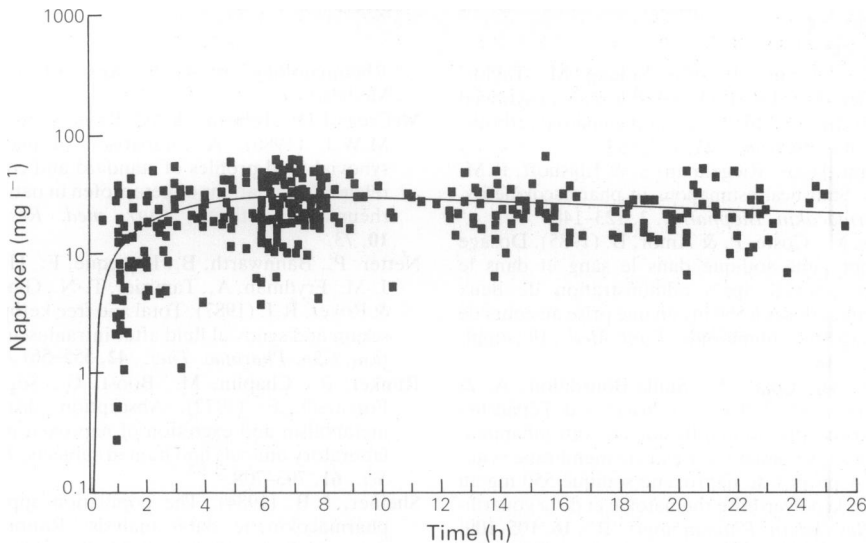
Figure 1 The concentration-time profile of naproxen in synovial fluid following a 1100 mg single oral dose of naproxen sodium. (■) observed (*n* = 407), (—) predicted.

Table 1 Pharmacokinetic parameters (s.d.) of naproxen in synovial fluid following a 1100 mg single oral dose of naproxen sodium to a population of osteoarthritic patients (*n* = 407)

σ_{res} (mg l^{-1})	A (mg l^{-1})	k_{0s} (h^{-1})	k_{s0} (h^{-1})	t_{lag} (h)	$t_{1/2}$ (h)
15	45 (7)	0.41 (0.15)	0.022 (0.009)	0.24 (0.36)	31 (12)

Discussion

Few attempts have been made previously to establish a model for the synovial pharmacokinetics of anti-inflammatory drugs (Wallis & Simkin, 1983; Aarons *et al.*, 1986), mainly owing to the small amount of data generally available.

The present data permitted the definition of a complete kinetic profile from a representative population of patients. The variability of the data was large, particularly at early time points. This was not surprising in such a large population of outpatients in whom the data were collected as part of their routine management. However, the data could be described by a simple biexponential function. The entry of naproxen into the synovial fluid was described by a first order rate constant (k_{0s}) which should depend on both absorption and blood to synovial fluid transfer kinetics. Separate identification of these processes was not possible without plasma data. A similar model has been used to describe the synovial profile of flurbiprofen in patients with rheumatoid arthritis (Aarons *et al.*, 1986). Following dosing with naproxen sodium, the entry of naproxen into the synovial fluid was rapid and its elimination was slow. The elimination half-life estimate agrees well with that previously reported from a small number of patients following dosing with naproxen (Katona *et al.*, 1980). The magnitude of the inter-individual variability of the pharmacokinetic parameters could not be estimated since a single sample was drawn from each patient (Sheiner, 1984). The estimated variability reflects not only inter-individual but also intra-individual and experimental variabilities.

The synovial half-life of naproxen is twice to three times its plasma half-life (Runkel *et al.*, 1972; Van Den Ouweland *et al.*, 1987). On this basis, a once-daily dosage regimen would appear adequate to maintain the therapeutic effect. Although relevant estimations of synovial half-life are lacking in the literature, there is a tendency to find a delayed elimination of NSAIDs from the synovial fluid relative to plasma (Wallis & Simkin, 1983; Aarons *et al.*, 1986; McCrea *et al.*, 1986; Netter *et al.*, 1987).

In conclusion, the concentration-time profile of naproxen in synovial fluid is consistent with a once daily dosage regimen for naproxen sodium, although measurement of treatment outcome is needed to confirm this.

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