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Disappearance kinetics of solutes from synovial fluid after intra-articular injection

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1 Five rheumatoid patients with a knee joint effusion participated in the study. An aqueous solution (0.1 to 0.2 ml) containing paracetamol, salicylate, diclofenac and [^{125}I]-albumin was injected into a given joint to yield target concentrations of approximately 20 μg ml^{-1} for diclofenac, salicylate and paracetamol and 10^8 counts ml^{-1} for [^{125}I]-albumin.

2 Paracetamol, salicylate and diclofenac were analysed in synovial fluid by h.p.l.c. [^{125}I]-albumin was analysed using gamma counting.

3 The clearances (± s.d.) obtained for the solutes were [^{125}I]-albumin (0.0053 ± 0.0019 l h^{-1}), diclofenac (0.0096 ± 0.0061 l h^{-1}), salicylate (0.024 ± 0.022 l h^{-1}) and paracetamol (0.055 ± 0.041 l h^{-1}). The corresponding fractions unbound of these solutes in synovial fluid were 0.0, ≤ 0.01, 0.34 ± 0.09 and 0.85 ± 0.10, respectively.

4 Diffusion of unbound solute through the synovium is estimated to account for (± s.d.) 0.52 ± 0.08, 0.87 ± 0.06 and 0.99 ± 0.01 of the total clearance of diclofenac, salicylate and paracetamol from the joint space, respectively. The remaining proportion of clearance is accounted for by efflux of solute bound to albumin.

5 An expression for the ratio of synovial fluid to total plasma concentrations after systemic administration was developed to include both diffusion of unbound solute and albumin flux. Most solutes appear to satisfy the conditions in which this expression reduces to the limiting case where the unbound concentration of the solute is identical in the synovial fluid and plasma under steady state conditions.

Keywords synovial fluid kinetics albumin efflux bound drug transport

Introduction

The concentration of non-steroidal anti-inflammatory drugs (NSAIDs) in synovial fluid is considered to be an important determinant of clinical response [1]. The diffusion of unbound drugs between the blood and the synovial fluid appears to be the main mechanism by which significant NSAID concentrations are attained and maintained in the joint [1]. A major determinant of the steady state concentrations of a solute in the blood and synovial fluid is the relative protein binding of the NSAID in the plasma and synovial fluid. Most NSAIDs are highly bound to albumin [2]. The synovial fluid to plasma AUC ratio for total NSAID concentration is between 0.25 and 0.75 [1], consistent with synovial fluid/plasma concentration ratios of 0.3 to 0.7 for total proteins [3] and 0.54 to 0.8 for albumin [4].

Relatively little is known about other physiological processes involved in solute transfer into and out of joints. Wallis & Simkin [5] noted that 'the failure to recognise the importance of local volume and permeability in ... (the synovial fluid) ... has prevented determination of specific trans-synovial rate constants which alone can permit meaningful comparisons with different protein binding, solubility characteristics and molecular radii'. A number of studies have been reported on the clearance of various solutes from joints

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after intra-articular injection and include sodium [6, 7], iodine [8] and xenon [9]. Simkin & Pizzorno [10] injected a number of solutes together into healthy knees and reported that the synovial fluid to blood flux of small molecules is limited mainly by diffusion. Simkin & Nilson [11] reported that the synovial permeability of glucose was lower in rheumatoid patients than in normals, whereas the permeability of proteins was higher. Few studies have considered the role of lymphatic transport of NSAID bound to protein [12].

The present study was designed to provide preliminary information on the importance of efflux of protein bound drug for the clearance of NSAIDs from joints. An expression relating synovial fluid concentrations of solutes to their plasma concentrations incorporating albumin efflux was also developed and examined in relation to existing data on synovial fluid/plasma concentration ratios.

Methods

Five rheumatoid arthritis patients with knee joint effusions participated in the study. All subjects were drug free for at least 2 days prior to the study. There were four males and one female with a mean age of 44.4 ± 11.5 years. All subjects were examined clinically and provided specimens for laboratory screening. The study was approved by the Royal Hobart Hospital Ethics Committee and the patients gave written informed consent.

On the morning of the study, a blank sample of synovial fluid (2 ml) was removed from the knee and 0.1–0.2 ml of a sterile aqueous solution containing diclofenac, salicylate, paracetamol and [^{125}I]-albumin was injected. The volume injected was varied depending on an estimate of the effusion volume to yield a target concentration of approximately 20 μg ml^{-1} for diclofenac, salicylate and paracetamol and 108 counts ml^{-1} for [^{125}I]-albumin. Serial samples were withdrawn through a 23g butterfly needle for the first 90 min after which time the needle was changed. Two later samples were taken at approximately 12 and 24 h in each subject where possible. The average number of samples per subject was 9 ± 2, each of 0.5 to 1 ml. The low sample volume was chosen in order not to perturb the initial volume of effusion significantly. At the end of the study, the remaining effusion was aspirated.

The blank sample of synovial fluid was used to measure albumin concentration, white cell count, rheumatoid factor, pH, pCO_2, C_3 and C_4. These estimations were repeated 24 h later. The fraction of [^{125}I]- remaining was estimated by counting 200 μl synovial fluid aliquots in a gamma counter. A h.p.l.c. method was used to measure diclofenac, salicylate [13] and paracetamol [14]. The coefficients of variation for all solutes in the assay procedures were less than 5%. The fraction unbound in each sample was estimated by ultrafiltration of synovial fluid which had been spiked with radiolabelled solutes or using literature values. All data are reported as mean ± s.d.

Theory and data analysis

Figure 1 shows the kinetic model used in the analysis of data obtained from these studies. The terminal half-life ($t_{1/2,z}$) of each solute was defined as 0.693/k, where k is the terminal slope of the logarithm of the fraction remaining in the synovial capsule *vs* time. The area under the synovial concentration-time curve (AUC_s) was estimated using the linear trapezoidal rule and C_t/k where C_t is the concentration of the solute at the last sample time.

The synovial clearance of a given solute (CL_s) was calculated from dose/AUC_s. An estimate of the volume of distribution in the synovial space at steady state (V_{ss}) was given by CL_s/k.

The total flux of solute leaving the synovial fluid is defined by

(a) The permeability coefficient-surface area product (PS) for individual solutes across the synovium by diffusion,
(b) The solute removed by lymphatic transport of albumin as a drug-albumin complex with 1 mole of solute bound per mole of albumin (Figure 1) and
(c) Unbound solute removed by lymphatic transport assuming a clearance equal to that of albumin, CL_{alb}. If it is assumed that only unbound solute diffuses across the synovium, the total clearance of solute from a joint effusion CL_s is defined by:

$$\begin{array}{lcll} \text{total clearance} & = & \text{clearance of unbound drug} & + \text{ clearance of bound drug} \\ CL_s & = & fu_s\,(PS + CL_{alb}) & + (1 - fu_s)\,CL_{alb} \end{array} \quad (1)$$

where CL_s is the total clearance of solute from the joint, C_s is the total concentration of solute in the synovial fluid, fu is the fraction of solute unbound and CL_{alb} is the clearance of radiolabelled albumin from the joint. Thus, the total flux of solute from the effusion, Js, is given by:

$$Js = CL_s C_s = fu_s\,PS\,C_s + CL_{alb} C_s \quad (2)$$

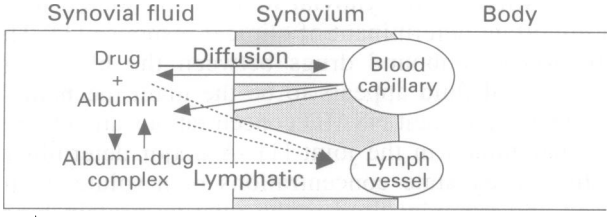

Figure 1 Pharmacokinetic model showing (1) transfer of drug between synovial fluid and the body by diffusion through the synovium into the blood perfusing the joint, (2) transfer of albumin and albumin-drug complex into the body via the lymphatic and circulatory systems and (3) transfer of unbound solute via the lymphatic system. The model is based on the injection of drug into the synovial fluid.

The PS product was estimated by rearranging equation (2)

$$PS = \frac{CL_s - CL_{alb}}{fu_s} \quad (3)$$

The fraction of the solute clearance due to the clearance of protein bound solute from the knee effusion (CLb_s) was defined as the ratio CLb_s/CL_s:

$$\frac{CLb_s}{CL_s} = \frac{(1 - fu_s)\, CL_{alb}}{CL_s} \quad (4)$$

We now consider the situation in which a drug is given systemically and the drug moves into and out of the synovium from the systemic circulation. The rate of change in the amount of solute in the synovial fluid (dA_s/dt) will be dependent on the clearance of bound solute by albumin influx clearance (CL^{in}_{alb}), efflux clearance from the joint (CL^{out}_{alb}) and on the permeability coefficient-surface area product (PS) for the influx/efflux of unbound solute:

$$\frac{dA_s}{dt} = CL^{in}_{alb}\, Cb_b + PSCu - CL^{out}_{alb}\,(Cb_s + Cu_s) - PSCu_s \quad (5)$$

where Cb_b and Cu are the concentrations of solute bound and unbound in the blood, respectively, and Cb_s and Cu_s are the concentrations of solute bound and unbound in synovial fluid. Expressing equation (5) in terms of total blood (C_b) and synovial fluid (C_s) concentrations and the fraction of solute unbound in the blood (fu_b) and synovial fluid (fu_s) yields

$$\frac{dA_s}{dt} = [CL^{in}_{alb}\,(1 - fu_b) + fu_b\, PS]\, Cb - [CL^{out}_{alb} + fu_s PS]\, C_s \quad (6)$$

Under steady state conditions $dA_s/dt = 0$ and equation (6) reduces to:

$$\frac{C_s}{C_b} = \frac{CL^{in}_{alb}\,(1 - fu_b) + fu_b PS}{CL^{out}_{alb} + fu_s PS} \quad (7)$$

An identical expression exists for the ratio of the area under the synovial fluid concentration-time profile (AUC_s) to that for the blood (AUC_b) after a single dose.

Two limiting cases follow from equation (7):

(1) If synovial membrane permeability is much greater than albumin efflux then $fu_b PS \gg CL^{in}_{alb}\,(1 - fu_b)$ and $fu_s PS \gg CL^{out}_{alb}$, and

$$\frac{C_s}{C_b} \simeq \frac{fu_b}{fu_s}$$

or since $Cu = fu_b C_b$ and $Cu_s = fu_s C_s$

$$Cu \simeq Cu_s \quad (8)$$

Equation (8) states that the steady state concentrations and AUC_s of unbound solute in the blood and synovial fluid are equal, and

(2) If the solutes are almost completely bound to albumin then fu_b, $fu_s \geq 0$ and

$$\frac{C_s}{C_b} \simeq \frac{CL^{in}_{alb}}{CL^{out}_{alb}} \quad (9)$$

Under steady state conditions, the flux of albumin from the blood into the synovial space (CL^{in}_{alb}, C^b_{alb}) is equal to the flux of albumin out of the synovial space (CL^{out}_{alb}, C^s_{alb}), where C^b_{alb} is the albumin concentration in the blood and C^s_{alb} is the albumin concentration in the synovial space. Accordingly, equation 9 can also be expressed as:

$$\frac{C_s}{C_b} \simeq \frac{C^s_{alb}}{C^b_{alb}} \quad (10)$$

Equation (10) states that the total steady state concentration and AUC ratio of solute in the synovial fluid and blood is equal to the ratio of albumin concentrations in these two fluids. It should also be noted that as $Cu = fu_b C_b$, $Cu_s = fu_s C_s$ and at low solute concentrations $KC^b_{alb} = (1 - fu)/fu$ and $K^s_{alb} = (1 - fu_s)/fu_s$ where K is the association constant of the solute for albumin [15]. Noting that fu, $fu_s \geq 0$ and substituting into equation 10 yields $Cu_s = Cu_b$. Thus, unbound concentrations of solute should be equal in the synovial fluid and blood, irrespective of the rate determining mechanisms for transport.

Results

Table 1 shows the biochemical data on synovial fluid collected from each subject. Each subject had a synovial fluid pH which was acidic relative to the normal plasma pH of 7.4. The lowest synovial fluid pHs were associated with high pCO_2s. Albumin concentrations ranged from 12 to 22 g l^{-1} and appeared unrelated to the concentrations of inflammatory mediators present.

Figure 2 shows the fraction remaining *vs* time profiles obtained for each of the solutes in the subjects studied. In all cases the rate of loss was paracetamol > salicylate > diclofenac > albumin. The presence of metabolites of the solutes was not indicated in any of the chromatograms.

The total clearance (CL_s) and terminal half-life ($t_{1/2}$) data obtained for each subject are shown in Table 2. The mean clearance of paracetamol was approximately twice that of salicylate, which in turn was about double the clearance of diclofenac. The mean diclofenac clearance was about twice that of albumin.

Table 2 also shows the volumes of distribution at steady state in the synovial space (V_{ss}) estimated for each subject. Similar volumes were estimated for each solute. The fraction of salicylate unbound in the synovial fluid of subjects at concentrations of 2 and

Table 1 Biochemical data for control synovial fluid collected from each subject

Subject	Age (years)	Sex	Albumin ($g\ l^{-1}$)	pH	pCO_2 (mm Hg)	pO_2 (mm Hg)	C_3 ($g\ l^{-1}$)	C_4 ($g\ l^{-1}$)	WCC[1] ($\times 10^9\ l^{-1}$)	RF[2]
1	29	F	22	7.32	38.6	88.8	—	—	6.4	—
2	27	M	20	7.37	37.8	50.3	—	—	18.5	–ve
3	53	M	12	7.01	80.2	54.7	<0.5	<0.1	35.9	1/64
4	69	M	13	7.29	49.2	20.7	0.6	0.13	4.4	1/160
5	44	M	21	6.82	96.3	8.8	0.7	0.14	29.4	1/320
Mean	44.4		17.6	7.16	60.4	44.7	—	—	18.9	—
s.d.	17.5		4.7	0.24	26.4	31.4	—	—	13.8	—

[1]White cell count; [2]rheumatoid factor.

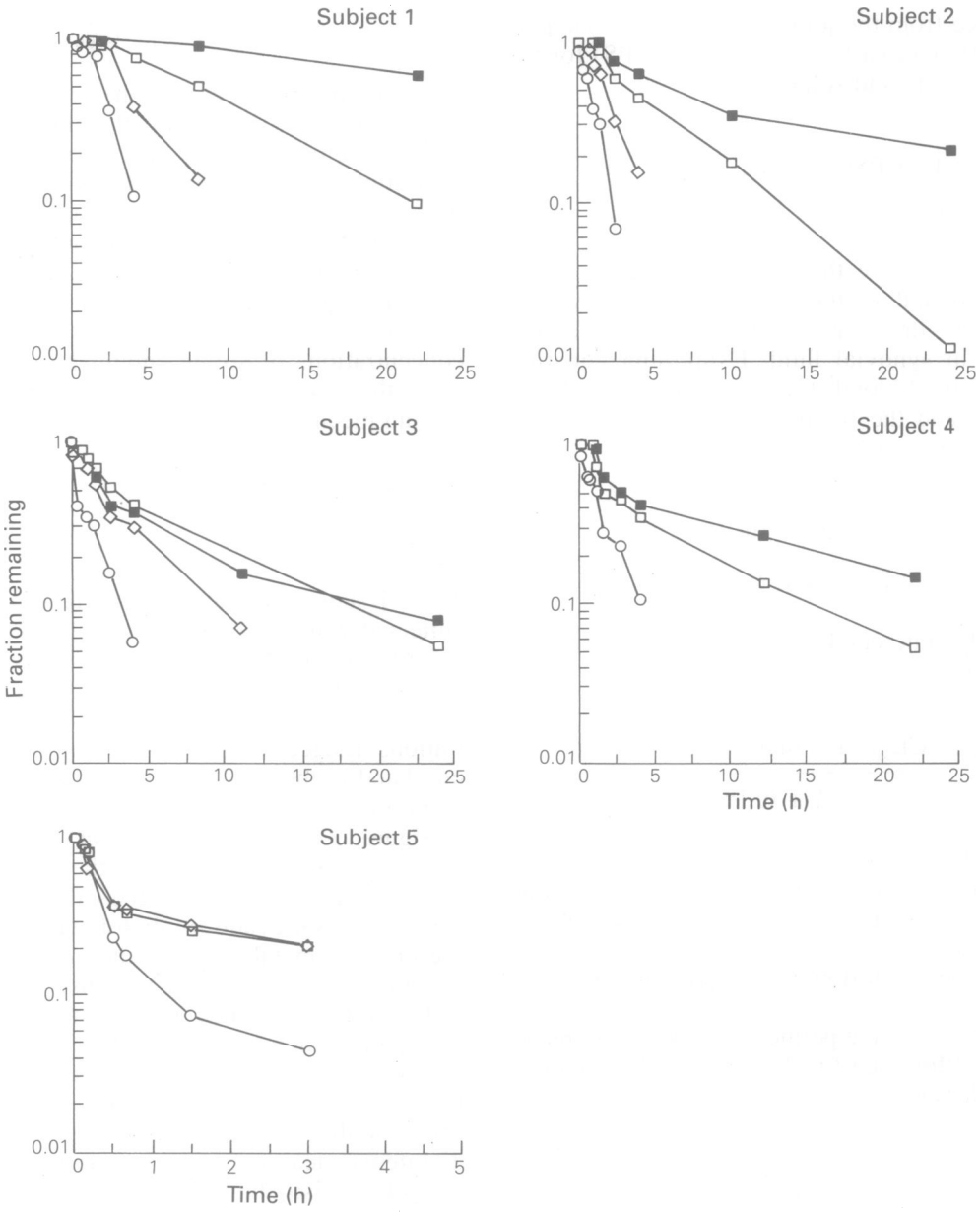

Figure 2 Fraction remaining *vs* time plots for paracetamol (○), salicylate (◇), diclofenac (□) and albumin (■) after injection of a mixture of all solutes into the knee effusions of the five subjects studied.

Table 2 Clearance (CL_S), volume of distribution in synovial space at steady state (V_{ss}) and terminal half-lives ($t_{1/2}$) based on synovial fluid drug concentrations observed after injection of a cocktail of [^{125}I]-albumin (A), diclofenac (D), salicylate (S) and paracetamol (P) into knee joint effusions

	CL_s (ml h^{-1})				V_{ss} (ml)				$t_{1/2}$ (h)			
Subject	*A*	*D*	*S*	*P*	*A*	*D*	*S*	*P*	*A*	*D*	*S*	*P*
1	—	5.1	5.4	19.8	—	33	21	31	—	4.5	2.8	1.1
2	7.6	20.2	5.5	12.5	149	151	175	162	13.6	5.2	2.2	0.9
3	4.9	9.0	—	42.9	80	72	—	86	11.4	5.6	—	1.4
4	3.9	7.9	22.8	44.6	79	43	46	38	14.1	3.8	1.4	0.6
5	3.2	5.9	12.9	40.4	61	57	59	64	13.3	6.7	3.2	1.1
Mean	4.9	9.6	11.7	32.0	92	71	75	76	13.1	5.2	2.4	1.1
s.d.	1.9	6.1	8.2	14.8	38	47	68	52	1.2	1.1	0.8	0.3

Table 3 Estimated PS products for individual solutes and the contribution to the efflux of bound solute to the total clearance from the synovial space

Subject	fu_s	CL_s (ml h^{-1})	CL_{alb} (ml h^{-1})	PS (ml h^{-1})	$\frac{CLb_s}{CL_s}$
Diclofenac					
1	—	20.2	7.6	—	0.38
2	—	7.9	3.7	—	0.47
3	—	5.9	3.2	—	0.54
4	—	9.0	4.9	—	0.54
5	—	5.0	—	—	—
Mean		9.6	4.9	—	0.48
s.d.		6.1	2.0	—	0.08
Salicylate					
1	0.40	55.2	7.6	119.0	0.08
2	0.33	22.8	3.7	57.9	0.11
3	0.19	12.9	3.2	51.1	0.20
4	0.42	—	4.9	—	—
5	0.36	5.0	—	—	—
Mean	0.34	24.0	4.9	76.0	0.13
s.d.	0.09	22.1	2.0	37.4	0.06
Paracetamol					
1	0.91	125.0	7.6	129.0	0.01
2	0.71	45.0	3.7	58.2	0.02
3	0.78	40.0	3.2	47.2	0.02
4	0.94	43.0	4.9	45.4	0.01
5	0.90	20.0	—	—	—
Mean	0.85	54.6	4.9	69.0	0.01_5
s.d.	0.10	40.6	2.0	40.6	0.00_6

16 mg ml^{-1} were (± s.d.) 0.29 ± 0.09 and 0.36 ± 0.09, respectively. The corresponding values for paracetamol were 0.80 ± 0.10 and 0.89 ± 0.11.

Table 3 shows the estimated PS product for each drug due to diffusion and the fraction of the total clearance due to efflux of bound solute from the synovial space. Almost all of the removal of paracetamol and salicylate could be accounted for by clearance of unbound solute from the synovial space. However, the analysis suggested that about half of the diclofenac is removed from the synovial space bound to albumin. Table 3 also shows that the PS products for salicylate and paracetamol were of a similar magnitude.

Discussion

Most studies on the pharmacokinetics of drugs in synovial fluid have been based on single or serial sampling of the knee effusion after oral administration of drug [1, 5]. The present work sought to assess drug efflux from the joint after intra-articular injection. Our approach was similar to that applied to normal human knee joints by Simkin & Pizzorno [10] and to human knee effusions [16]. Simkin and coworkers limited their work to the transport of solutes which are essentially not bound to proteins (sucrose, glucose, urate, creatinine, urea, benzyl alcohol and water). Our results confirm that binding of drugs to proteins in synovial fluid retards drug transport out of the joint space.

Paracetamol is poorly bound to synovial proteins (fu ± s.d.: 0.85 ± 0.10) and has a half-life (± s.d.) of 1.1 ± 0.3 h, whereas diclofenac has a half-life (± s.d.) of 5.2 ± 1.1 h (Table 2). The fraction of diclofenac unbound in synovial fluid was not measured in this study. Chan *et al.* [17] reported an unbound fraction of diclofenac in synovial fluid of 0.005 ± 0.002. Salicylate with a fraction unbound (± s.d.) of 0.34 ± 0.09 has a half-life of 2.4 ± 0.8 h, which is intermediate between those for paracetamol and diclofenac.

To estimate the permeability-surface area (PS) product for different solutes across the synovium, the contribution of the clearance of solutes bound to albumin in the synovial fluid to total clearance must be defined. In this work we have used the albumin clearance (CL_{alb}) from the synovial fluid and the fraction of solute bound to define the clearance of bound solutes, (1 − fu) CL_{alb} (Figure 1). The mean albumin clearance (± s.d.) observed (0.0053 ± 0.0019 l h^{-1}) was similar to that reported by Wallis *et al.* [19] for rheumatoid arthritic patients (0.0043 ± 0.0017 l h^{-1}). Wallis *et al.* [18] also reported that albumin clearance from the synovial effusions of osteo-arthritic patients was about half (0.0023 ± 0.0018 l h^{-1}) that in patients with rheumatoid arthritis. The lowest clearance possible for a highly bound diffusible solute from a synovial effusion is, therefore, defined by the albumin efflux.

In the absence of protein binding, the clearance of a solute is dependent solely on its permeability-

surface area (PS) product across the synovium. The present work indicates similar values for salicylate and paracetamol (Table 3). Both solutes are of comparable size (MW salicylate 138.1, MW paracetamol 151.2). However, salicylate (pKa 3.0) is almost completely ionised at the synovial pH observed in this study (Table 1) whereas paracetamol (pKa 9.2) is almost completely unionised. The similarity in PS products despite differences in ionisation is consistent with the synovial-plasma compartment barrier being porous rather than lipoidal.

Solutes have been represented as moving from the capillary bed through a fenestrated endothelium into the interstitial space between synovial lining cells and then into the joint space [16]. Consistent with a porous barrier, the rate constants for disappearance of other solutes is also similar, irrespective of charge [16]. The PS products obtained for salicylate and paracetamol (0.04–0.14 l h^{-1}) (Table 3) were similar to values (± s.d.) obtained for iodine in rheumatoid arthritic effusions (0.12 ± 0.018) h^{-1}) [18] and for small molecules in normal subjects (e.g. benzyl alcohol, 0.051 ± 0.004 l h^{-1}) [10]. Simkin & Nilsen [16] have reviewed the rate constants obtained after intra-articular injection of various isotopes. Rate constants for ^{24}Na, ^{131}I, ^{133}Ye, ^{99m}Tc- and ^{42}K appear to be generally between 0.01 and 0.1 min^{-1}. If an average synovial fluid volume (accessible by aspiration) of 33 ml is assumed [18], the approximate clearance of these solutes is 0.02 to 0.2 l h^{-1}. The clearance of methotrexate after intra-articular injection is 0.017 l h^{-1} [19].

The present analysis also suggests that albumin flux may contribute to the synovial fluid to systemic circulation clearance of highly bound solutes. Approximately 48% of diclofenac clearance from the knee may be due to clearance of the bound solute (Table 3). Solutes exhibiting either poor (paracetamol) or moderate (salicylate) protein binding are essentially removed by clearance of unbound solute from the synovial space, the contribution of albumin (bound) flux to overall clearance being relatively small (Table 3). Removal of bound solutes by albumin flux will limit the efflux half-time for any solute from the joint to that of albumin (approximately 13 h, Table 2). If a solute has a long elimination half-life in the body (such as oxicams), the terminal phase of the concentration-time plot of solute in the synovial fluid will reflect that half-life. The possible role of protein efflux from the synovial fluid on the distribution of ibuprofen enantiomers was considered by Day *et al.* [20]. Using data for the diffusion of labelled protein out of synovial fluid, they suggested that 10–20% of the total rate of movement of ibuprofen out of synovial fluid is due to the efflux of bound drug and, in some patients, this proportion may be higher.

A significant albumin efflux may also affect the ratio of solute concentrations in the synovial fluid and plasma after systemic administration of highly bound compounds (equation 7). When a solute is moderately bound, such as salicylate, the flux of bound solute is slow relative to the diffusion of unbound solute and makes little contribution to the synovial fluid-plasma clearance (Table 2). In these circumstances, steady-state unbound concentrations in the synovial fluid and plasma should be equal (equation 8), as demonstrated experimentally for salicylate [21]. Identical unbound concentrations for a solute in the plasma and synovial fluid should also be anticipated when the albumin concentration in the synovial space is at steady state (equation 10). The observed findings for flurbiprofen [22] and ketoprofen [23] are consistent with this expectation. All of the synovial fluid to plasma concentration ratios of either steady state concentrations or AUC values for total solute are reported to be less than 1 [1, 4].

We are aware of only one study where the AUC ratio for unbound solute between synovial fluid and plasma was found to be substantially different from unity. Kraml *et al.* [24] reported an AUC ratio of 1.72 for unbound etodolac and 0.67 for total etodolac. An unbound AUC ratio greater than 1 could indicate a contribution of bound solute flux to the observed concentrations in the synovial fluid (equation 10) but with one or more of the assumptions made in reducing equation 10 to equal unbound concentrations being violated. The total concentration ratio of 0.67 is similar to a concentration ratio of 0.56 predicted from equation 10 and albumin concentrations of 2.02 and 3.63 g dl^{-1} in synovial fluid and plasma [25]. Substituting a CL_{alb}^{out} of 5.3 ml h^{-1} (Table 3), fu of 0.0093, fu_s of 0.0247 [26] and a CL_{alb}^{in} of 0.0019 ml h^{-1}, a PS product of 0.02 l h^{-1} is estimated from equation 7. (The value of CL_{alb}^{in} is based on substituting albumin concentrations in synovial fluid and plasma [24] with CL_{alb}^{out} in the steady state approximation given for equation 10). The PS product estimate of 0.02 l h^{-1} is slightly lower than values obtained in this work (Table 3). Recently, Simkin and coworkers [25] proposed a model based on association-dissociation of NSAIDs to albumin to account for an apparent influx rate of solutes exceeding the expected input from passive diffusion and movement of albumin-bound drug. An enhanced influx rate of solute due to such a mechanism is a possible explanation for a synovial to plasma unbound concentration ratio greater than 1.

The extent to which the flux of bound solute will influence synovial fluid solute concentrations depends not only on the binding of the solute to albumin in the synovial fluid and plasma but also on the likely albumin flux. An increased flux is more likely in highly diseased arthritic joints with large effusions and poor mobility. Higher intra-articular pressures are observed in such joints for a given effusion volume owing to a reduced elasticity of the joint space [26]. In addition, the permeability of the rheumatoid knee to albumin is about six times that in control knees [27]. The rate of protein removal from synovial fluid is also faster in exercised joints [12]. Therefore, a slower clearance of albumin would be anticipated in those studies where a knee was kept immobile for serial synovial fluid sampling than in this work where the subjects were mobile after the initial sampling period. Finally, the synovial fluid/plasma albumin ratio in arthritic patients is also two-fold greater than that in normal subjects [27]. In accordance with equation 8, similar AUCs for unbound drug in the synovial fluid and plasma should be observed.

It is concluded that the efflux of solutes bound to albumin may contribute significantly to the clearance of highly protein bound drugs from the joints of rheumatoid arthritis patients. In practice, the conditions associated with most studies examining the transport of drugs from plasma into synovial fluid are such that, at steady state, the unbound concentrations of solute in the synovial fluid and plasma are likely to be equal. However, further studies are required to examine the role of albumin efflux on synovial clearance of drugs in more detail.

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