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A Two-compartment Dispersion Model Describes the Hepatic Outflow Profile of Diclofenac in the Presence of its Binding Protein

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Abstract—The residence-time distribution (RTD) of diclofenac in the rat single-pass isolated perfused in-situ liver (n = 4) was determined after bolus input into the hepatic portal vein. Addition of human serum albumin (5 g L^{-1}) ensured extensive (>98%) binding of diclofenac within the perfusate. The one-compartment form of the axial dispersion model of hepatic elimination, which assumes instantaneous radial distribution of substrate within the accessible spaces of the liver, failed to describe adequately the RTD of diclofenac. In contrast, the two-compartment form of this model, which assumes that the radial transfer of unbound substrate between the vascular and cellular space is non-instantaneous, provided an excellent description of the diclofenac data. Moreover, the mean (±s.d.) value for the hepatic dispersion number (D_N) for diclofenac (0·354 ± 0·076) compared well with that determined for simultaneously injected [^{125}I]human serum albumin (0·456 ± 0·078) using the one-compartment dispersion model. These estimates of D_N, a stochastic parameter which characterizes the axial spreading of individual elements during transit through the liver, were similar in magnitude to those reported for other tracers in the rat perfused liver. The findings suggest that common factors influenced the RTD of diclofenac and its binding protein, and indicate that the two-compartment dispersion model may be a valuable tool for interpreting hepatic impulse-response data for solutes whose hepatic distribution and elimination is influenced by membrane permeability.

Factors known to influence the behaviour of an eliminated solute in the liver include organ blood flow, hepatocellular activity, the local architecture of the hepatic microvasculature, the ability of the solute to permeate the hepatocyte membrane and the extent to which it binds to vascular and cellular components (Roberts et al 1988). When a unit impulse (bolus) of solute is injected into the rat single-pass isolated perfused liver, the observed elution profile, referred to as a residence-time distribution (RTD), provides a global index of hepatic events and, with the aid of a suitable model, can provide valuable insight into the relationships among the various influential factors mentioned above (Goresky 1983; Roberts et al 1988).

Physiological models which have been used to interpret organ impulse-response data include the distributed model of Goresky and coworkers (Wolkoff et al 1979; Goresky 1983; Tsao et al 1986; Miyauchi et al 1987; Schwab et al 1990), and one- and two-compartment forms of the axial dispersion model (Roberts & Rowland 1986a; Roberts et al 1988, 1990; Yano et al 1989a, 1990). Because the liver is an organ of appreciable anatomical and functional heterogeneity (Gumucio 1983), these models are stochastic in nature. In the axial dispersion model, the heterogeneity of the hepatic microvasculature, which arises from factors such as intermixing of blood elements and variations in sinusoidal path lengths and flow velocities, is characterized by a dimensionless parameter (the dispersion number, D_N). The steady-state form of the axial dispersion model has also been extended to incorporate enzyme heterogeneity (Bass et al 1987).

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Although the dispersion model has been successfully used to describe the RTD of non-eliminated tracers such as radiolabelled erythrocytes, human serum albumin and water (Roberts et al 1988), it has not been extensively applied to substances for which membrane permeability, plasma (perfusate) and cellular protein binding and hepatic extraction may influence the shape of the RTD. The primary objective of this communication, therefore, is to describe the application of the axial dispersion model to the hepatic RTD of an extractable solute (diclofenac) under conditions of extensive binding within the perfusate.

Theory

Defining the model equations

Assuming linear conditions, the outflow profile of a substance injected into a rat single-pass isolated perfused liver, $y(t)_{+L}$, is determined by the amount of substance injected (D); the perfusate flow rate (Q); the function which describes the form of the input, x(t); and the weighting functions of the hepatic (liver) and non-hepatic (injector, tubing, cannulas and collection apparatus) regions of the experimental system, denoted $w(t)_H$ and $w(t)_{NH}$, respectively, according to the equation

$$y(t)_{+L} = \left[\frac{D}{Q}\right] \cdot x(t) * w(t)_H * w(t)_{NH} \quad (1)$$

Outflow profile | Input function | System weighting functions

where * denotes the convolution integral. If the outflow data are expressed as frequency output (the fraction of the dose eluting per unit time, f(t)) vs time, equation 1 becomes

$$f(t)_{+L} = x(t) * w(t)_H * w(t)_{NH} \quad (2)$$

On taking Laplace transforms, equation 2 becomes one of simple multiplication

$$f(s)_{+L} = x(s) \cdot w(s)_H \cdot w(s)_{NH} \quad (3)$$

where s is the Laplace operator. For an experimental system which does not include a liver (when the inflow and outflow cannulas are connected), the Laplace-transform of the frequency output vs time profile, $f(s)_{-L}$, is given by

$$f(s)_{-L} = x(s) \cdot w(s)_{NH} \quad (4)$$

When the input takes the form of a unit impulse (bolus), the input function, x(s), is equal to unity, and equations 3 and 4 can be simplified accordingly. Hence, the RTD of a substance in the perfused liver preparation can be defined in terms of the transfer functions for the hepatic and non-hepatic systems, as defined below.

The transfer function for the liver, $w(s)_H$, was defined using the axial dispersion model (Roberts & Rowland 1986a; Roberts et al 1988; Yano et al 1989a). This model is described by a second-order partial differential equation, and therefore can only be solved after boundary conditions have been specified. In the present work, the physiologically compatible and mathematically convenient 'mixed' or 'type 1' boundary conditions were assumed (Roberts et al 1988; Yano et al 1989a).

When the radial transfer of substance between the hepatic spaces into which it distributes is instantaneous (i.e. the liver behaves as a single compartment and distribution is flow-limited) the transfer function for the dispersion model is (Roberts & Rowland 1986a; Yano et al 1989a)

$$w(s)_H = \exp\left[\frac{1 - \left[1 + \frac{4D_N}{Q}\left[V_H \cdot s + \rho.fu.CL_{int}\right]\right]^{0.5}}{2D_N}\right] \quad (5)$$

where D_N is the hepatic dispersion number (the magnitude of which is determined by the degree of axial dispersion within the liver), Q is the blood (or perfusate) flow rate, V_H is the apparent hepatic volume into which the substrate distributes, fu is the unbound fraction of solute in blood (perfusate), CL_{int} is the intrinsic metabolic clearance of substrate and ρ is the effective partition coefficient for unbound species, given by

$$\rho = \frac{P}{P + CL_{int}} \quad (5a)$$

where P is the membrane permeability of unbound substrate. For a non-eliminated substance ($CL_{int} = 0$) such as human serum albumin (HSA), equation 5 can be simplified to

$$w(s)_H = \exp\left[\frac{1 - \left[1 + \frac{4D_N \cdot V_H \cdot s}{Q}\right]^{0.5}}{2D_N}\right] \quad (6)$$

When the radial transfer of solute between the central (vascular) compartment and the peripheral (cellular) compartment is non-instantaneous, the liver behaves as a two-compartment system, and the distribution of the solute is said to be barrier-limited (Goresky 1983). The transfer function describing the two-compartment dispersion model, under mixed-boundary conditions with elimination from the peripheral compartment, is (Roberts et al 1988; Yano et al 1989a)

$$w(s)_H = \exp\left[\frac{1 - \left[1 + \frac{4D_N.V_B}{Q}\left[k_{12} + s - \frac{k_{12} \cdot k_{21}}{s + k_{21} + k_{el}}\right]\right]^{0.5}}{2D_N}\right] \quad (7)$$

where V_B is the volume of the central compartment into which the substrate spontaneously distributes radially (assumed in the present case to be the combined volume of the blood space and the space of Disse), k_{12} and k_{21} are the influx and efflux first-order rate constants, respectively, and k_{el} is the first-order rate constant for irreversible metabolism from the peripheral compartment.

When a tracer was injected into the non-hepatic system (injector, tubing, cannulas and collection apparatus) used in the present investigations, the outflow appeared as a delayed wave function which could be modelled using an equation similar in form to that for a non-eliminated substance in the liver (eqn 6). Thus

$$w(s)_{NH} = \exp\left[\frac{1 - [1 + 4D_{N.NH} \cdot MRT_{NH} \cdot s]^{0.5}}{2D_{N.NH}}\right] \quad (8)$$

where $D_{N.NH}$ and MRT_{NH} are the dispersion number and mean residence time, respectively, associated with the non-hepatic regions of the perfusion system. Note that MRT_{NH} has been used in place of a volume/flow ratio, and is defined explicitly for the entire liver-free system at a given perfusate flow rate and sample collection protocol.

Fitting the model equations to experimental data

The inverse of Laplace transformed-equations must be determined before they can be applied to experimental data expressed in real time. In the present work, this inversion was performed numerically using a Fast Inverse Laplace Transform (FILT) algorithm, and the model equations were fitted to the experimental RTD using MULTI-FILT, a computer programme which couples the FILT algorithm to a multiple non-linear regression package (Yano et al 1989b).

In applying equation 7 to the RTD values of diclofenac, it was assumed that the volume of the central compartment (V_B) is equal to the combined anatomical volume of the blood space and the space of Disse, shown to comprise about 15% of liver weight (Roberts et al 1990). Hence, in each case, V_B was calculated from the weight of the liver determined at the completion of the experiment.

Materials and Methods

Experimental

The single-pass isolated perfused in-situ liver system, using male Sprague Dawley rats (300–400 g; liver weight 12–15 g) was essentially that described previously (Pang & Rowland 1977). The perfusate, maintained at 37°C and oxygenated with 95% O_2– 5% CO_2, consisted of freshly prepared and filtered (0·2 μM) Krebs bicarbonate buffer (pH 7·4) to which had been added 3 g L^{-1} of D-glucose and 5 g L^{-1} of human serum albumin (Kabi AB, Sweden). Perfusate was delivered to the liver at a constant rate of 15 mL min^{-1} via a cannula inserted into the hepatic portal vein, and liver effluent was

collected via a cannula inserted into the vena cava through the right atrium. By monitoring the hepatic extraction of diclofenac under steady-state conditions (constant infusion of diclofenac into the hepatic portal vein), it was found that the perfused rat liver preparation remained viable for at least 2 h (manuscript in preparation), which confirmed earlier findings in which similar liver perfusion techniques were used to measure drug extraction (Schary & Rowland 1983; Rowland et al 1984). Liver viability was also assessed by monitoring perfusate recovery and bile flow, and by visually examining the liver during, and at the completion of each experiment.

After a stabilization period of at least 10 min, 50 μL of perfusate solution containing 0·25 μCi (12·5 μg) of [^{125}I]HSA (Iodine-125 Human Albumin Injection B.P., Amersham, UK) and 0·50 μCi of [^{14}C]diclofenac (20 μCi mg^{-1} > 99% purity, Ciba-Geigy AG, Switzerland) was rapidly injected into the hepatic portal vein without disruption of perfusate supply. Automatically, the total effluent from the cannulated superior vena cava was collected, at 2 s intervals, using a purpose-built, motor-driven carousel with 57 sample holes. An aliquot of each sample (200 μL) was placed into a liquid scintillation vial and the concentration of [^{125}I]HSA determined using an LKB Compugamma Universal gamma counter (Finland). After adding 5 mL of liquid scintillation fluid (LKB Optiphase Hisafe II) [^{14}C]diclofenac was determined using an LKB Rackbeta liquid scintillation counter, with appropriate correction for quenching and [^{125}I]HSA activity. Preliminary investigations, comparing the RTD of diclofenac determined specifically by HPLC (Raz et al 1988) and non-specifically (radiochemically) established that diclofenac metabolites did not contribute to outflow radioactivity. Further, it was established that diclofenac did not bind to the experimental apparatus (injector, tubing, cannulas or collection apparatus) used in the perfusion studies.

Data analysis

When analysing the RTDs the sampling time was taken to be the mid-point of the sampling interval. The area under the outflow concentration vs mid-point time profile (AUC) was determined by the trapezoidal rule with extrapolation to infinite time. The fractional recovery of injected material (availability, F) was calculated using the relationship

$$F = \frac{AUC \cdot Q}{D} \quad (9)$$

Before model fitting, concentration (c(t)) data were transformed to frequency output using the relationship

$$f(t) = \frac{c(t) \cdot Q}{D} \quad (10)$$

Plotted in such a manner, the area under the curve from time zero to infinity is equal to the availability of the injected dose. A non-linear regression program (MULTI-FILT, Version 2·0) was used to fit the full forms of equation 3 to the outflow profiles of [^{125}I]HSA and [^{14}C]diclofenac. A weighting scheme of (observation)$^{-1}$ was chosen for curve fitting. When analysing the RTDs, it was necessary to compensate for the transitional delay and dispersion within the non-hepatic regions of the experimental system. The experimental apparatus was associated with a mean residence time (MRT_{NH}) and dispersion number ($D_{N,NH}$) of 4·5 s and 0·040, respectively, at a perfusate flow rate of 15 mL min^{-1}. These parameter values were substituted into equation 8 which was used to define $w(s)_{NH}$ in equation 3. The RTDs obtained for [^{125}I]HSA and [^{14}C]diclofenac in the perfused liver system were then analysed using this modified form of equation 3, in which the hepatic transfer function was defined by the one-compartment dispersion model with no elimination (equation 6) for [^{125}I]HSA and by the one- and two-compartment forms of the dispersion model (equations 5 and 7, respectively) for [^{14}C]diclofenac.

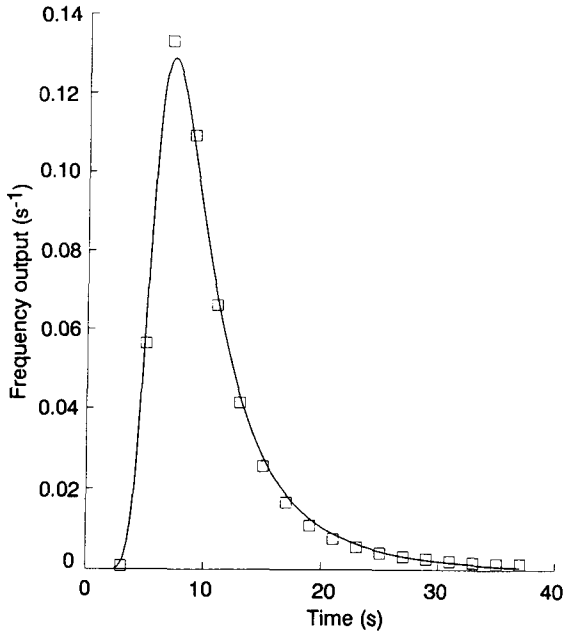

FIG. 1. Representative outflow profile of [^{125}I]HSA after bolus injection into a rat perfused liver (15 mL min^{-1}). Data (□) are presented as frequency output vs mid-point sampling time. The solid line represents the relationship predicted by the one-compartment dispersion model.

Results

The one-compartment dispersion model for a non-eliminated solute was suitable for describing the RTDs of [^{125}I]HSA in the perfused liver preparation. A representative RTD and the corresponding model fit are illustrated in Fig. 1. The dispersion number and hepatic distribution volume of the binding protein were determined with good precision and varied minimally between preparations (Table 1). The

Table 1. Summary of model parameters describing the RTDs of [^{125}I]HSA and [^{14}C]diclofenac in the rat isolated perfused in-situ liver.

	[^{125}I]HSA		[^{14}C]Diclofenac			
Preparation	D_N	V_H (mL)	D_N	k_{12} (s^{-1})	k_{12} (s^{-1})	k_{el} (s^{-1})
1	0·411	1·52	0·342	0·286	0·0317	0·00840
2	0·488	1·55	0·424	0·302	0·0354	0·00521
3	0·549	1·70	0·399	0·383	0·0429	0·00942
4	0·375	1·76	0·252	0·338	0·0526	0·00600
Mean	0·456	1·64	0·354	0·327	0·0407	0·00726
s.d.	0·078	0·12	0·076	0·043	0·0092	0·00198

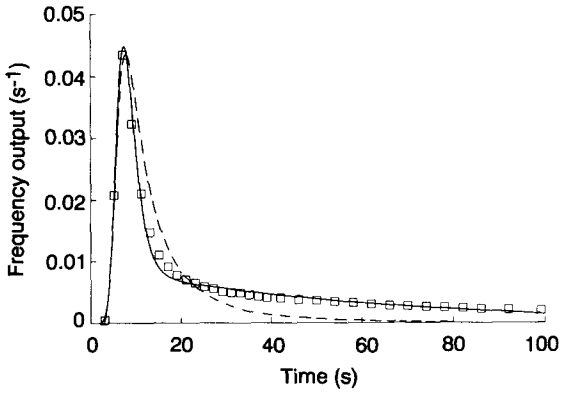

FIG. 2. Representative outflow profile of [^{14}C]diclofenac after bolus injection into a rat perfused liver (15 mL min^{-1}). Data (□) are presented as frequency output vs mid-point sampling time. The relationships predicted by the one-compartment (- - - - - -) and two-compartment dispersion model (———) are shown.

recovery of injected [^{125}I]HSA, determined by applying equation 9 to the outflow data, was virtually complete (0·98 ± 0·05).

Fig. 2 shows a representative RTD for [^{14}C]diclofenac together with the relationships predicted by fitting the one-compartment and two-compartment dispersion models. In all cases, the RTD appeared as a sharp peak, which eluted over the first 20 s, followed by a slowly eluting tail. Based on the area under the outflow concentration vs mid-point time profile, it was estimated that the availability of [^{14}C]diclofenac was 0·81 ± 0·064. The one-compartment dispersion model was unsuitable for describing the RTD of [^{14}C]diclofenac and, in those cases when the iterative procedure converged, the parameter estimates were associated with a high degree of uncertainty. In contrast, the two-compartment dispersion model provided an excellent description of the diclofenac RTD (e.g. Fig. 2) and the parameter values (D_N, k_{12}, k_{21} and k_{el}), summarized in Table 1, were estimated with a high degree of precision.

Discussion

The axial dispersion model of drug elimination, in its original form, was developed to provide a more plausible alternative to the physiologically unrealistic well-stirred (venous equilibration) and undistributed parallel-tube models which have been commonly used to interpret hepatic extraction data obtained under steady-state conditions (Roberts & Rowland 1986 a,b). One of the most attractive features of the dispersion model is that it is also suitable for describing the residence time distribution of radiolabelled tracers, such as erythrocytes, albumin and water, in perfused liver preparations (Roberts et al 1988). In the present work, for example, the one-compartment dispersion model provided an excellent description of the RTDs of radiolabelled human serum albumin. Furthermore, the distribution volume determined for this protein (equivalent to 0·123 ± 0·019 mL (g wet liver)$^{-1}$) was similar to that reported by others who have used the impulse-response technique for exploring rat liver physiology (Tsao et al 1986, 1988; Roberts et al 1990). The extracellular space available to albumin is marginally less than that of small molecular weight extracellular markers, such as sucrose and sodium, because of the exclusion properties of the hepatic interstitium (Goresky 1983). In the application of the two-compartment dispersion model to the RTDs of diclofenac it was necessary to include in the model equation (eqn 7) a volume term for the central compartment, V_B. Rather than including V_B as a parameter to be determined, it was decided to incorporate it as a constant fraction of liver weight, as determined by others (Roberts et al 1990). When the estimated volume of distribution of [^{125}I]HSA was used for V_B, the quality of fit of the two-compartment dispersion model to the [^{14}C]diclofenac data, and the so-derived parameter values, were only marginally affected.

The main reason for the success of the one-compartment dispersion model in describing the RTDs of non-eliminated substances such as erythrocytes, albumin and water (Roberts et al 1988) may be that the assumption of instantaneous radial distribution is likely to hold. Interestingly, Goresky found that the RTDs of a wide range of non-eliminated tracers, including [^{14}C]sucrose, $^{24}Na^+$ and [^{3}H]water, could be described using a flow-limited distributed model (Goresky 1983). For many xenobiotics, however, the hepatocyte membrane may impede radial distribution such that the liver no longer acts as a single compartment (Goresky 1983; Wolkoff et al 1979; Tsao et al 1986, 1988; Schwab et al 1990). Yano et al (1989a) found that the hepatic RTDs of oxacillin and ampicillin were more suitably described by a form of the axial dispersion model in which the radial transfer of substrate between a central and a peripheral compartment were defined by influx and efflux rate constants (the two-compartment dispersion model).

We were interested in investigating the hepatic disposition kinetics of diclofenac because it represented a lipophilic drug that is extensively bound to a protein (human serum albumin) which can be added to the perfusion medium. The perfusate HSA concentration selected (0·50%) ensured that more than 98% of diclofenac was bound. Under these conditions, the availability of [^{14}C]diclofenac was in the order of 80%. The RTD for diclofenac typically appeared as a sharp peak followed by an exponentially declining terminal phase, which is in complete contrast to the form of profile for [^{125}I]HSA (Fig. 1), and that predicted by the one-compartment (flow-limited) dispersion model (Roberts & Rowland 1986a). The one-compartment dispersion model was completely inappropriate for describing the [^{14}C]diclofenac profile (see, for example, Fig. 2).

One possible interpretation of the diclofenac RTD is that the rapidly eluting peak represented injected material which did not leave the vascular compartment during transit through the liver. This may have been due to the combined effect of short hepatic sinusoidal path lengths (and therefore short residence times), extensive binding to perfusate protein (HSA) and limited hepatocyte membrane permeability. In other words, the rapidly eluting peak of diclofenac may have been carried through the liver by its perfusate binding protein with insufficient time to enter the hepatocytes. The slowly eluting tail of diclofenac may represent material which enters the hepatocytes, but whose efflux is retarded by intracellular binding and limited membrane permeability. These two regions of the RTD correspond to the throughput

and returning components referred to by Goresky (1983). The two-compartment dispersion model gave an excellent description of the diclofenac RTDs, providing estimates for the influx (k_{12}), efflux (k_{21}) and irreversible sequestration (k_{el}) rate constants which varied minimally between preparations (Table 1). The hepatic dispersion number obtained for [^{14}C]diclofenac using the two-compartment dispersion model (0·354) is close in magnitude to that determined for albumin (0·456) and within the range of values reported by others (0·2–0·5) for non-eliminated substances in the rat perfused liver (Roberts et al 1988, 1990). Dispersion numbers of similar magnitude were also obtained by analysing data on the effect of perfusate flow rate on the availability of colloidal chromic phosphate, and on the effect of altered perfusate protein binding on the availability of diazepam (Roberts & Rowland 1986b).

The general similarity of dispersion numbers estimated for different substances, using different approaches, gives support to the concept that this dimensionless parameter characterizes hepatic morphology, and is relatively independent of the injected material itself. It is important to note, however, that extremely high hepatic dispersion numbers have been reported by others from analysis of the steady-state extraction of sodium taurocholate under conditions of altered protein binding within perfusate (Smallwood et al 1988; Ching et al 1989). The fact that hepatic RTD values of some substrates may be better described by a two-compartment dispersion model does not help to explain this discrepancy between D_N estimates because, under steady-state conditions, the equations governing the one- and two-compartment dispersion models are identical (Roberts et al 1988; Yano et al 1989a). Very recently, Roberts et al (1990) found that the effect of altered perfusate flow rate on taurocholate availability in the rat single-pass isolated perfused liver conformed to the predictions of the dispersion model with a D_N of about 0·25, but under conditions of altered perfusate albumin concentrations (and therefore altered perfusate taurocholate binding) an albumin-mediated transport system was required to explain the change in taurocholate availability. Hence, the extremely high dispersion number reported for taurocholate under conditions of altered protein binding (Smallwood et al 1988; Ching et al 1989) may be attributable to an unidentified influence of perfusate binding protein content on taurocholate elimination (Forker & Luxon 1981; Smith et al 1987). It is envisaged that studies employing a combination of bolus and steady-state inputs of the same drug under altered perfusate binding and perfusate flow may help to resolve such issues.

In conclusion, a two-compartment form of the axial dispersion model, in which radial distribution is barrier-limited, was suitable for modelling the hepatic RTD of diclofenac in the presence of its binding protein, HSA. The hepatic dispersion number determined for diclofenac was within the range of values reported previously for eliminated and non-eliminated substances in the rat perfused liver. The two-compartment dispersion model may prove to be a powerful tool for analysing organ RTD values and for exploring the physiological factors influencing hepatic drug elimination, particularly relationships involving drug binding to blood components.

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