A Physiological Pharmacokinetic Model for Solute Disposition in Tissues Below a Topical Application Site

Michael S. Roberts[1,2] and Sheree E. Cross[1]

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Purpose. Many compounds are applied to the skin with the aim of targeting deeper underlying tissues. This work sought to define the pharmacokinetics of solutes in tissues below a topical application site in terms of perfusate binding, tissue binding and perfusate flow rate.
Methods. The disposition kinetics of diclofenac in a single pass perfused limb preparation after dermal application disposition was studied using dextran and bovine serum albumin (BSA) containing perfusates. A pharmacokinetic model was then developed to relate the tissue retention half lives for diclofenac, diazepam, water, lignocaine and salicylate to their fraction unbound in the tissues, their fraction unbound in the perfusate and the perfusate flow rate.
Results. Diclofenac had estimated tissue retention half lives of 18.1 hr and 3.5 hr for the dextran and BSA containing perfusates, respectively. The fraction of diclofenac and other solutes unbound in the tissues correlated with their corresponding fraction unbound in the perfusate. The tissue retention half lives for diclofenac and other solutes could be described in terms of the fraction of solute unbound in the tissues and perfusate, together with the flow rate.
Conclusion. The tissue pharmacokinetics of solutes below a topical application are a function of their binding in the tissues, binding in perfusate and local blood flow.

KEY WORDS: topical application; dermal absorption; cutaneous perfusion; pharmacokinetics; binding; half life.

INTRODUCTION

Drugs are frequently applied to the skin to relieve local pain and inflammation. We have shown that significant concentrations of drugs applied topically are found in dermis, subcutaneous tissue and muscle below the application site (1–9). The extent of direct penetration of most drugs appears to be limited to a depth of 3–5 mm. Deeper tissue concentrations are determined by recirculation from the systemic blood supply (1–7). Solute metabolism during transport through superficial tissues may also limit the amount of parent solute reaching deeper tissues (8–10). Deeper tissue penetration has also been observed for indomethacin (11,12), ibuprofen (13), piroxicam (14) and triethanolamine salicylate (15,16) after topical application, although significant concentrations of diclofenac have been reported in finger joint synovial fluid and tissue after topical administration (17). Radermacher *et al.* (18) suggested that the absorption of diclofenac applied topically to rheumatoid patient knees into the underlying synovial fluid occurred mainly via the systemic blood supply. The penetration of biphenyl acetic acid into knee joints after topical application also appears to be by the systemic blood supply (19). The discrepancies in these findings can be related to the pharmacokinetics of deep tissue penetration after topical application. Singh & Roberts (1–7) showed that, whereas the initial superficial tissue concentrations can be accounted for by direct penetration from the application site, deeper tissue concentrations and concentrations in superficial tissues at long times was mainly due to systemic blood supply recirculation.

Few studies have examined the interrelationship between the duration of local effects of topically applied drugs and the physicochemical properties of the drugs. Most studies have been limited to demonstrating that the epidermis can act as a reservoir for topically applied solutes such as amethocaine (20), iododeoxyuridine (21), benzoic acid (22) and hydrocortisone (23). We have used an in-situ perfused rat hindlimb model to show that perfusate protein binding and flow rate affect solute concentrations in tissues and rate of removal by the perfusate (24,25).

In the present study, we have attempted to characterise the retention of several solutes in the dermis, subcutaneous tissue, muscle and fat in terms of the physicochemical properties of the solutes and the perfusion conditions. Studies were carried out with the highly protein bound solute diclofenac was applied to the dermis of a single pass perfused limb and with perfusion conditions in perfusates containing dextran and bovine serum albumin (BSA) were used. Dermatomed skin was used in this study for a number of reasons (1–7). Firstly, it allows the lag time associated with transport across the stratum corneum barrier (10) to be avoided, desirable in using a single pass perfused limb which is viable for only a limited time (26). Secondly, the dermatomed skin model is independent of drug delivery release characteristics and the interaction of these systems and other formulations with the stratum corneum barrier (10). Finally, dermatomed skin allows the flux-time profiles obtained with drug delivery systems applied to excised epidermis *in vitro* to be combined with the underlying tissue pharmacokinetics by convolution, enabling the underlying tissue pharmacokinetics associated with any delivery system to be predicted (1–7). A pharmacokinetic model was then used to inter-relate the disposition kinetics of diclofenac and other solutes with their tissue binding, perfusate binding and flow rate.

METHODS

Absorption Studies

Single pass hindlimb perfusions using male Wistar rats (300 ± 25 g) were carried out as described in our previous

[1] Department of Medicine, University of Queensland, Princess Alexandra Hospital, Brisbane, Queensland 4102, Australia.
[2] To whom correspondence should be addressed. (e-mail: m.roberts@mailbox.uq.edu.au)

ABBREVIATIONS: BSA, bovine serum albumin; Cp, concentration in the perfusate; F_T, fraction remaining in tissues; fu_p, fraction of solute unbound in perfusate; fu_T, fraction of solute unbound in extravascular tissue; k_a, absorption rate constant; k_{el}, elimination rate constant; F_{eluted}, cumulative fraction of solute applied that is eluted in the perfusate; M_T, total amount of solute in the tissues; M_0, the initial amount; NSAIDs, nonsteroidal antiinflammtory drugs; p, probability; Q_p, perfusate flow rate; t, time; $t_{0.5el}$, half life for elimination from tissues; t_{peak}, time to reach peak concentration; V_D, apparent volume of distribution; V_v volume of the tissue vascular space; V_{TE}, volume of the extravascular tissue space; y_{obs}, observed dependent variable value.

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studies (24–27). Perfusates containing oxygenated Krebs buffer at pH 7.4 and either BSA or dextran were perfused at 4 ml/min. Glass diffusion cells (8 cm high, 1.8 cm internal diameter) were adhered to the posterior skin of the hindlimb after depilation with commercial Nair™ hair-removal cream and stratum corneum removal using a dermatome. Solutions (2 ml) containing 1.5 μCi of 14C-diclofenac (donated by Ciba-Geigy, Sydney, Australia) in phosphate buffered saline (pH 7.4) were then introduced into the cells. Samples (10 μl) being taken from the cell at 15 min intervals for a total absorption study period of 90 min.

Perfusate Studies

Outflowing perfusate samples (200 μl), collected at 5 min intervals, were added to Emulsifier safe scintillation cocktail and analysed by liquid scintillation counting (24,25). The cumulative amount of the solute eluted in the perfusate at various times t was calculated from the product of perfusate flow rate and the cumulative area under the curve of perfusate concentrations at different times using the trapezoidal rule (24,25). This amount was divided by the initial applied amount to estimate the fraction of the applied dose in the outflow. The amount of solute in the tissues at any time was estimated as the difference between the amount of solute lost from the absorption cell and that eluted from the limb at that time. The fraction of the absorbed amount remaining in the tissues was then determined as the ratio of this amount to that lost from the diffusion cells.

Tissue Concentrations

Diclofenac concentrations in tissues underlying the dermal application site, and in equivalent contralateral tissues, were measured at the end of each perfusion as described previously (25). Concentrations in each tissue sample were expressed as a fraction of the initial amount applied.

Perfusate Binding

The fraction of diclofenac unbound in 4% BSA-Krebs buffer (pH 7.4) and 2.5% dextran-Krebs buffer (pH 7.4) were determined using equilibrium dialysis (Spectra/Por® molecular porous membrane; Spectrum Medical Industries, LA) against Krebs buffer saline(pH 7.4) at 37°C (25).

Pharmacokinetic Model

The pharmacokinetic model developed in this analysis an extension of the model described previously (24,25). We assume that the change in the amount of solute in the tissue compartment (dM_T/dt) can be expressed in terms of exponential absorption kinetics from the dermal solution at a rate constant k_a and by clearance from the tissue by the perfusate:

$$\frac{dM_T}{dt} = k_a M_o \exp(-k_a t) - Q_p C_p \qquad (1)$$

where M_o is the initial amount in the applied solution, Q_p is the perfusate flow rate in the tissue and C_p is the concentration of solute in the perfusate in the tissue. Recognising that M_T can be related to C_p by its apparent volume of distribution V_D (i.e., $M_T = V_D C_p$), $Q_p C_p$ can be re-expressed as $Q_p M_T/V_D$ or as $k_{el} M_T$, where k_{el} is the elimination rate constant ($= Q_p/V_D$). Substituting into equation (1) and integrating yields the usual one compartment model equation:

$$M_T = \frac{k_a M_o}{(k_a - k_{el})} [\exp(-k_{el} t) - \exp(-k_a t)] \qquad (2)$$

The corresponding cumulative fraction eluted, F_{eluted}, defined by $\int_0^t Q_p C_p \, dt/M_o$, is:

$$F_{eluted} = 1 + \frac{1}{(k_{el} - k_a)} [k_a \exp(-k_{el} t) - k_{el} \exp(-k_a t)] \qquad (3)$$

We now consider the physicochemical determinants of k_{el}. When the unbound concentrations of solute in the extravascular tissue and tissue vascular space are assumed to be in equilibrium, the solute volume of distribution in the tissues V_D can be expressed in terms of the unbound fractions of solute in the perfusate fu_p and extravascular tissue fu_T and the volume of the tissue vascular space V_p and volume of the extravascular tissue space V_{TE} in a manner analogous to that described by Rowland & Tozer (28) for the whole body:

$$V_D = V_p + \frac{fu_p}{fu_T} V_{TE} \qquad (4)$$

Since $k_{el} = Q_p/V_D$, k_{el} can now be expressed in terms of perfusate flow rate (Q_p), perfusate protein binding (fu_p), tissue protein binding (fu_T).

$$k_{el} = \frac{Q_p}{V_D} = \frac{Q_p}{V_p + \frac{fu_p}{fu_T} V_{TE}} = \frac{Q_p}{\left[\frac{V_p}{V_{TE}} + \frac{fu_p}{fu_T}\right] V_{TE}} \qquad (5)$$

Of practical interest is the fraction remaining in the tissue F_T at a given time t after absorption has ceased ($F_T = \exp[-k_{el} \cdot t]$) and the tissue retention half life, $t_{0.5el}$ ($=0.693/k_{el}$). When $fu_p/fu_T > V_p/V_{TE}$, F_T and $t_{0.5el}$ can be defined as:

$$\ln F_T \approx -\frac{fu_T Q_p}{fu_p V_{TE}} t \qquad (6)$$

and

$$t_{0.5el} = \frac{0.693 V_D}{Q_p} \approx \frac{0.693 fu_p V_{TE}}{fu_T Q_p} \qquad (7)$$

Hence, the retention of solutes in tissues after topical application is dependent on the relative magnitude of binding in blood fu_p and tissue binding fu_T as well as on the tissue blood flow Q_p.

Statistical and Nonlinear Regression Analysis

Data were compared using a one way or two way ANOVA, with significance taken at $P < 0.05$, and differences between groups identified with the Tukey test. Estimates for k_a were obtained by nonlinear regression of the fraction of solute remaining in solution versus time assuming a monoexponential decline with a weighting of $1/y_{obs}$ (24,25). Parameter estimates for k_{el} were obtained by nonlinear regression of the cumulative fraction eluted against time (equation (3)) with the computer program MINIM (25) on a Macintosh IIsi using a fixed parameter estimate for k_a and a weighting of $1/y_{obs}$.

Pharmacokinetic Analysis

Equations 2–7 were used in this analysis. The perfused limb vascular space and water distribution volumes of 1.48 ml and 9.24 ml, respectively, for the perfusate flow of 4 ml/min (26) was used to estimate the V_p/V_{TE} ratio of 0.19 (= 1.48/[9.24 − 1.48]) in this analysis. In addition, as no significant binding was found for diclofenac in the dextran perfusate, an assumption was made that the fu_p for all solutes in the dextran perfusate was unity. The estimated Q_p/V_{TE} of 0.06 for the underlying tissues was deduced from the k_{el} for ^3H water after topical application using the dextran perfusate, the V_p/V_{TE} ratio and assuming $fu_p = fu_T = 1$ using equation (5). Estimates for fu_T of the other solutes could then be made by substituting the k_{el} values for the solutes from dextran containing perfusate studies ($fu_p = 1$) and the deduced values for Q_p/V_{TE}, V_p/V_{TE} into equation (5). The validity of the model was then examined in terms of its ability to predict k_{el} for studies using BSA perfusate by using the determined values of fu_p into equation (5). The times to reach peak concentration t_{peak} were calculated using k_a and k_{el} (24,25).

RESULTS

Diclofenac

The fraction of diclofenac remaining in solution after application to the dermatomed skin for the dextran and BSA containing perfusates are shown in Fig. 1A. It is apparent that greater loss has occurred for the BSA perfusate but the differences in the extent of loss from aqueous solution into the dermis for the two perfusates are similar. Also shown in Fig. 1A are the regression lines for an exponential decline in fraction remaining. Fig. 1B shows the cumulative outflow profiles of diclofenac in perfusate after a single pass perfusion of the rat hindlimb and application to dermatomed skin. It is readily apparent that the fraction of the applied diclofenac recovered in the dextran containing perfusate is small and only 4% that eluted for the perfusate containing BSA. The low recovery is consistent with the differences in the fractions of diclofenac found to be unbound in dextran containing perfusate (fu_p = 1.04 ± 0.012) and in BSA containing perfusate (fu_p = 0.025 ± 0.007). It is therefore apparent that the BSA containing perfusate acts as a partitioning medium to facilitate diclofenac removal from the tissues. Consistent with the differences in the recovery of diclofenac in the tissues, the fractions of the absorbed dose of diclofenac present in the tissues at the end of the 90 min perfusion for the dextran and BSA containing perfusates were 0.99 ± 0.00 and 0.88 ± 0.02 (mean ± s.e.; n = 3).

The individual tissue concentrations of diclofenac (expressed as a fraction of applied concentration and normalised to per g of tissue) below the treated site and at a contralateral site following 90 min. of perfusion are shown in Fig. 2. It is apparent that the concentrations of diclofenac are substantially higher in all tissues following perfusion with dextran containing perfusate than in BSA containing perfusate. In contrast, the concentrations of diclofenac in the contralateral tissues appear to be higher for the BSA containing perfusate than for the dextran containing perfusate. These results are consistent with BSA acting as a medium to transport diclofenac, not only out of the tissues underlying the application site, but to other tissues subsequently being reached by perfusate draining from the tissues underlying the site.

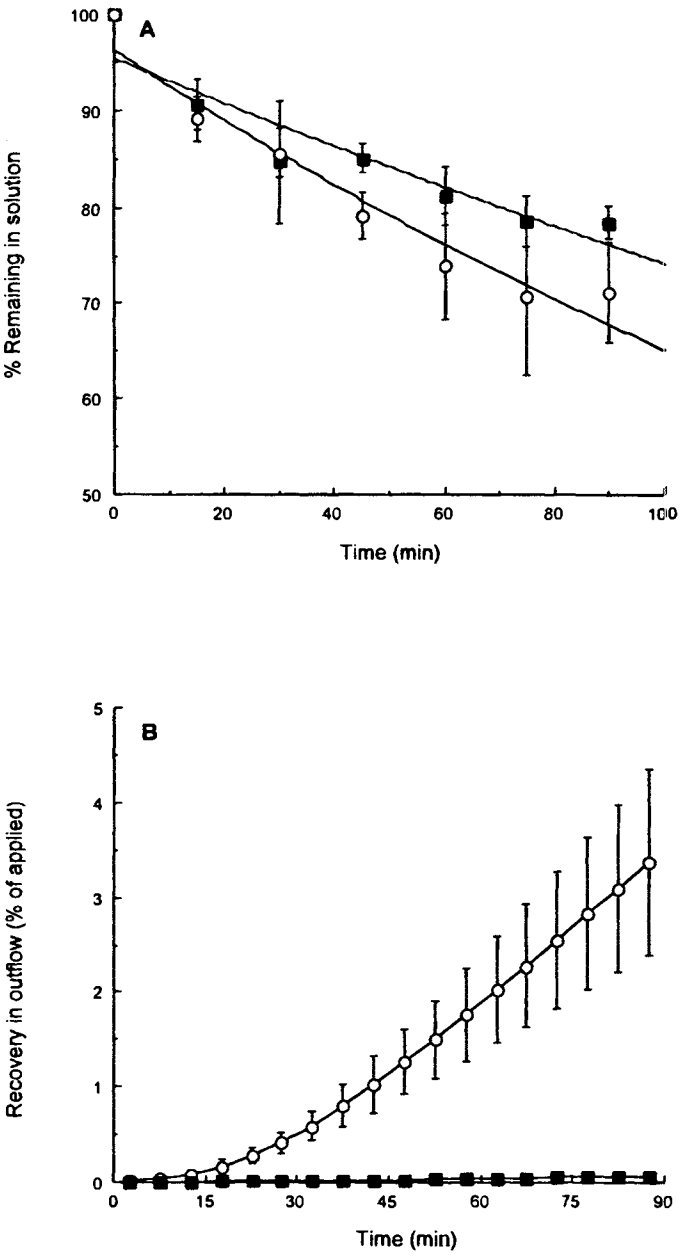


Fig. 1. A: Fraction of diclofenac remaining in solution compartment after application to dermatomed skin for 4% BSA (○) and for 2.5% dextran (■) containing perfusates at 4 ml/min. B: Cumulative fraction of diclofenac recovered in the perfusate for 4% BSA (○) and for 2.5% dextran (■). Mean ± S.E., n = 3.

The pharmacokinetic parameters deduced for diclofenac from the diclofenac disappearance from the dermal cells and recovery of diclofenac in the eluting perfusate are shown in Table I. It is apparent that although the k_a values associated with the two perfusates are of a similar order of magnitude, all other determined parameters differ substantially. In particular, k_{el}, $t_{0.5el}$ and t_{peak} differ by approximately 20 fold for the two perfusates. It is thus apparent that whilst perfusate binding

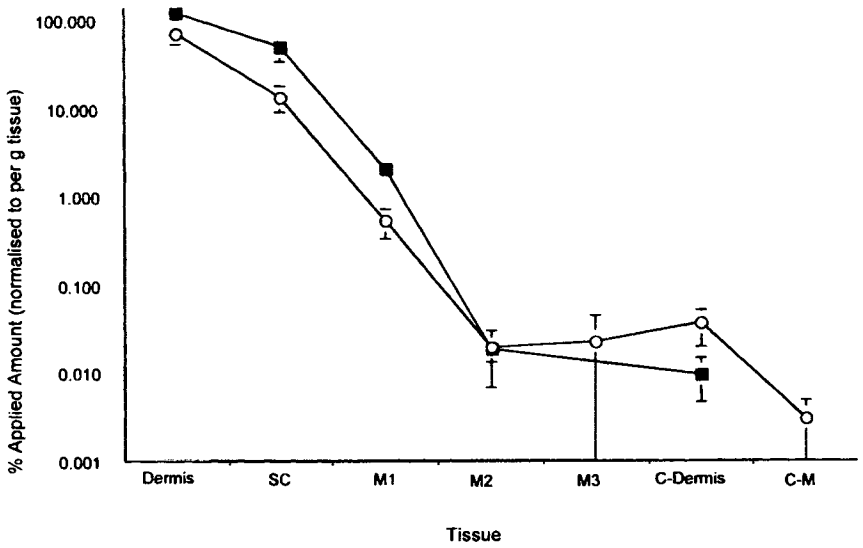


Fig. 2. Observed diclofenac concentrations in tissue samples after 90 min perfusion, expressed as a fraction of the initial amount applied with (○) 4% BSA and (■) 2.5% dextran containing perfusates at 4 ml/min. D = dermis, SC = subcutaneous tissue, M1 = superficial muscle, M2 = muscle, M3 = deep muscle, C-Dermis = contralateral Dermis (underneath the limb) and C-M = contralateral muscle. Mean ± S.E., n = 3.

has marked effects on the clearance of solutes from tissues underlying a dermal absorption site, the absorption from a solution into the dermis is relatively unaffected by the perfusate composition.

Solute Physicochemical Properties and Tissue Pharmacokinetics

Table II shows the observed and predicted elimination rate constants (k_{el}) for diclofenac and other solutes from hindlimb tissues after dermal application. Also included in Table II is the fractions of the solute unbound in the perfusates (fu_p) and in the tissues (fu_T). It is apparent that the observed k_{el} for dextran containing perfusates decreases with a decreasing fu_T. It is also apparent that the k_{el} values for BSA containing perfusates differ most markedly from k_{el} values for dextran containing perfusate for the more highly bound solutes. The k_{el} values are apparent for ^3H water are similar for the two perfusate compositions. The predicted k_{el} values for the perfusate containing BSA obtained from fu_T, fu_p and k_{el} are of the same order of magnitude, although the predicted values are slightly higher than the observed k_{el} values for the BSA containing perfusate (Table II). Figure 3A shows there is a strong correlation between fu_T and fu_p (r^2 = 0.96), although the data set is limited.

The lowest value of fu_p/fu_T estimated in this work is more than 4 times the value of V_p/V_{TE} (=0.19) suggesting that the approximations described by equations (6) and (7) should be applicable. Figure 3B shows that logarithm of the fraction of solute retained in the tissues at 90 min appears to be linearly related the ratio of fu_p to fu_T (r^2 = 0.88). A linear relationship was also found between $t_{0.5el}$ and fu_p/fu_T (r^2 = 0.99) (Fig. 3C).

Table I. Summary of Absorption and Elution Data for Diclofenac

Pharmacokinetic parameter	Perfusate condition	Observed value[b]
k_a (min^{-1})	BSA (4 ml/min)	0.0043 ± 0.0008
	Dextran (4 ml/min)	0.0028 ± 0.0002
Total in Perfusate[a]	BSA (4 ml/min)	6.76 ± 1.73
	Dextran (4 ml/min)	0.14 ± 0.04
k_{el} (min^{-1})	BSA (4 ml/min)	0.0033 ± 0.012
	Dextran (4 ml/min)	0.00016 ± 0.00005
$t_{1/2}$ elimination (min)	BSA (4 ml/min)	210
	Dextran (4 ml/min)	4331
t_{peak} (min)	BSA (4 ml/min)	264.7
	Dextran (4 ml/min)	1084.2

Note: k_a-absorption rate constant.
[a] Percentage of applied dose; k_{el}-elimination rate constant.
[b] Mean ± S.E., n = 3.

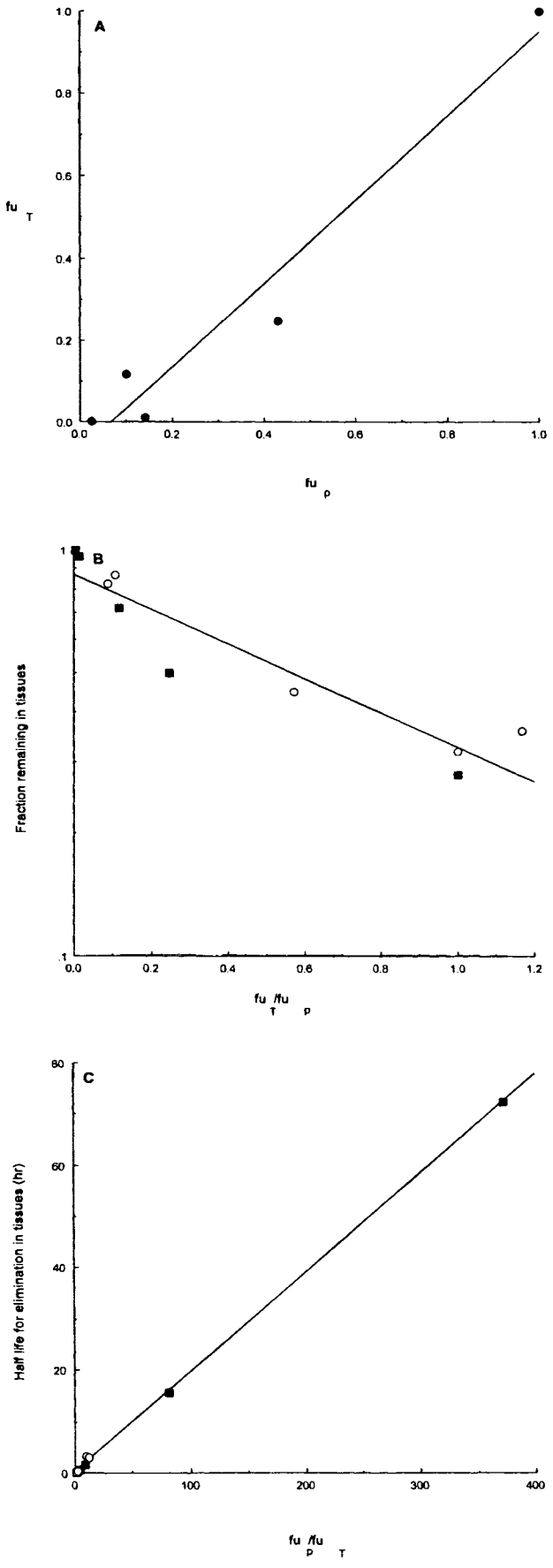
DISCUSSION

The retention of solutes in tissues below a topical application site is of potential clinical importance. A prolonged retention may be of particular value in conditions in which a long

Table II. Experimentally Determined Values for k_{el} and fu_p for BSA and Dextran Containing Perfusates and Predicted Values for fu_T and k_{el} for BSA Containing Perfusate

Solute	fu_p dextran	fu_p BSA	fu_T	k_{el} dextran (min^{-1}) (observed)	k_{el} BSA (min^{-1}) (observed)	k_{el} BSA (min^{-1}) (predicted)[a]
Water	1	1	1	0.050	0.036	0.05
Salicylate	1	0.1	0.12	0.0068	0.028	0.068
Lignocaine	1	0.43	0.25	0.014	0.022	0.027
Diazepam	1	0.14	0.012	0.00073	0.0036	0.0053
Diclofenac	1	0.025	0.0027	0.00016	0.0033	0.0060

[a] Based on equation (5), fu_p for BSA and fu_T (see text for details).



duration of action may be desired. Possible examples include the management of morning stiffness in joints and amelioration of pain in sporting injuries where the potential dislodgment of a topical delivery system, be it a patch or semisolid dosage form, can occur during sleep or strenuous physical activity. This work suggests that such retention is most likely for the more highly bound solutes.

Absorption and Clearance Kinetics for Diclofenac

A relatively simple first order absorption into a single compartment disposition model has been shown to adequately describe the absorption of diclofenac from solutions applied to dermatomed skin (Fig. 1A) and the elution of the diclofenac in the perfusate (Fig. 1B). We have shown that this model also adequately described the absorption of a range of solutes applied to dermatomed skin (24,25). Consistent with our earlier work, the dermal absorption of diclofenac was not greatly affected by the large difference between the two perfusates in the binding of diclofenac (BSA, $fu_p = 0.025$; dextran, $fu_p = 1.0$). Perfusate conditions can affect the transport of solutes across membranes when the receptor medium does not provide sink conditions. The slightly higher rate of loss of diclofenac from solutions for the BSA perfusate could be interpreted in terms of an inadequate receptor phase "sink conditions" when the dextran containing perfusate is used. We have previously shown that removal of solutes by blood perfusing dermal tissues is more important than diffusion to deeper tissues in determining the absorption of solutes from aqueous solutions into dermatomed skin (1–7). We have also shown that both the *in vivo* and *in vitro* absorption of a range of solutes into the dermis from aqueous solutions is independent of solute octanol-water partition coefficients and protein binding (7). A k_a independent of solute lipophilicity is consistent with the partitioning of a solute from an aqueous solution into the dermis, with matrix of loose connective tissue and a water content of 60–70%.

The present dermatomed model was used to allow prediction of underlying tissue solute quantities from various drug delivery systems and formulations using mathematical convolution of the mathematical function describing the solute kinetics defined by the delivery system with the one compartment disposition function described in this work (1–7). The delivery of a solute from a drug delivery system is complicated by its transport kinetics in the stratum corneum and epidermis (10). The absorption kinetics of drugs under such circumstances can be modelled by convoluting the observed flux of the drugs through epidermal membranes *in vitro* with the disposition kinetics obtained in the skin from an aqueous solution applied to dermatomed skin (1–3).

A relatively simple one compartment model has been used to represent the underlying tissues in this work. We and other workers have used multi-compartmental models to represent

Fig. 3. (A) Relationship between fu_T and fu_p for BSA containing perfusate for water, salicylate, lidocaine, diazepam and diclofenac. (B) Fraction of solute remaining in tissues at 90 min after absorption and fu_T/fu_p for (○) 4% BSA and (■) 2.5% dextran containing perfusates at 4 ml/min. C: Solute half lives in tissues underlying a topical absorption site ($t_{0.5el}$) for (○) 4% BSA and (■) 2.5% dextran containing perfusates at 4 ml/min and fu_p/fu_T.

individual tissues (1–7). The present model is effectively a lumping of the tissues involved in the disposition process after topical application. Other physiologically based pharmacokinetic models applied to the perfused hindlimb (26,27) add an unnecessary complexity given the long time frame of interest. However, as the diclofenac concentrations in the tissues are not uniform after application (Fig. 2), the simple one compartment model is unsuitable for than as a simple pharmacokinetic model. The biexponential equation derived from the model (Eq. 3) appeared to adequately describe the absorption (Fig. 1A) and elution of diclofenac (Fig. 1B) and other solutes (24,25) from the perfused hindlimb after topical application to dermatomed skin.

Pharmacokinetic Determinants of Solute Retention in Underlying Tissues

The important outcome of this paper is the definition of k_{el}, $t_{0.5el}$ and F_T in terms of the underlying pharmacokinetic determinants of fu_T, fu_p, V_{TE} and Q_p. A good correspondence between the observed and deduced k_{el} for solutes eluted using a BSA containing perfusate was found (Table II). It is therefore suggested that the pharmacokinetic model proposed is adequate, not only in describing the data obtained in this work, but also in predicting the effects of other perfusate compositions on underlying tissue pharmacokinetics. Further, the approximations of the model enable the fraction of solute remaining in the underlying tissues at a given time to be directly related to fu_T/fu_p (Fig. 3B) and the retention half life of solutes in the tissues to be related to fu_p/fu_T (Fig. 3C). Of importance in applying the present model to the clinical situation is the observation that the fu_p values for salicylate, lidocaine, diazepam and diclofenac in BSA containing perfusates (Table II) are similar to the fu_p reported for these solutes in human plasma. The values for fu_p in human plasma are: salicylate 0.1–0.2, lidocaine 0.5, diazepam 0.02 and diclofenac <0.01 (29).

These relationships between k_{el}, $t_{0.5el}$ and F_T and fu_T, fu_p, V_{TE} and Q_p are also relevant to the washout of cytotoxics from isolated organ perfusions after treatment of diseases such as recurrent melanoma and sarcoma. Wu *et al.* (30) recently showed that washouts with a 4.7% albumin containing perfusate (fu_p = 0.52) enhanced the removal of melphalan from perfused limbs compared to washouts using 2.8% dextran containing perfusate (fu_p = 0.87) (30).

Whilst this work has focussed on fu_T and fu_p as determinants of k_{el}, F_T and $t_{0.5el}$, we have shown previously that the k_{el} is increased by more than 2 fold by doubling flow (24). This change is consistent with the model prediction that k_{el} is directly related to the local tissue flow Q_p (Eq. (5)). The more than 2 fold change for water may be related to the increase in vascular volume and vessel recruitment associated with an increased flow rate in an isolated perfused hindlimb preparation (26). The higher concentrations of water, lignocaine and salicylate in deeper tissues after application of solutes to dermatomed skin and the co-administration of vasoconstrictors (15) is consistent with a higher F_T when Q_p is reduced. We have also previously used multiple indicator dilution and wet-dry weight ratios to show V_{TE} may be affected by the oncotic pressure of the perfusing medium (26,27).

The apparent higher concentrations of diclofenac in contralateral tissues for BSA containing perfusate relative to dextran containing perfusate suggests that in this single pass preparation the blood supply perfuses tissues subsequent to the tissues underlying the application site. McNeil *et al.*(14) have previously suggested a convective process in which the local blood supply carries solute to deeper tissues.

CONCLUSIONS

In conclusion, the elimination of solutes from tissues below a dermal absorption site can be related to the perfusion flow rate and fraction of solute unbound in the perfusate and in the tissues. Prolonged retention is to be anticipated for solutes highly bound in tissues underlying a topical absorption site.

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