Pharmaceutical Research, Vol. 11, No. 12, 1994

Research Article

Transsynovial Drug Distribution: Synovial Mean Transit Time of Diclofenac and Other Nonsteroidal Antiinflammatory Drugs

William F. Elmquist,[1,2] Keith K. H. Chan,[1,3] and Ronald J. Sawchuk[1,4]

Received March 11, 1994; accepted July 18, 1994

The synovial mean transit time of diclofenac was determined by two methods from existing plasma and synovial fluid concentration-time data. These data were obtained from single- and multiple-dosing regimens of diclofenac in patients with osteoarthritis and rheumatoid arthritis. Plasma and synovial fluid concentration-time data taken from the literature for four other nonsteroidal antiinflammatory drugs (etodolac, ibuprofen, indomethacin, and tenoxicam) were also analyzed. The two methods of data analysis rely on the determination of the ratio of the area under the synovial fluid concentration-time curve to the area under the plasma concentration-time curve. Both methods can be considered noncompartmental because in determining the first-order exit rate constant for the synovial fluid (the inverse of the synovial mean transit time), an analysis of the overall distribution and elimination characteristics of the drug is unnecessary. Method 1 makes use of the information contained in the postdistributional synovial fluid to plasma concentration ratio whereas method 2 is a linear pharmacokinetic model using a partial-areas analysis. The single dose mean ± S.D. synovial fluid exit rate constant for diclofenac was 0.39 ± 0.33 hr^{-1} (n = 6), which was not significantly different from that determined by method 2; which was 0.49 ± 0.52 hr^{-1}. The steady state mean ± S.D. diclofenac synovial fluid exit rate constants for methods 1 and 2 were 0.43 ± 0.18 and 0.54 ± 0.71 hr^{-1} (n = 8), respectively, which were not significantly different. These values of synovial fluid exit rate constants result in a synovial mean transit time for diclofenac that is approximately 2 to 2.5 hours. The synovial mean transit time calculated using method 1 from literature data for etodolac, ibuprofen, indomethacin, and tenoxicam were 6.8, 2.2, 4.8, and 3.5 hours, respectively. The synovial mean transit times calculated by method 2 for the same drugs were 5.3, 3.4, 4.7, and 4.0 hours, respectively. Similar values of the synovial mean transit time of nonsteroidal antiinflammatory drugs were achieved by using either of these two methods, both of which avoid complex equation fitting which is statistically problematic in the frequently data-sparse environment of extravascular sampling.

KEY WORDS: synovial drug distribution; extravascular pharmacokinetics; mean transit time; nonsteroidal antiinflammatory drugs; diclofenac.

INTRODUCTION

Diclofenac sodium, the sodium salt of o-(2,6-dichlorophenylamino)-phenyl acetic acid is a nonsteroidal antiinflammatory drug with potent cyclooxygenase inhibition activity (1,2) and has been recently approved for use in the United States. One site of action for nonsteroidal antiinflammatory agents is the synovium; however, synovial tissue sampling to determine drug concentrations at the effect site is impractical and therefore synovial fluid is often sampled to examine the penetration of the drug into the joint (3,4).

The objective of this study was to develop methods to quantitate the synovial distribution kinetics of diclofenac using existing diclofenac plasma and synovial fluid concentration-time data. The diclofenac data were generated from our laboratory and some of the patients presented hereinafter have been reported as mean data in a previous publication (5). We have also analyzed plasma and synovial fluid concentration-time data from the literature for four other nonsteroidal antiinflammatory drugs: etodolac (6), ibuprofen (7), indomethacin (8), and tenoxicam (9).

The mean transit time (MTT) in a tissue space is defined as the average interval of time spent by a molecule from its entry into the tissue space to its next exit (10,11). The mean residence time (MRT) of a drug in a tissue space is the product of the MTT in the space and the average number of visits to the tissue space (10,11). Therefore, the MTT of a drug in the synovial fluid is an important parameter in determining the exposure of the synovial fluid to the drug. We present two methods to determine the first-order exit rate constant

[1] Department of Pharmaceutics, University of Minnesota, Minneapolis, Minnesota 55455.

[2] Current Address: Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska, Omaha, Nebraska 68198.

[3] Department of Clinical Pharmacokinetics and Disposition, Ciba Geigy, Ardsley, New York 10502.

[4] To whom correspondence should be addressed at Department of Pharmaceutics, College of Pharmacy, Health Sciences Unit F, 308 Harvard Street SE, Minneapolis, Minnesota 55455.

0724-8741/94/1200-1689$07.00/0

of a compound from a kinetically distinct tissue space, in this case the synovial fluid. The inverse of this exit rate constant is the synovial fluid mean transit time, $MTT_{synovial}$.

MATERIALS AND METHODS

Patients

This study included ten patients (two male, eight female) who had either rheumatoid arthritis or osteoarthritis and a significant synovial fluid effusion of the knee. The patient characteristics are listed in table I. Written informed consent was obtained from each patient before enrollment in the study.

Drug Administration and Sample Collection

Upon study entry, patients underwent a one-week washout period of all nonsteroidal antiinflammatory drugs. Patients received diclofenac sodium administered as one 75mg enteric-coated tablet every 12 hours for one week. Concommitent antiinflammatory treatments such as penicillamine, predinisone, and gold were permitted, provided the dosage had been consistent for at least three months prior to the study. Simultaneous venous blood samples and synovial fluid samples (same knee joint of same patient) were collected, where possible, predose (0 hour) and at 2, 4, 8 and 12 hours postdose on day 1 (single dose) and day 8 (steady state). Plasma and synovial fluid specimens were frozen at −70°C until analysis.

Assay

Diclofenac plasma and synovial fluid concentrations were measured by high-performance liquid chromatography (12,13). The plasma calibration curves were linear from 5 to 1000 ng/ml and the between-day coefficient of variation ranged from 2 to 20%. The lower limit of quantification for this method was 5 ng/ml. An excellent linear relationship is obtained between calibration curves from blank plasma and synovial fluid (13). Therefore, due to the difficulty in obtaining blank synovial fluid, a plasma calibration curve was used to quantitate synovial fluid concentrations.

Table I. Patient Characteristics

Patient	Age (yr)	Gender	Height (cm)	Weight (kg)	ARA Class*	Diagnosis**
1	63	male	174	72	II	RA
2	70	female	159	74	II	RA
3	62	female	164	65	II	RA
4	70	male	175	86	II	OA
5	38	female	163	65	II	RA
6	31	female	170	73	II	RA
7	44	female	165	75	II	RA
8	55	female	171	113	II	OA
9	24	female	163	58	II	RA
10	55	female	156	61	III	RA
Mean	51		166	74		
Std Dev	16		6	16		
RSD%	32		4	21		

* Functional class: I = complete ability, II = adequate for normal activities, III = limited ability, IV = incapacitated largely or wholly.

** Diagnosis: RA = rheumatoid arthritis, OA = osteoarthritis.

Pharmacokinetic Analysis

We employ two methods of pharmacokinetic data analysis to determine the synovial fluid exit rate constant, from which the mean transit time in the synovial fluid can be calculated. Both methods rely on the determination of the area under the concentration-time curve (AUC) for synovial fluid and plasma. The $AUC_{synovial}$ and AUC_{plasma} were determined using the trapezoidal rule and extrapolated to infinity where necessary by division of the last measured concentration by the corresponding terminal rate constant. Generally, two to three data points were used to determine the terminal phase rate constants.

Method 1. Equations for drug concentration as a function of time in a reservoir (plasma) and a noneliminating tissue (e.g., synovial fluid) were derived from a flow-volume based physiological perfusion model as described by Bischoff and Dedrick (14–16). The following equation describes the ratio of the synovial fluid concentration to the plasma concentration in the postdistributional (terminal) phase:

$$\left(\frac{Cs}{Cp}\right)_{\beta eta} = \frac{Qs/Vs}{Qs/(Vs*Ks) - \beta} \quad (1)$$

where Cs and Cp are the drug concentrations in the synovial fluid and plasma, respectively, Qs is the plasma flow to the synovial space, Vs is the volume of the synovial space, Ks is the synovial fluid to emergent plasma drug partition coefficient, and β is the terminal phase elimination rate constant. Multiplying the numerator and denominator on the right side of equation 1 by Vs yields:

$$\left(\frac{Cs}{Cp}\right)_{\beta eta} = \frac{Qs}{Qs/Ks - \beta*Vs} \quad (2)$$

where the flow terms Qs and Qs/Ks represent the clearance into (Cl_{in}) and clearance out of (Cl_{out}) the synovial fluid, respectively. An equation similar to equation 2 can be derived for the membrane-limited case, where the permeability of the synovial membrane is limiting transport, i.e., the flux across the membrane is slow compared to the tissue perfusion rate. Therefore,

$$\left(\frac{Cs}{Cp}\right)_{\beta eta} = \frac{Clin}{Clout - \beta*Vs} \quad (3)$$

and since,

$$Clout = ksp*Vs \quad (4)$$

then,

$$\left(\frac{Cs}{Cp}\right)_{\beta eta} = \frac{Clin/Clout}{1 - \beta/ksp} \quad (5)$$

where ksp is the first-order transfer rate constant from the synovial fluid to plasma. The ratio of the clearances into and out of the synovial fluid, Cl_{in}/Cl_{out}, is actually the partition

coefficient, *Ks*, and can be estimated by the area ratio $AUC_{synovial}/AUC_{plasma}$ from time zero to infinity following a single dose or the area ratio $AUC_{synovial}/AUC_{plasma}$ over one dosing interval following multiple dosing to steady state (17,18). Therefore the synovial exit rate constant, *ksp*, can be estimated from the following equation:

$$\left(\frac{Cs}{Cp}\right)_{\beta eta} = \frac{AUC_{synovial}/Auc_{plasma}}{1 - \beta/ksp} \tag{6}$$

The $(Cs/Cp)_{\beta eta}$ ratio used in equation 6 is the average of all the concentration ratios (usually two) observed in the terminal phase of an individual patient, either at steady state (day 8) or following a single dose (day 1).

Method 2. The second method developed to determine the synovial exit rate constant is a linear pharmacokinetic model using a partial-areas analysis. This method of pharmacokinetic analysis has been used in this laboratory to examine the exit transfer kinetics of zidovudine from the cerebrospinal fluid of the rabbit (19).

The differential equation describing the rate of change of drug concentration with respect to time in the synovial fluid is:

$$\frac{Vs*dCs}{dt} = Clin*Cp - Clout*Cs \tag{7}$$

with each term as defined above.
Integrating equation 7 over a discrete time interval yields:

$$Vs*\Delta Cs|_{ti}^{ti+1} = Clin*\int_{ti}^{ti+1} Cpdt - Clout*\int_{ti}^{ti+1} Csdt \tag{8}$$

and since

$$\frac{Clin}{Clout} = \frac{AUC_{synovial}}{AUC_{plasma}} \tag{9}$$

then it follows that,

$$Vs*\Delta Cs|_{ti}^{ti+1} = Clout*\left(\left[\frac{AUC_{synovial}}{AUC_{plasma}}* AUC_{plasma}|_{ti}^{ti+1}\right] - \left[AUC_{synovial}|_{ti}^{ti+1}\right]\right) \tag{10}$$

Dividing both sides of equation 10 by *Vs* and substituting equation 4 on the right hand side results in:

$$\Delta Cs|_{ti}^{ti+1} = ksp*\left(\left[\frac{AUC_{synovial}}{AUC_{plasma}}* AUC_{plasma}|_{ti}^{ti+1}\right] - \left[AUC_{synovial}|_{ti}^{ti+1}\right]\right) \tag{11}$$

which is an equation for a straight line with an intercept of zero and a slope that is equal to *ksp*, the synovial fluid exit rate constant.

These two methods of data analysis result in the determination of the first-order transfer rate constant for drug transport out of the synovial space. This exit rate constant would be the sum of the rate constants for both diffusion and lymphatic bulk flow out the synovial fluid space. The synovial mean transit time ($MTT_{synovial}$) can be easily calculated (10,11) from the exit rate constants as:

$$MTT\ synovial = 1/ksp \tag{12}$$

Statistical Analysis

Perpendicular least squares regression analysis (20) was used to fit equation 11 to the data (Method 2) since both variables in the linear equation:

$$(\Delta Cs|_{ti}^{ti+1}) \text{ and } \left(\left[\frac{AUC_{synovial}}{AUC_{plasma}}* AUC_{plasma}|_{ti}^{ti+1}\right] - \left[AUC_{synovial}|_{ti}^{ti+1}\right]\right)$$

are subject to error. The synovial exit rate constant (*ksp*) values determined by the two methods were compared by means of a paired t-test and the significance level chosen was $p \leq 0.05$.

RESULTS

The diclofenac synovial and plasma areas under the curve following the initial 75 mg dose and after dosing to steady state are listed in table II. Due to the difficulty in collecting synovial samples, not all patients had the necessary frequency of sampling that would lead to adequate data analysis and therefore data from six patients on day 1 and eight patients on day 8 are reported. The terminal plasma elimination rate constants, β, and the synovial fluid to diclofenac concentration ratios are also listed in table II. These values are used to calculate the synovial fluid exit rate constant by the two methods via equations 6 and 11. The areas under the curve reported in table II are extrapolated to infinity in the single-dose data and represent one dosing interval in the steady-state case. The average concentration ratio, $(Cs/Cp)_{\beta eta}$, in the postdistributional phase was 4.59 ± 1.17 for day 1 and 4.73 ± 3.67 for day 8 and was significantly greater than the average area ratios (which would represent the partition coefficient, *Ks*), 0.92 ± 1.31 and 1.11 ± 0.49 for days 1 and 8, respectively. This synovial to plasma concentration relationship in the terminal phase is clearly seen in figure 1, a representative synovial fluid and plasma diclofenac concentration-time profile. The corresponding perpendicular least squares fit of equation 11 for this patient is shown in figure 2.

The diclofenac synovial exit rate constants, *ksp*, calculated either by equation 6 or by the fit of equation 11, are listed in table III and table IV. The mean *ksp* value in the single dose case was 0.39 ± 0.33 hr^{-1} as calculated by equation 6. This was not statistically different than the mean value of 0.49 ± 0.52 hr^{-1}, computed from the fit of equation 11. The corresponding synovial mean transit time values calculated by equation 11 are also listed in table III and table IV. The harmonic mean values for the synovial fluid mean transit time for the single dose case were 2.55 and 2.04 hours calculated from *ksp* values derived from equations 6 and 11, respectively. The mean *ksp* values for the steady state data were 0.43 ± 0.18 and 0.54 ± 0.71 hr^{-1} for equations 6 and 11, respectively, and there was no significant difference between them. The corresponding synovial mean transit times

Table II. Diclofenac Transsynovial Distribution

Single dose (day 1)					
Patient	$(Cs/Cp)_{\beta eta}$	$AUC_{synovial}$ (ng * hr/ml)	AUC_{plasma} (ng * hr/ml)	$AUC_{synovial}/AUC_{plasma}$	βeta (hr^{-1})
1	5.98	1832	7085	0.26	0.21
2	3.38	1846	3213	0.57	0.15
3	3.98	1237	10432	0.12	0.34
5	5.36	2890	811	3.56	0.35
8	3.33	1183	2211	0.54	0.21
9	5.53	1881	4250	0.44	0.28
Mean	4.59	1812	4667	0.92	0.26
Std Dev	1.17	616	3529	1.31	0.08
RSD%	25	34	76	143	31
Steady state (day 8)					
Patient	$(Cs/Cp)_{\beta eta}$	$AUC_{synovial}$ (ng * hr/ml)	AUC_{plasma} (ng * hr/ml)	$AUC_{synovial}/AUC_{plasma}$	βeta (hr^{-1})
2	4.03	1701	854	1.99	0.19
3	1.94	1129	831	1.36	0.23
4	2.23	1420	2309	0.61	0.34
6	4.38	1745	2673	0.65	0.35
7	12.93	3410	3038	1.12	0.19
8	2.68	2587	1906	1.36	0.23
9	2.82	2208	1799	1.23	0.30
10	6.83	2891	5027	0.58	0.17
Mean	4.73	2136	2305	1.11	0.25
Std Dev	3.67	781	1351	0.49	0.07
RSD%	78	37	59	44	28

for the steady-state case were 2.34 and 1.84 hours for equations 6 and 11, respectively.

Data from the literature for four other nonsteroidal antiinflammatory drugs were analyzed using both methods of data analysis. The mean synovial and plasma concentration-time profiles were analyzed for etodolac (6), ibuprofen (7), and indomethacin (8), while the individual profiles of six patients were analyzed for tenoxicam (9). The synovial exit rate constants and mean transit times determined for these compounds are reported in table V. The fits of equation 11 to the mean data of etodolac, ibuprofen and indomethacin, and a representative tenoxicam patient are shown in figure 3. The tenoxicam synovial fluid to plasma area under the curve and concentration ratios are listed in table VI. The synovial exit rate constants and mean transit times determined by both methods for tenoxicam are reported in table VII.

DISCUSSION

We have determined the synovial mean transit times of diclofenac and other nonsteroidal antiinflammatory drugs using two methods of data analysis. The overall mean synovial exit rate constants for the five compounds reported in table V were 0.32 ± 0.12 hr^{-1} and 0.33 ± 0.15 hr^{-1} as

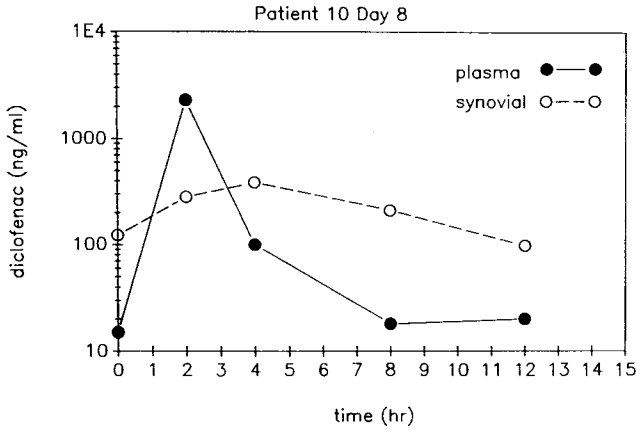

Fig. 1. Representative plasma (solid line) and synovial fluid (dashed line) diclofenac concentration-time profiles (patient 10).

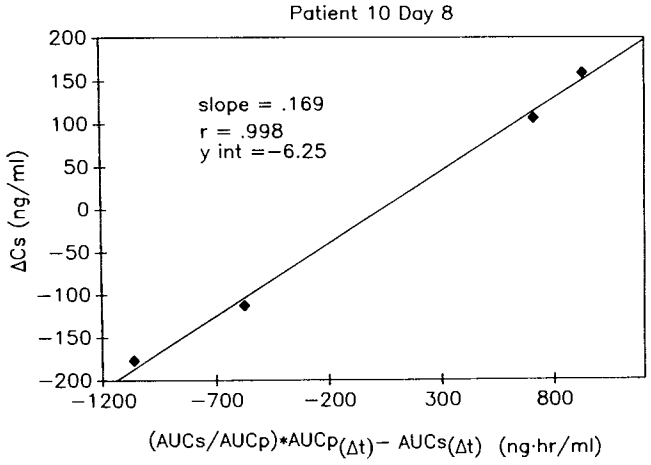

Fig. 2. Perpendicular least squares fit of equation 11 for diclofenac data from patient 10 (see figure 1).

Table III. Diclofenac Synovial Exit Rate Constants (*ksp*) and Mean Transit Times ($MTT_{synovial}$) Following a Single Dose (Day 1) Using Two Methods of Data Analysis

	Equation #6		Equation #11	
Patient	*ksp* (hr^{-1})	$MTT_{synovial}$ (hr)	*ksp* (hr^{-1})	$MTT_{synovial}$ (hr)
1	0.22	4.56	0.19	5.26
2	0.18	5.53	0.19	5.24
3	0.35	2.85	0.54	1.87
5	1.04	0.96	1.52	0.66
8	0.25	4.00	0.24	4.10
9	0.30	3.29	0.27	3.73
Mean	0.39	2.55*	0.49	2.04*
Std Dev	0.33		0.52	
RSD%	83		106	

* Harmonic mean.

determined by equations 6 and 11, respectively, and were not significantly different. This result, along with the fact that each method yielded *ksp* values that were statistically indistinguishable for the individual diclofenac and tenoxicam patients, indicates that the two methods provide similar estimates of the synovial fluid exit rate constant and provides a degree of validation for each method of data analysis.

The synovial fluid exit rate constant has been estimated for certain nonsteroidal antiinflammatory drugs in the literature. Hinderling et al (21) estimated the *ksp* for tenoxicam in four patients with arthritis to be $0.31 \pm 0.2\ hr^{-1}$ using visual fitting of the plasma and synovial fluid concentration time profiles by applying the program CSMP (22). The authors state that "the small number of data points and/or scattering of the data in plasma and synovial fluid did not lead to satisfactory fits by nonlinear regression in all cases" (21). The *ksp* determined by Hinderling et al (21) compares well with the tenoxicam *ksp* determined in the present analysis: $0.29 \pm 0.19\ hr^{-1}$ and $0.25 \pm 0.19\ hr^{-1}$ as calculated by equations 6 and 11, respectively. Day et al (23) have studied the stereoselective disposition of ibuprofen in synovial fluid and determined the *ksp* values for R and S ibuprofen to be $0.27 \pm 0.18\ hr^{-1}$ and $0.33 \pm 0.22\ hr^{-1}$, respectively. These exit rate constants for ibuprofen that were determined by Day et al are similar to those in this study determined by equations 6 and 11; which were $0.45\ hr^{-1}$ and $0.29\ hr^{-1}$, respectively.

Table IV. Diclofenac Synovial Exit Rate Constants (*ksp*) and Mean Transit Times ($MTT_{synovial}$) Following Dosing to Steady State (Day 8) Using Two Methods of Data Analysis

	Equation #6		Equation #11	
Patient	*ksp* (hr^{-1})	$MTT_{synovial}$ (hr)	*ksp* (hr^{-1})	$MTT_{synovial}$ (hr)
2	0.38	2.66	0.41	2.46
3	0.77	1.30	2.27	0.44
4	0.47	2.13	0.36	2.81
6	0.41	2.43	0.23	4.27
7	0.21	4.81	0.08	12.20
8	0.47	2.15	0.45	2.22
9	0.53	1.88	0.37	2.70
10	0.19	5.39	0.17	5.92
Mean	0.43	2.34*	0.54	1.84*
Std Dev	0.18		0.71	
RSD%	43		131	

* Harmonic mean.

A pharmacological effect at the tissue level would be expected to be some function of both drug concentration and duration of tissue exposure to the drug molecule. The mean residence time in a tissue space is defined as the average time spent by a drug molecule in all its passages through it (10). The synovial fluid mean residence time ($MRT_{synovial}$) is a measure of the duration of the synovial exposure to the drug molecule. The $MRT_{synovial}$ is the product of the synovial fluid mean transit time (a single pass mean residence time) and the average number of passages of a drug molecule through the synovial fluid. The average number of passes through a noneliminating tissue, R, is dependent on both a distributional factor, clearance into the tissue, Cl_{in}, and an elimination factor, clearance from the body, Cl_{tot}, by the following relationship; $R = Cl_{in}/Cl_{tot}$ (10,11). Therefore, the duration of exposure of the synovial fluid to a nonsteroidal antiinflammatory depends on a distributional characteristic of the drug, $MTT_{synovial}$, and a factor which includes a combination of both distribution and elimination characteristics, R, the average number of passages of the nonsteroidal antiinflammatory drug molecule through the synovial fluid.

The *ksp* values were similar among the different drugs analyzed; a mean of approximately $0.32\ hr^{-1}$ with a standard deviation of $0.12\ hr^{-1}$ (table V). The narrow distribution of *ksp* values among nonsteroidal antiinflammatory drugs that have widely varying overall pharmacokinetics of distribution and elimination (terminal halflives ranging from 2 to 58 hours) indicates that the specific determinants of the mean transit time in the synovial fluid are similar across the group of drugs studied. In other words, this result indicates that the drugs studied exhibited similar synovial permeability under similar tissue flow-volume conditions and therefore exhibit comparable specific distributional characteristics, such as the synovial fluid mean transit time.

An analysis of the synovial fluid concentration-time profile relative to the plasma concentration-time profile of diclofenac and tenoxicam may provide additional insights concerning the synovial permeability to nonsteroidal antiinflammatory agents. Diclofenac and tenoxicam represent extremes in the terminal elimination halflife for the drugs listed in table V with an average halflife of approximately 3 and 40 hours, respectively. The synovial fluid concentration-time curve of diclofenac, an antiinflammatory with a short halflife, is initially lower than the plasma diclofenac concentration-time curve, then crosses over and remains above the plasma curve at a relatively constant proportion in the postdistributive phase (figure 1). Conversely, for tenoxicam, an antiinflammatory with a long terminal halflife, the synovial fluid concentration-time profile is closely proportional to the plasma curve at all times and remains below the plasma curve throughout the profile, as can be seen in figure 4 (9,20). This type of profile has also been observed for piroxicam, another antiinflammatory with a long halflife (24). The difference in the shape of the concentration-time profiles

Table V. Synovial Exit Rate Constants (*ksp*) and Mean Transit Times ($MTT_{synovial}$) of Selected Nonsteroidal Antiinflammatory Agents Using Two Methods of Data Analysis

	Equation #6		Equation #11		
Drug	*ksp* (hr^{-1})	$MTT_{synovial}$ (hr)	*ksp* (hr^{-1})	$MTT_{synovial}$ (hr)	Reference
Diclofenac[a]	0.39	2.55	0.49	2.04	—
Diclofenac[b]	0.43	2.34	0.54	1.84	—
Etodolac[b]	0.15	6.76	0.19	5.29	6
Ibuprofen[b]	0.45	2.22	0.29	3.44	7
Indomethacin[a]	0.21	4.81	0.21	4.67	8
Tenoxicam[a,c]	0.29	3.50	0.25	4.03	9
Mean	0.32	3.14[d]	0.33	3.04[d]	
Std Dev	0.12		0.15		
RSD%	38		45		

[a] Single dose results (see Table III).
[b] Steady state results (see Table IV).
[c] Mean of six patients (see Table VII).
[d] Harmonic mean.

reflects the difference in *relative* synovial permeability of the two types of antiinflammatory drugs.

The permeability or membrane transport of a drug to a site of action must be discussed relative to the time scale of other kinetic processes that occur simultaneously. These other kinetic processes will have an impact on the relationship between the plasma concentration-time course and the synovial fluid concentration-time course. A drug with "low" relative synovial permeability would be one where the synovial mean transit time is long relative to the mean residence time in the body. In terms of rate constants, if the magnitude of the terminal elimination rate constant, β, approaches that of the synovial exit rate constant, *ksp*, then the compound would have a low relative permeability. On the other hand, if the magnitude of the terminal rate constant is much less than the synovial fluid exit rate constant, then the apparent rate to equilibrium between the plasma and synovial fluid is fast and the synovial fluid concentration-time profile will be proportional to the plasma at all times, an example of "high" relative permeability. A compound with high relative permeability would be one where the synovial fluid mean transit time is short relative to the mean residence time in the body.

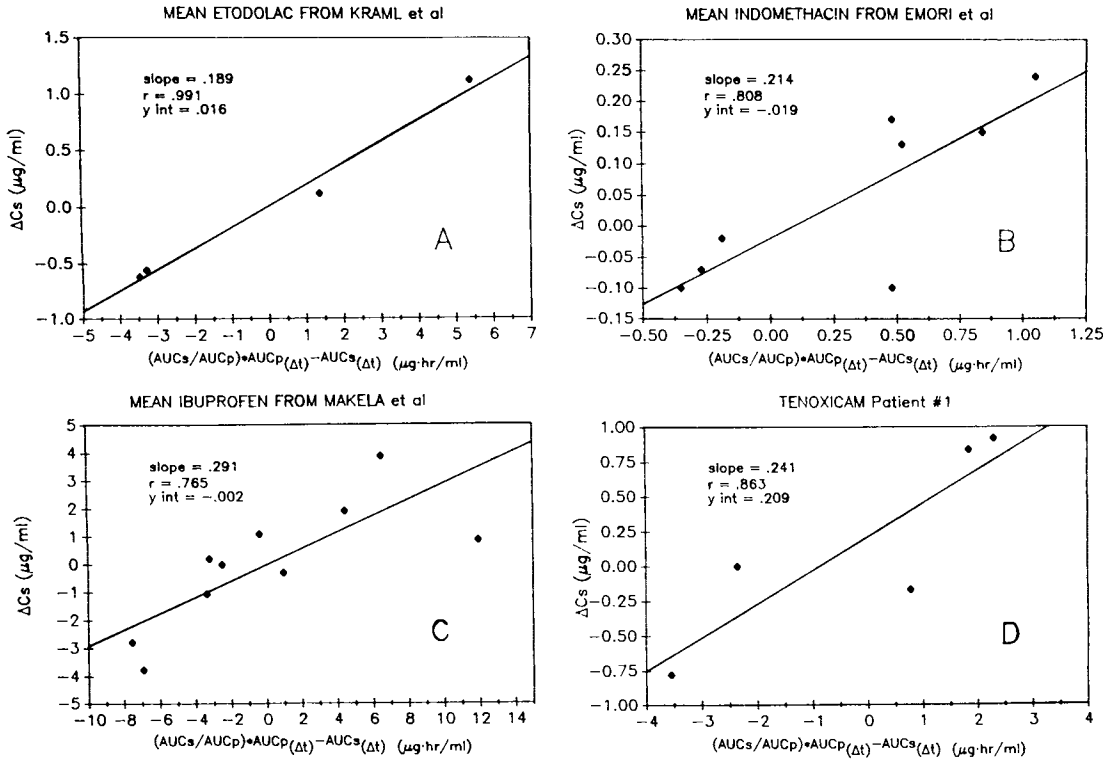

Fig. 3. Perpendicular least squares fits of equation 11 for A) etodolac, B) indomethacin, C) ibuprofen, and D) tenoxicam.

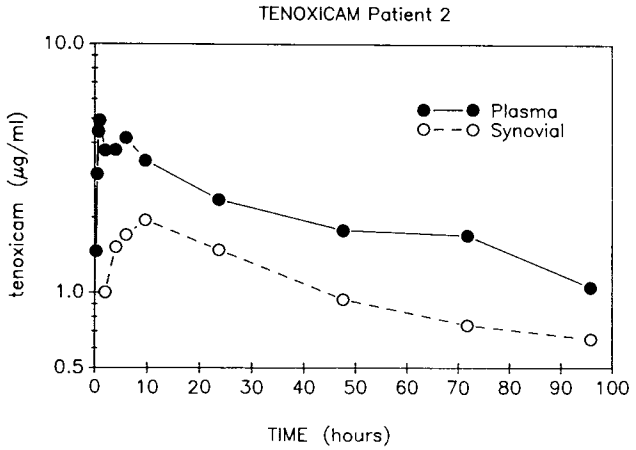

Fig. 4. Representative plasma (solid line) and synovial fluid (dashed line) tenoxicam concentration-time profiles.

Diclofenac would represent a drug with low relative permeability and tenoxicam would be an example of a drug with high relative permeability. If the synovial mean transit time is characteristic of the inherent or intrinsic synovial permeability, in other words, if the *ksp*Vs* product is related to a permeability*surface-area product, then these two drugs are similar in their inherent or intrinsic joint permeability, as can be seen from the similar values of the $MTT_{synovial}$ for the two drugs. However, the relative shape of the synovial fluid versus plasma concentration-time profiles are different (contrast figures 1 and 4); an indication of the fact that diclofenac is a low relative permeability compound and tenoxicam is a high relative permeability compound with regards to the synovial space. These observations illustrate that the determination of the relative permeability of a nonsteroidal antiinflammatory drug in the joint space can only be made with respect to the other kinetic processes that occur simultaneously, i.e. the overall pharmacokinetic time scale of the measurements as determined by the mean residence time in the body relative to the mean transit time in the synovial fluid.

Further evidence to illustrate this concept of relative joint permeability is seen in the synovial fluid and plasma kinetics of indomethacin. Fowler and Dawes (26) have studied the effect of the slow-release dosage form 'Osmosin' on the synovial fluid/plasma concentration-time profile. They found the pattern of a low relative permeability drug (concentration in the synovial fluid is greater than the plasma concentration in the terminal phase) following the administration of conventional quick-release indomethacin. This synovial fluid/plasma profile changed to the pattern of a high relative permeability drug (synovial fluid concentration more closely tracks the plasma concentrations and remains below the plasma throughout the profile) following the sustained-release dosage form 'Osmosin'. The inherent or intrinsic synovial permeability to indomethacin was presumably the same following each type of dosage form and the change in relative or apparent synovial permeability was due to the dosage form effect on the overall pharmacokinetic characteristics of the drug (i.e., the plasma concentration-time profile).

If a critical drug concentration were required in the synovial fluid to produce a particular pharmacologic effect (e.g., inhibition of cyclooxygenase), it is clear that the effect would be more prolonged than would be expected on the basis of the plasma concentration alone if the drug follows the pattern of low relative permeability. The synovial fluid/plasma concentration ratio in the terminal phase, $(Cs/Cp)_{\beta eta}$, is also a marker of the relative synovial permeability to drug. This concentration ratio will approach the synovial fluid to emergent plasma partition coefficient (the area ratio in equation 6) as the synovial permeability relative to other kinetic processes increases. This is evident upon examination of equation 6. When the terminal rate constant, β, is small relative to the synovial fluid exit rate constant, *ksp*, then the terminal phase concentration ratio between synovial fluid and plasma, $(Cs/Cp)_{\beta eta}$, approaches the tissue partition coefficient, which is equivalent to the area ratio. Tenoxicam is an example of a drug in which this occurs. The terminal phase synovial fluid to plasma concentration ratio is 0.58 ± 0.06, which is approaching, yet still statistically greater than, the area ratio, 0.53 ± 0.2 (see table VI). Conversely, the diclofenac terminal phase concentration ratio is approximately 4.5 times greater than the area ratio, as would be predicted for a drug with low relative synovial permeability.

Both methods of determining the synovial exit rate constant depend on the determination of the synovial to plasma areas under the concentration-time curve ratio. This ratio may have been poorly estimated in the case of diclofenac in this study. The diclofenac sampling schedule was probably adequate to characterize the more slowly changing synovial concentration-time profile (see figure 1), however the plasma area under the concentration-time curve may have been un-

Table VI. Tenoxicam Transsynovial Distribution

Tenoxicam patient	$(Cs/Cp)_{\beta eta}$	$AUC_{synovial}$ (μg * hr/ml)	AUC_{plasma} (μg * hr/ml)	$AUC_{synovial}/AUC_{plasma}$	βeta (hr^{-1})
A	0.54	143	283	0.51	0.014
B	0.56	153	289	0.53	0.012
C	0.57	130	236	0.55	0.020
D	0.58	114	225	0.51	0.020
E	0.55	141	266	0.53	0.016
F	0.70	122	215	0.57	0.017
Mean	0.58	134	252	0.53	0.016
Std Dev	0.06	14	31	0.02	0.003
RSD%	10	11	12	5	20

Table VII. Tenoxicam synovial exit rate constants (*ksp*) and mean transit times ($MTT_{synovial}$) using two methods of data analysis

Tenoxicam patient	Equation #6 *ksp* (hr^{-1})	Equation #6 $MTT_{synovial}$ (hr)	Equation #11 *ksp* (hr^{-1})	Equation #11 $MTT_{synovial}$ (hr)
A	0.22	4.52	0.24	4.15
B	0.22	4.55	0.21	4.88
C	0.60	1.68	0.09	11.42
D	0.16	6.21	8.42**	0.12**
E	0.43	2.31	0.16	6.29
F	0.09	11.36	0.55	1.82
Mean	0.29	3.49*	0.25	4.03*
Std Dev	0.19		0.19	
RSD%	66		76	

* Harmonic mean.
** Not included in summary statistics.

derestimated in some instances. After the onset of absorption, diclofenac is rapidly absorbed and plasma concentration fall rapidly after the peak is reached (27). Therefore a large proportion of the area under the plasma concentration-time curve following oral dosing is in this "area spike" following the onset of absorption. The time lag for the onset of absorption is often quite variable for an enteric-coated tablet due to variability in gastric emptying time (28). This variability would show up in area determinations for a drug whose absorption after the onset of absorption is rapid and a fixed sampling schedule is employed without regard to the variability in the lag time for absorption. We have previously shown (29), using simulated diclofenac plasma concentration-time profiles and variable lag times, that on average the true plasma area under the curve was underestimated by 45% when the sampling schedule used in this study was employed. Underestimation of the plasma area under the curve would lead to overestimation of the synovial to plasma area under the curve ratio and hence an overestimation of the true synovial fluid exit rate constant. This in turn would result in lower than true values for the synovial mean transit time. This may explain why diclofenac has a somewhat lower calculated $MTT_{synovial}$ than the other drugs studied.

These observations have important implications in the study design of extravascular pharmacokinetics. While simultaneous plasma and tissue (e.g. synovial fluid) sampling is useful, especially in the terminal phase, one should not limit the sampling schedule of plasma to that of the extravascular space because this will often lead to a poorly characterized plasma-concentration time profile due to difficulties and limitations in extravascular sampling procedures.

We present two methods of pharmacokinetic data analysis to quantify the transsynovial distribution of diclofenac and other nonsteroidal antiinflammatory drugs through the estimation of the synovial fluid mean transit time. These methods have advantages over other methods that use the fitting of complex parametric equations in that often the specimen collection in extravascular sampling is difficult, and therefore the data do not contain adequate information to obtain satisfactory results. These two methods are quite general in their derivation and can be considered "noncompartmental" since only the transfer from plasma to a kinetically distinct tissue space, in this case the synovial fluid, is described, without the necessity of fitting equations that describe the entire plasma and synovial fluid concentration-time profiles.

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