Br. J. clin. Pharmac. (1986), **21**, 155–163

Plasma and synovial fluid kinetics of flurbiprofen in rheumatoid arthritis

L. AARONS, R. SALISBURY, M. ALAM-SIDDIQI, L. TAYLOR & D. M. GRENNAN
University of Manchester Rheumatic Diseases Centre, Hope Hospital and Department of Pharmacy, University of Manchester, Manchester.

1 Clinical assessment, plasma and synovial fluid kinetics were studied in 29 rheumatoid patients receiving 100 mg flurbiprofen twice daily.

2 Clinical assessment and pharmacokinetic measurements varied widely within the group of patients.

3 The average values for plasma clearance, volume of distribution and elimination half-life of flurbiprofen were 0.65 ± 0.24 ml min^{-1} kg^{-1}, 0.160 ± 0.093 l kg^{-1} and 3.1 ± 1.7 h, respectively.

4 Synovial fluid drug concentrations peaked later and were lower than corresponding plasma concentrations: 5.2 h and 4.4 mg l^{-1} as against 1.49 h and 12.5 mg l^{-1}, respectively. At 48 h after an oral dose of flurbiprofen, all the drug had been cleared from the synovial fluid.

5 Synovial fluid drug concentrations were not related to synovial fluid albumin concentration or pH. There was a weak relationship between synovial fluid drug concentration and the thermographic measurements of disease activity. The fractions of flurbiprofen not bound to protein in synovial fluid and plasma were not significantly different.

6 A simple model is proposed to account for the plasma and synovial fluid pharmacokinetics.

Keywords flurbiprofen pharmacokinetics synovial fluid concentrations protein binding

Introduction

Flurbiprofen (2-(2-fluoro-4-biphenyl) propionic acid) is one of the propionic acid group of non-steroidal anti-inflammatory drugs (NSAID) used in the treatment of inflammatory joint disorders, including rheumatoid arthritis. As with other NSAIDs the action of flurbiprofen is thought to be mediated by inhibition of prostaglandin synthetase enzymes (Adams *et al.*, 1977). In man, flurbiprofen is well absorbed, extensively bound to plasma proteins and rapidly eliminated, with an apparent half-life of 3.8 h. There is no evidence of accumulation following repeated dosing (Cardoe *et al.*, 1977).

There is a poor correlation between the plasma pharmacokinetics of NSAIDs and clinical response in rheumatoid arthritis (Grennan *et al.*, 1983), which may be partly attributable both to disease heterogeneity and to inter-individual differences in disease severity, but which may also reflect inter-individual differences in penetration of drug into inflamed tissues. The examination of synovial tissue drug concentrations is not usually practicable but their measurement may help to understand some of the mechanisms influencing tissue drug concentrations.

The distribution of several NSAIDs into synovial fluid has been studied in rheumatoid arthritis patients (Wanwimolruk *et al.*, 1983; Wallis & Simkin, 1983). The binding of these drugs is significantly lower in synovial fluid than

in plasma, mainly due to the lower albumin content of synovial fluid. For ibuprofen the unbound concentration has been reported to be the same as in plasma (Whitlam *et al.*, 1981). Chalmers *et al.* (1977) measured the synovial fluid distribution of flurbiprofen in three rheumatoid arthritis patients and found that the peak concentration in synovial fluid was lower, occurred later and fell more slowly than in plasma.

The aim of the present study was to examine the plasma and synovial fluid kinetics of flurbiprofen in a group of patients with rheumatoid arthritis and to investigate the factors which influence the distribution of flurbiprofen between plasma and synovial fluid. Factors investigated included local measures of inflammatory disease activity, synovial blood flow and synovial fluid albumin concentration and pH.

Methods

Patients

Twenty-nine patients, aged between 17 and 73 years (mean 56) with classical or definite rheumatoid arthritis (Ropes *et al.*, 1959) participated in the study. All patients had knee effusions with acute synovitis of at least one knee and required aspiration.

Patients were referred to the study from the general rheumatology out-patient clinics at Hope Hospital, Salford. No patient was receiving corticosteroids, second line treatment (gold or penicillamine) or other NSAIDs at the time of the study. Patients with renal or liver impairment were excluded. All patients gave their full and informed consent to participate, and Ethics Committee approval was obtained.

Clinical assessment

The following clinical measurements were made: tenderness on firm pressure over the joint margin, modified from Ritchie *et al.* (1968), soft tissue swelling and pain on walking. Each category was graded on a scale of 0–3 and the sum of these grades taken as a numerical value for an index of knee joint inflammation (CI). Clinical observations were made by the same observer throughout.

Thermography

All thermography was carried out between 09.30 h and 12.00 h in a temperature and humidity controlled, draught-free room. Ambient temperature was maintained at 21.0 ± 0.5°C and relative humidity at 50 ± 5%.

An AGA 680M Thermovision camera was interfaced through an OSCAR analogue to digital converter to an Apple II micro-computer. All absolute temperature calculations were made relative to an electrical black body reference with accuracy ± 0.1°C. A camera sensitivity of 10 isotherm units for the scale range was used throughout.

Patients were seated with both knees exposed for 20 min in the environmentally controlled room prior to thermography. Standard views of the knee were obtained, and recommended thermographic procedures were observed (Engel *et al.*, 1978). All thermograms were recorded on magnetic tape for subsequent computer analysis.

Thermographic evaluations of the knee were made by measurement of the Heat Distribution Index (HDI) and Mean Thermal Gradient (MTG) (Salisbury *et al.*, 1983), Thermographic Index (TI) (Collins *et al.*, 1974) and a differential temperature (ΔT) measured between the mean temperature over the knee joint and a 1 cm^2 reference area 10 cm below the tibial tubercle. In all thermograms a region of interest was defined over the knee joint which corresponded to a fixed area of surface anatomy bounded by the upper border of the patella superiorly and the tibial tubercle inferiorly.

Xenon clearance

The synovial blood flow can be measured indirectly by the rate of clearance of the inert gas ^{133}Xenon from the joint following intra-articular injection (Dick, 1972; Grennan *et al.*, 1975). 10 μCi of ^{133}Xenon gas were dissolved in 3 ml saline and 1 ml injected into the knee joint. A Harshaw Integral Line Scintillation Counter was positioned 10 cm vertically above the knee joint with the patient lying supine on a couch. The time taken for the count to fall to half its initial value ($t_{½}$) was measured. Synovial blood flow is inversely related to ($t_{½}$).

Protocol

All patients were given flurbiprofen 100 mg every 12 h for a minimum of 5 days prior to the day of study. No other analgesics or NSAIDs were permitted. Patients were admitted to hospital on the day preceding the study and the time of their evening dose of flurbriprofen noted. Patients were fasted from midnight and at 08.00 h an indwelling venous catheter was inserted into the forearm from which all subsequent venous

samples were taken. A basal blood sample was taken for routine haematology and biochemistry, including serum albumin.

Thermography was carried out prior to clinical assessment and joint aspiration. A pre-dose blood sample (5 ml) was taken and the timed morning dose of flurbiprofen given 12 h following the preceding evening dose. Blood samples were taken subsequently at 15 min, 30 min, 45 min, 1 h, 2 h, 3 h, 5 h, 7 h and at the time of synovial fluid aspiration for flurbiprofen and protein binding measurement. The patient was given a light breakfast following the 15 min sample.

A 21 gauge needle was inserted into the knee under full aseptic technique at either 3 h, 5 h, 12 h, 24 h or 48 h after the morning dose, and synovial fluid aspirated. Xenon clearance was performed at the end of aspiration. A combination of steroid and local anaesthetic was given intra-articularly on completion of the procedure and the needle withdrawn.

Measurement of flurbiprofen in plasma and synovial fluid

Flurbiprofen was measured by reverse phase high pressure liquid chromatography. The mobile phase (30% v/v isopropanol, 15% v/v methanol made up to volume with 1% acetic acid) was pumped through a 100 × 4.6 mm column packed with 5 μm ODS (Spherisorb, Phase Separation Ltd) using a Waters M6000A pump and with a mobile phase flow rate of 1 ml min^{-1}. Detection was achieved using a Pye Unicam LC3 variable wavelength UV detector set at 250 nm. Plasma and synovial fluid samples were treated identically. An aliquot (0.5 ml) and 0.5 ml 1M sulphuric acid were extracted with 5 ml of an ether-hexane mixture (50/50 by volume) for 15 min. After centrifugation 4 ml of the organic phase was removed and evaporated to dryness under nitrogen. The residue was reconstituted in 200 μl of mobile phase containing the internal standard (*p*-ethylbenzoic acid 10 mg l^{-1}) and 20 μl was injected onto the column. Calibrators were made up in drug-free plasma. The calibration (peak height ratio of flurbiprofen to *p*-ethylbenzoic acid) was linear over the range 1–20 mg l^{-1}. Retention times for *p*-ethylbenzoic acid and flurbiprofen under the conditions of the assay were 3.3 min and 5.8 min respectively. All reagents were of analytical grade.

Protein binding determination

Protein binding was determined using ultracentrifugation similar to the method previously described for ibuprofen (Aarons *et al.*, 1983). ^{14}C radiolabelled flurbiprofen (specific activity 22mCi g^{-1}) and cold flurbiprofen were supplied by the Boots Company PLC, Nottingham.

Pharmacokinetic calculations and statistics

Where possible, elimination rate constants (k_{el}) were determined by log linear regression of the post-peak flurbiprofen concentrations. The area under the plasma concentration-time curve between 0 and 12 h ($AUC_{(0,12)}$) was calculated in two parts. The area between 0 and 7 h was estimated using the trapezoidal rule and the area between 7 h and 12 h by exponential extrapolation. Clearance (CL) and volume of distribution (V) were calculated from the $AUC_{(0,12)}$ using the following relationships

$$CL = \frac{Dose}{AUC_{(0,12)}}$$

$$V = \frac{CL}{k_{el}}$$

assuming the drug is totally absorbed. Relationships between clinical assessments and pharmacokinetic variables were analysed by means of Spearman's rank correlation coefficients.

Results

Clinical assessments

The correlations between individual clinical and laboratory measurements are shown in Table 1. All patients were selected for the study on the basis of having acute synovitis of the knee with effusion which is reflected in the mean clinical index (4.74) and standard deviation (1.75). Different thermographic measurements showed a significant ($P < 0.05$) correlation with each other (MTG, TI and ΔT) and there were statistically significant correlations between the synovial fluid flurbiprofen and albumin concentrations with certain thermographic measurements (MTG, TI). Synovial fluid flurbiprofen and albumin concentrations did not correlate significantly with each other. Xenon clearance did not correlate with any of the other measurements.

Pharmacokinetics

The mean plasma drug concentration–time profile is shown in Figure 1. Pharmacokinetic parameters derived from the plasma concentration-time profiles are given in Table 2. There was considerable variability in the kinetics — even correcting for body weight—but on average the

Table 1 Summary of clinical and laboratory results showing Spearman's rank correlation coefficients

Variable	*Mean s.d.*	*SFpH*	*SF[Alb]*	*SF[F]*	*AUC*
Clinical index (CI)	4.74 (1.75)	−0.19 NS	0.19 NS	0.08 NS	0.20 NS
Heat distribution index (HDI)	1.18 (0.61)	−0.37 *	0.08 NS	0.57 *	−0.39 **
Mean thermal gradient (MTG °C cm^{-1})	0.44 (0.11)	−0.20 *	0.31 *	0.57 *	0.05 NS
Thermographic index (TI)	4.59 (1.28)	−0.19 NS	0.41 **	0.50 *	−0.02 NS
Differential temperature (ΔT°C)	0.97 (1.28)	−0.17 NS	−0.02 NS	0.31 NS	0.02 NS
Xenon clearance (XeC min)	18.96 (9.91)	−0.13 NS	0.32 NS	−0.09 NS	−0.15 NS

* indicates significance at the 90% level
** indicates significance at the 95% level
NS = Not significant
Synovial fluid pH = SF pH
Synovial fluid albumin concentration = SF[Alb]
Synovial fluid flurbiprofen concentration = SF[F]
Area under plasma concentration-time curve = AUC

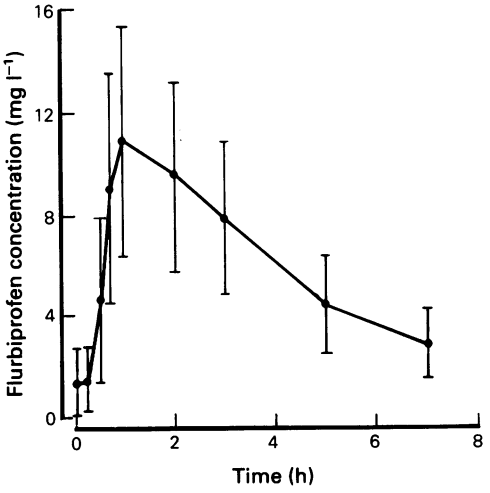

Figure 1 Average flurbiprofen plasma concentrations in rheumatoid arthritis patients receiving 100 mg of flurbiprofen every 12 h. Bars represent 1 s.d.

results agreed with those reported by Cardoe *et al.* (1977). There was little accumulation after multiple dosing but a noticeable time delay of about 15 min between drug administration and absorption. Plasma protein binding did not vary with flurbiprofen concentration over the range of concentrations seen in these patients. The fraction of flurbiprofen not bound to plasma proteins was 0.00110 ± 0.00051 (s.d.), i.e. the drug is 99.89% bound.

Synovial fluid concentrations

The synovial fluid data are summarized in Figure 2. It can be seen that the peak flurbiprofen concentration occurs later in synovial fluid than in plasma and the whole profile is flatter. Unfortunately, it was not possible to determine the concentration–time profile of flurbiprofen in synovial fluid for each patient as only one synovial fluid sample was drawn per patient. Consequently, the synovial fluid data were analyzed by pooling all the samples and treating them as if they had come from one individual. Sheiner (1984) refers to this approach as the 'naive pooled data method' and discusses the inherent problems. 'The naive pooled data approach' can lead to biased parameter estimates and more particularly, the confounding of intra- and intersubject variability. Nevertheless, in the absence of more sophisticated software, it does provide popula-

Table 2 Average plasma pharmacokinetic parameters

*Parameter**	C_{max} *(mg l^{-1})*	t_{max} *(h)*	*CL (ml min^{-1} kg^{-1})*	V *(l kg^{-1})*	$t_{½}$ *(h)*
Mean	12.5	1.49	0.65	0.160	3.1
s.d.	4.0	0.76	0.24	0.093	1.7

*C_{max} = maximum plasma concentration
t_{max} = time-to-maximum concentration
CL = clearance normalized for body weight
V = volume of distribution normalized for body weight
$t_{½}$ = elimination half-life

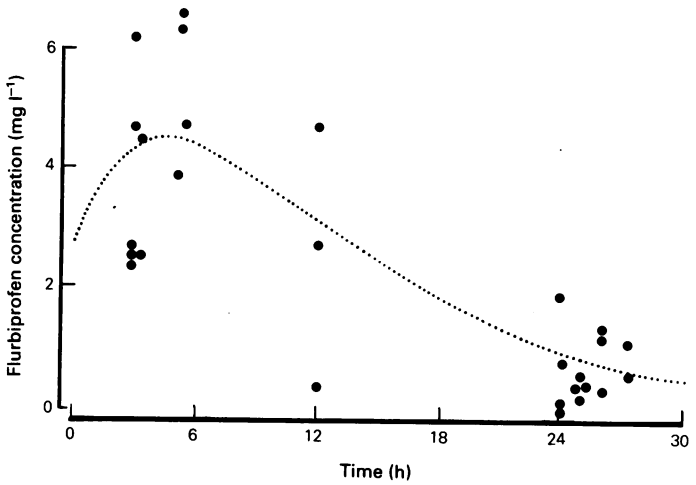

Figure 2 Synovial fluid flurbiprofen concentration *vs* time data showing bi-exponential fit to the data (--------).

tion estimates of the parameters which are a useful first approximation. Therefore, a bi-exponential equation was fitted to the pooled data using nonlinear least squares regression (Metzler *et al.*, 1974) and the maximum flurbiprofen concentration in synovial fluid and the time-to-maximum concentration was estimated to be 4.45 (± 0.60 s.e. mean) mg l^{-1} and 5.2 (± 3.7 s.e. mean) h, respectively.

In two patients, synovial fluid was aspirated 48 h after the dose and no flurbiprofen was detectable. The fraction of flurbiprofen not bound to protein in synovial fluid was 0.00114 ± 0.00049 (s.d.) which was not significantly different to that in plasma (0.00110 ± 0.00051; s.d.). However, the average albumin concentration in synovial fluid (21.6 ± 5.8 g l^{-1} s.d.) was significantly smaller than in plasma (35.9 ± 11.1 g l^{-1}; s.d.). Synovial fluid pH ranged from 7.0–8.2 with a mean of 7.47 ± 0.32 (s.d.). The fraction of flurbiprofen not bound in synovial fluid did not correlate with either pH or albumin concentration.

Discussion

The aim of the present study was to examine plasma and synovial fluid pharmacokinetics of flurbiprofen and to determine factors which might influence synovial fluid drug concentration. A large inter-individual variation in both plasma and synovial fluid profiles after a 100 mg oral dose was noted. Even after correcting for body weight the coefficient of variation of the plasma measurement for C_{max} was 32% and for plasma clearance was 37%. The major route of elimination of flurbiprofen is oxidative metabolism (Brogden *et al.*, 1979), and consequently, variability in plasma clearance and hence steady

state concentrations would be expected in a heterogeneous patient population. Factors such as liver function, other drugs and smoking may contribute to this variability (see for example Gibaldi, 1977). Synovial fluid concentration is partly related to plasma drug concentration although peak synovial fluid concentrations are lower and occur later after oral dosage than corresponding plasma drug concentrations. After a single oral dose the drug persists longer in synovial fluid than in plasma, although 48 h after dosage with this short half-life NSAID the drug has been completely cleared from synovial fluid. However, the ratio of synovial fluid to plasma flurbiprofen concentration still shows a variability of ± 32% at 3 h. It therefore seems likely that a large proportion of this variability is due to differences in distribution of drug from the blood stream into the synovial cavity.

Factors which might influence distribution of drug from the blood stream into synovial fluid include synovial blood flow (which itself is influenced by local inflammatory disease activity), endothelial vascular permeability to albumin, diffusion of free drug from vascular endothelium across the synovium to the synovial cavity, ratio of synovial fluid to plasma albumin concentration and local synovial pH. Inflammatory disease activity may influence both synovial blood flow and vascular permeability as well as the distance for diffusion across synovial tissue (Wallis & Simkin, 1983). The lack of a single clinical measure of disease activity makes it necessary to use a number of methods of varying sensitivity which may each measure different aspects of inflammation. Previous studies have shown a correlation between extremes of inflammatory disease activity and thermographic measurements (Salisbury *et al.*, 1983; Bird *et al.*, 1979; Bacon *et al.*, 1975). The rate of clearance of ^{133}Xenon from the joint is an indirect measure of synovial blood flow and is an objective measurement of another aspect of inflammation. Thus, the poor correlation noted in the present study between clinical and laboratory measurements of disease activity may be partly related to different facets of inflammation which each measurement reflects. This poor correlation may also be partly attributable to the narrow clinical spectrum of disease activity of patients examined. In this study synovial fluid drug concentration showed a statistically significant (although weak) correlation with the thermographic measurement of inflammation, but not with either the clinical assessment or Xenon clearance. Synovial fluid albumin concentrations in the present study ranged from 15 g l^{-1} to 37 g l^{-1}. Synovial fluid drug concentration did not correlate with either albumin concentration or pH and unbound drug concentration exhibited the same general time dependency as total drug concentration in both synovial fluid and plasma. The percentages of drug unbound in synovial fluid and plasma were equal. This is in agreement with the previous *in vitro* studies of Wanwimolruk *et al.* (1983). In parallel *in vitro* studies we have found that the relationship between drug binding, protein concentration and drug concentration is complex, although the fraction of drug unbound at albumin concentrations ranging from 20 g l^{-1} to 40 g l^{-1} is approximately equal (Aarons *et al.* 1985, unpublished). Thus, in the present study it seems likely that the major determinant of the variability found in synovial fluid concentration may be the diffusion rate of free drug across the synovium. Diffusion rates of free drug across the synovium from vascular endothelium to synovial cavity may be reduced in rheumatoid arthritis (Wallis & Simkins, 1983). Measurement of free drug diffusion rates across synovium are dependent on estimates of synovial fluid volume and such measurements were not made in the present study.

Ray *et al.* (1979) applied a two-compartment pharmacokinetic model in the analysis of carprofen concentrations in serum and synovial fluid following single oral doses of the drug. In this model, compartment 1 reflected the plasma concentration and compartment 2 the synovial fluid concentration. However, this model did not give accurate predictions of synovial fluid concentrations mainly because synovial fluid only accounts for a small part of the distribution of carprofen. We have modifed this model to accommodate our results (Figure 3). In this modified model flurbiprofen behaves as a one-compartment drug when viewed from plasma. The dose, D, is absorbed by a first order process, which is assumed to be complete, with a first order rate constant k_a. The drug binds reversibly to plasma proteins and its elimination is proportional to the unbound concentration Cu. Distribution into synovial fluid does not affect the plasma kinetics. The rate of transfer of drug between synovial fluid and plasma is dependent on unbound concentration and a diffusion constant, R. The volume of distribution of the drug is given by V and the volume of synovial fluid by V(sf). Equations describing the kinetic behaviour of the model are given below.

$$\frac{V \cdot dC}{dt} = D \cdot k_a \cdot e^{-k_a \cdot t} - CLu \cdot Cu \qquad (1)$$

$$\frac{V(sf) \cdot dC \cdot (sf)}{dt} = R \cdot Cu - R \cdot Cu(sf) \qquad (2)$$

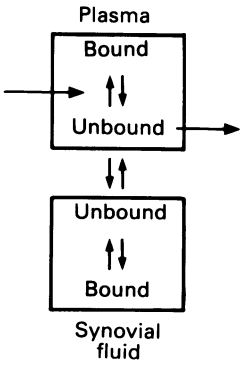

Figure 3 Pharmacokinetic model of flurbiprofen in plasma and synovial fluid.

where CLu is the clearance based on unbound concentration. The relationship between total concentration, C, and unbound concentration, Cu, is given by the following binding isotherm

$$C = Cu + \frac{n \cdot K \cdot Cu \cdot P}{1 + K \cdot Cu} \qquad (3)$$

where n is the number of binding sites on the protein molecule, K is the association constant and P is the protein concentration. The same values of n and K were used for synovial fluid and plasma but the protein concentration in synovial fluid was taken as 66% that in plasma which was set to 40 g l^{-1}.

Simulations using these equations are shown in Figure 4. The profiles shown represent the steady state situation for 100 mg given every 12 h. Parameters were chosen based on the results of the present study and previous work (Cardoe *et al.*, 1977). The plasma half-life is 3.4 h and the fraction bound in plasma is 0.999. The only adjustable parameter is the ratio of the diffusion constant to the volume of synovial fluid, R/V(sf). This parameter only affects the synovial fluid profile. The unbound drug concentration–time profile essentially parallels the total profile.

The predicted time-to-maximum and maximum concentrations for both plasma and synovial fluid are in reasonable agreement with the observed results. It should be remembered that the results shown in Figure 4 are simulations rather than fits to the data and that agreement between the results of the model and the observations does not establish causality. Nevertheless, the model does explain the major trends seen in the data; particularly the flatter synovial fluid profile and longer time-to-peak.

The terminal half-life of the synovial fluid profile is determined by R/V(sf) which for these simulations gives a half-life (based on total concentration) of 4.6 h. The longer terminal half-life in synovial fluid as compared to plasma results from the fact that the plasma half-life is shorter than that determined from R/V(sf). It is interesting to compare these results with those for tolmetin (Dromgoole *et al.*, 1982) which has a longer plasma half-life, 6.77 h, than flurbiprofen and consequently the half-life seen in synovial

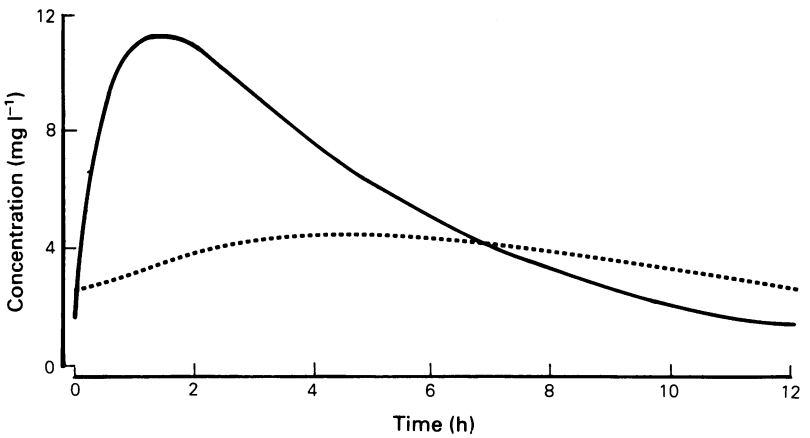

Figure 4 Simulation of steady state concentration–time profile of flurbiprofen in plasma (—) and synovial (----) fluid for 12 h dosing. Parameter values [eqns (1)–(3)]
V = 7 l; D = 100 mg; τ = 12 h; k_a = 1.5 h^{-1}.
CLu = 1400 l h^{-1}; V(sf) = 0.1 l; R = 10 l h^{-1}
n = 1; K = 1.67 × 10^6 M^{-1}.

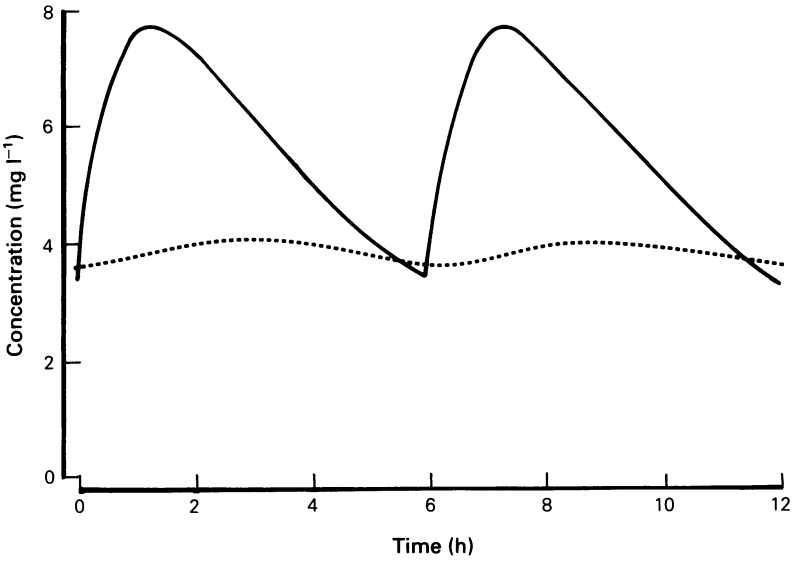

Figure 5 Simulation of steady-state concentration profile of flurbiprofen in plasma (—) and synovial (-----) fluid for 6 h dosing. Parameter values as for Figure 5 except D = 50 mg; τ = 6 h.

fluid is about the same, 6.90 h, presumably because it is longer than that determined by R/V(sf). The simulations also show that, in the 12 h interval, there are only two times—near 0 and 6.8 h—where the total drug concentrations in plasma and synovial fluid are the same. However, the average unbound concentrations at steady state, Cu_{av} and Cu_{av}(sf), are the same as can be seen by integrating equations (1) and (2) to give:

$$Cu_{av} = \frac{D}{CLu \cdot \tau} = Cu(sf)$$

where τ is the dosing interval, 12 h.

Based on the short plasma half-life of flurbiprofen, a twice daily dosage regime would appear insufficient for adequate therapeutic effect. However, it is clear that synovial fluid and tissue drug concentrations do not show the same extreme fluctuations as those found in the plasma kinetics. A computer simulation illustrates that a regimen of 50 mg every 6 h shows a smoother plasma profile but with little difference in synovial fluid profile compared to the less frequent dosing regime (Figure 5). Cu_{av} is the same for both regimens. These simulations illustrate the danger of dosage regimen design based on plasma kinetics alone, when the response is related to a more slowly equilibrating tissue.

In conclusion, the factors responsible for the variability in synovial fluid concentration are unclear. There is a suggestion from our data that the variability is due to distribution of drug from the blood stream into the synovial cavity possibly as a consequence of varying transport rates across the synovial tissue. In order to confirm this, it would be desirable to obtain complete synovial fluid concentration–time profiles and to measure synovial fluid volume. Ethical considerations make serial aspiration of synovial fluid difficult.

We are grateful to the Boots Co. for providing radiolabelled flurbiprofen and for financial support.

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(Received 7 May 1985, accepted 1 October 1985)