Research Article

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

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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 ± 0.32 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 = 6), 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

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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, $MT_{synovial}$. 

**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. Concomitant antiinflammatory treatments such as penicillin, prednisone, and gold were permitted, provided the dosages 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 $-70^\circ$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.

**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:

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

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 $\beta$ is the terminal phase elimination rate constant. Multiplying the numerator and denominator on the right side of equation 1 by $Vs$ yields:

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

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,

$$\left(\frac{Cs}{Cp}\right)_{\beta} = \frac{Cl_{in}}{Cl_{out} - \beta*Vs}$$

and since,

$$Cl_{out} = ksp*Vs$$

then,

$$\left(\frac{Cs}{Cp}\right)_{\beta} = \frac{Cl_{in}}{Cl_{out}} \frac{1 - \beta/ksp}{1}$$

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