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Drug metabolite concentration-time profiles: influence of route of drug administration

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1 In order to assess the contribution of an active metabolite to the overall pharmacological response following drug administration it is necessary to characterise the metabolite concentration-time profile. The influence of route of drug administration on metabolite kinetics has been investigated by computer simulation. Comparisons between simulated profiles and published concentration-time data have been carried out.

2 A route dependence in metabolite concentration-time curves is readily apparent provided the metabolite kinetics are formation rate limited and the hepatic clearance of drug is greater than 25 l/h (medium to highly cleared). Oral drug administration produces a triphasic metabolite concentration-time profile whereas only two phases are discernable after intravenous drug administration. The magnitude of the difference in maximum metabolite concentration is directly proportional to the hepatic clearance of drug due to first-pass metabolite production.

3 The route dependence in the shape of the metabolite concentration-time curves is most dramatic when the absorption and distribution of drug and the elimination of metabolite is rapid. A reduction in the rate of either of these processes alters the shape of the metabolite concentration-time profile such that the consequence of first-pass metabolite formation may be reduced.

Keywords first-pass kinetics active metabolite

Introduction

There are many examples of drugs which undergo biotransformation to metabolites which possess properties of either pharmacological or toxicological consequences. The clinical importance of this phenomenon is well documented (Drayer, 1976, 1982; Atkinson *et al.*, 1980; Verbeeck *et al.*, 1981a). However, the quantitative assessment of the kinetics of drug metabolites has received sparse attention and this aspect of pharmacokinetics is still in its formative stages of development (Houston, 1981).

The area under the plasma concentration-time curve for a metabolite (AUC(m)) is a useful parameter to help evaluate the relative importance of that particular metabolite. The determinants of this area have been investigated in a series of studies by Pang and Gillette (Pang & Gillette, 1978, 1979; Pang *et al.*, 1979). The following relationship was derived for AUC(m) following intravenous drug administration

$$\mathrm{AUC}(m) = \frac{fm.F_{\mathrm{H}}(m).\mathrm{D}}{\mathrm{CL}(m)} \qquad (1)$$

fm is the fraction of dose (D) of drug undergoing biotransformation to the metabolite of interest. $F_{\mathrm{H}}(m)$ is the systemic availability of the metabolite, that is the ratio of the amount of metabolite which enters the plasma to the amount actually formed. Although this ratio will be unity for a primary metabolite which undergoes only renal clearance, ratios less than one will occur when

the primary metabolite undergoes sequential metabolism to a secondary metabolite or biliary secretion followed by faecal excretion. Therefore the numerator in equation (1) dictates the appearance of metabolite as viewed from the plasma. CL(m) is the clearance of the metabolite. The clearances of metabolites vary greatly but are often larger than their parent drug clearances due to efficient elimination of metabolite by the kidney or by sequential biotransformation in the liver.

Although AUC(m) reflects the amount of metabolite circulating in the body it is a time averaged parameter which provides no information on the shape of the metabolite-time profile. To assess the contribution of a particular metabolite to the overall therapeutic or adverse effect observed after drug administration consideration of the entire metabolite time profile is necessary.

Following intravenous administration of drug the metabolite concentration-time curve can be described frequently by the biexponential equation where the two exponents are the elimination rate constants for drug and metabolite (Cummings *et al.*, 1967). The terminal phase of the metabolite curve reflects the slower of the two rate constants. Thus when the metabolite half-life is longer than the drug half-life a semi-logarithmic time plot of metabolite concentrations has a terminal slope governed by its own half-life. Alternatively if the metabolite half-life is shorter, then the metabolite concentration will be rate limited by its formation and the terminal slope of the semi-logarithmic concentration-time profile is the half-life of the parent drug. These two situations are known as elimination and formation rate limited metabolite kinetics, respectively. When a formation rate limitation occurs the decline in metabolite concentration reflects the time course of drug and any deviations from a simple monoexponential drug decline are reflected in the metabolite decline (Houston, 1981).

Half-life is a hybrid parameter which is dependent on both volume of distribution (V) and clearance (CL). The rate limitation in metabolite kinetics is controlled by the inter-relationship between the volume and clearance terms for both drug and metabolite. This can be appreciated by considering the ratio of metabolite half-life ($t_{½}$ (m)) to drug half-life ($t_{½}$).

$$\frac{t_{½}\,(m)}{t_{½}} = \frac{V(m).\,\mathrm{CL}}{\mathrm{CL}(m).\,V} \qquad (2)$$

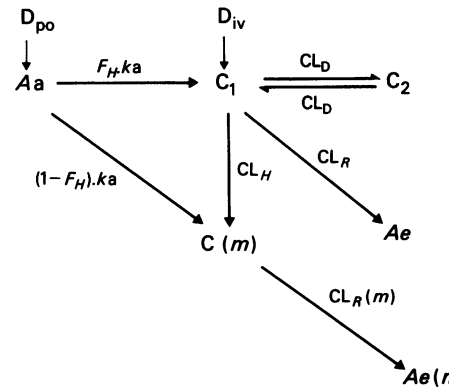
The most prevalent situation is that $V(m) < V$ and CL(m) > CL, thus the half-life ratio is less than one and formation rate limited metabolite kinetics occurs. It is comparatively rare that $V(m) > V$ therefore in order to achieve elimination rate limited kinetics the CL(m) must be lower than CL to such a degree as to outweigh the difference in volume of distribution (Houston, 1983).

The present investigations are concerned with the influence of route of drug administration on metabolite concentration-time curves. The impact of first-pass metabolite production has been studied by means of computer simulation and comparisons are made with published experimental metabolite concentration-time data.

Methods

The model

Scheme 1 provides a model to account for both systemic and first-pass formation of a metabolite from its parent drug. Similar models have been employed by other investigators (Rowland *et al.*, 1972; Koch *et al.*, 1978; Hasegawa *et al.*, 1982).



Scheme 1 A model to describe the kinetics of a drug and its metabolite which incorporates first-pass and systemic biotransformation.

The drug may be administered intravenously (D_{iv}) into a central compartment of volume V_1 to give a concentration C_1. Alternatively the drug may be administered orally (D_{po}) where Aa is the amount of drug at the absorption site in the gastrointestinal tract. Drug within the central compartment may be distributed into a peripheral compartment of volume V_2 according to its distribution clearance CL_D which is assumed to be equal in both directions. Elimination of drug may occur either by renal clearance CL_R or by hepatic metabolic clearance CL_H. The metabolite occupies a volume of distribution $V(m)$ to give a concentration $C(m)$ and is eliminated entirely by renal excretion according to $CL_R(m)$. Following oral administration a certain fraction

of the drug dose enters the central compartment intact (F_H) escaping hepatic metabolism whereas the remaining fraction undergoes hepatic extraction ($1 - F_H = E_H$) and first-pass metabolism entering the systemic circulation as the metabolite. Absorption from the gastrointestinal tract is complete and *ka* is the rate constant for absorption.

The following assumptions are made in this model—the kinetics of both drug and metabolite are linear with respect to concentration and time, neither drug nor metabolite is bound to blood constituents, the liver is the only site of metabolism, only one metabolite is formed and $(1 - F_H)$ is converted to that metabolite since no other presystemic elimination processes are operative, the metabolite has a $F_H(m)$ of unity.

Simulations of drug and metabolite concentration-time profiles

Blood concentration-time data were generated for drug and metabolite using the appropriate differential equations and selected parameter values according to scheme 1.

A unit dose of drug was administered either orally or intravenously. Renal clearance of drug was set to zero, hence the entire dose was metabolised to a single metabolite. V_1, V_2 and $V(m)$ were arbitrarily set at 300, 60 and 30 l respectively. The influences of altering CL_H, $CL_R(m)$ and *ka* were investigated. Clearance terms were confined to physiologically realistic values (that is below hepatic and renal blood flows). The systemic availability (F_H) was determined by the following equation

$$F_H = 1 - \frac{CL_H}{Q_H} \qquad (3)$$

where Q_H (hepatic blood flow) was assumed to be 90 l/h. In order to minimise the influence of drug distribution dynamics CL_D was set as a 1.1 multiple of CL_H for the majority of simulations (Figures, 1, 2, 3 and 4). To illustrate the consequences of distribution dynamics a multiple of 0.2 was used to simulate the data illustrated in Figure 5. The actual clearances and rate constants employed in the simulations discussed are listed in Table 1.

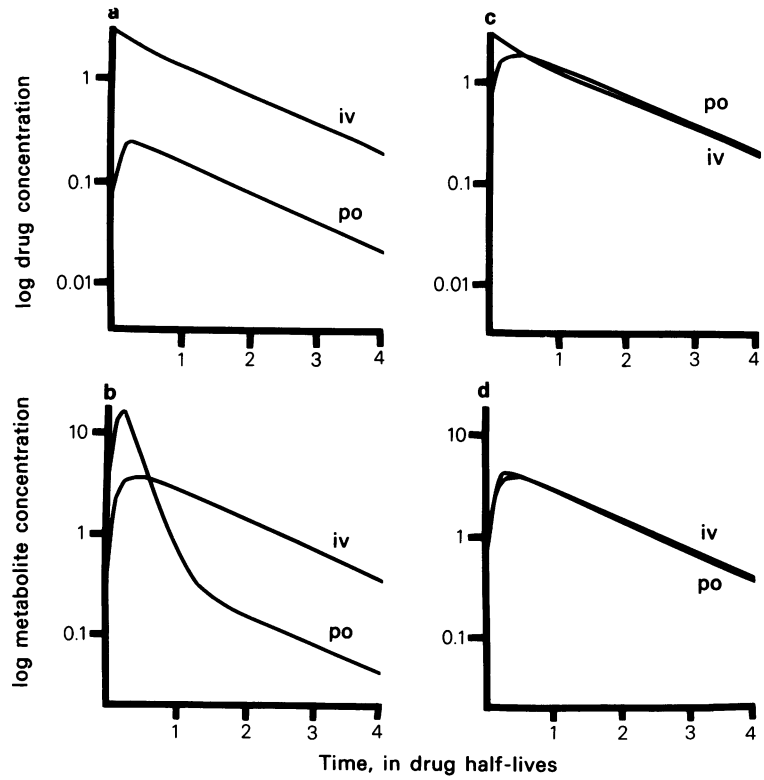


Figure 1 Drug and metabolite concentration-time profiles following intravenous (iv) and oral (po) drug administration simulated according to scheme 1. Panels **a** and **b** refer to drug and metabolite curves for a high clearance drug. Panels **c** and **d** refer to drug and metabolite curves for a low clearance drug. Parameter values employed are listed in Table 1 and distribution dynamics are rapid.

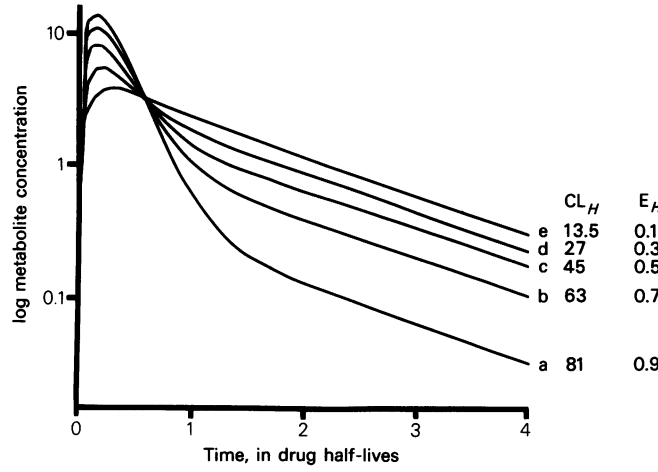


Figure 2 Metabolite concentration-time profiles following oral administration of drug simulated according to scheme 1. For each curve all parameters were held constant (see Table 1) except hepatic clearance (and hence systemic availability) which was altered as indicated.

In order to facilitate comparisons between the blood concentration-time curves simulated under the various conditions, the time axis for all the figures are expressed in terms of half-lives of the terminal phase of drug disposition.

Results

The initial conditions used in the simulations are rapid absorption and distribution of drug and rapid elimination of metabolite. Hence drug concentration-time profiles are essentially monoexponential and metabolite concentration-time profiles are formation rate limited where the terminal phase of the decline parallels the drug decline. By taking two extremes for CL_H the influence of route of administration on both drug and metabolite time profiles can be appreciated.

In Figure 1, panels **a** and **b** refer to drug and metabolite data following administration of a drug with a high CL_H where $F_H = 0.1$. As would

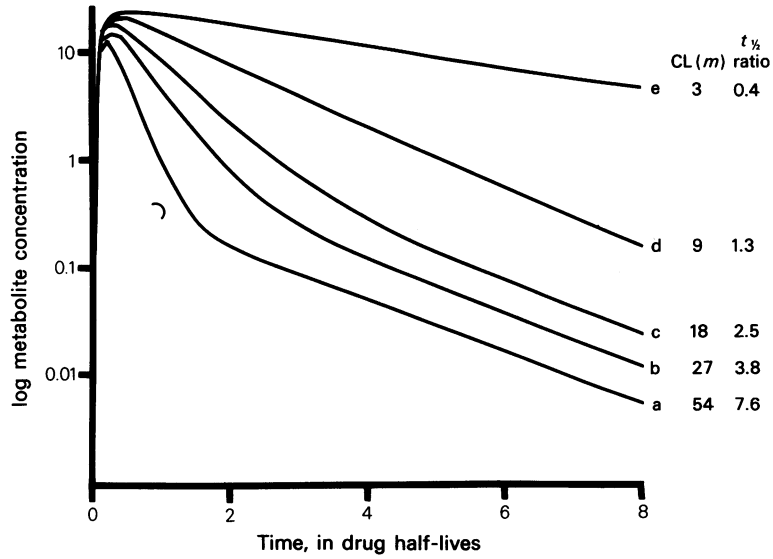


Figure 3 Metabolite concentration-time profiles following oral administration of a high clearance drug simulated according to scheme 1. For each curve all parameters were held constant (see Table 1) except metabolite clearance which was altered as indicated. Also shown for each curve is the ratio of metabolite half-life to drug half-life.

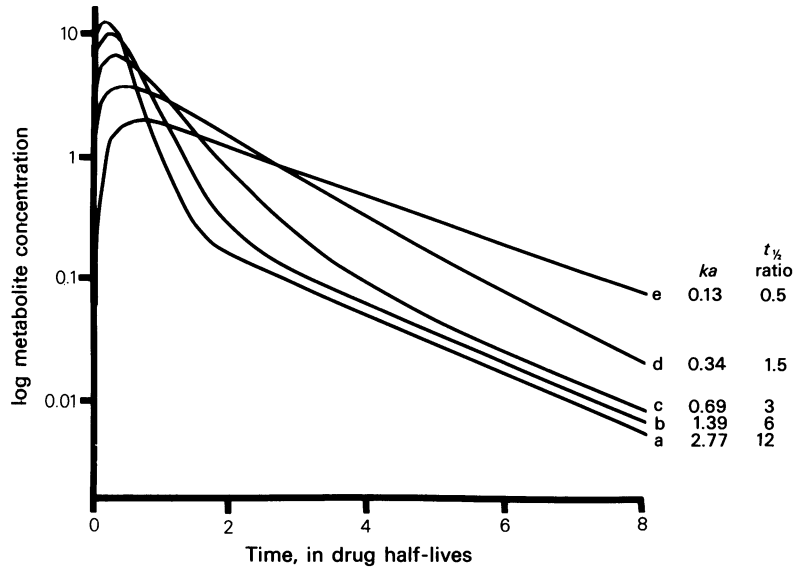


Figure 4 Metabolite concentration-time profiles following oral administration of a high clearance drug simulated according to scheme 1. For each curve all parameters were held constant except the absorption rate constant which was altered as indicated. Also shown for each curve is the ratio of drug disposition half-life to the drug absorption half-life.

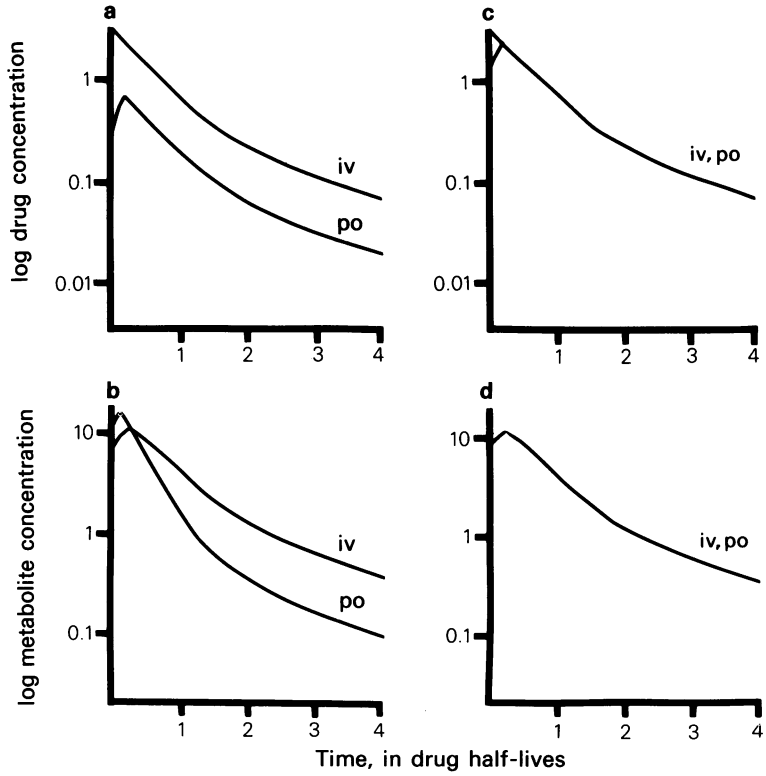


Figure 5 Drug and metabolite concentration-time profiles following intravenous (iv) and oral (po) drug administration simulated according to scheme 1. Conditions as defined in Figure 1 except distribution dynamics are slow.

Table 1 Parameter values employed in the simulation of drug and metabolite plasma concentration-time curves according to Scheme 1.

Figure number	*Absorption rate constant* (h^{-1})	*Drug hepatic clearance* (l/h)	*Metabolite renal clearance* (l/h)
1, 5	2.77	81, 13.5	54
2	2.77	81(a), 63(b), 45 (c), 27 (d), 13.5 (e)	54
3	2.77	81	54(a), 27(b), 18(c), 9(d), 3(e)
4	2.77(a), 1.39(b), 0.69(e), 0.34(d), 0.13(e)	81	54

Individual curves are identified by (a)–(e)

be anticipated there are large differences between the drug concentration-time profiles following oral and intravenous administration. The consequences of the high hepatic extraction result in a characteristic triphasic metabolite concentration-time curve after oral drug administration. In contrast only two phases are discernible when the drug is given intravenously. After oral administration of drug the maximum metabolite concentration is more than four fold that achieved from intravenous dosing. Also the maximum metabolite concentration is attained much earlier when the drug is administered orally. Panels **c** and **d** in Figure 1 refer to a drug with a low CL_H and hence a high F_H. There are only minimal differences between the two routes of administration for both the drug and metabolite concentration-time profiles.

The influence of the extent of first-pass metabolism resulting from CL_H is further explored in Figure 2. As the CL_H is decreased from 81 to 13.5 l/h there is a progressive decrease in the maximum metabolite concentration and in the degree of curvature of the metabolite decline. However even at a CL_H value of 27 l/h (F_H = 0.7) a triphasic metabolite profile is still apparent. Although the shape of the metabolite concentration-time profile varies substantially with CL_H the total AUC(m) is constant.

Despite the wide range of CL_H employed in Figure 2 the terminal phase for each metabolite parallels that for its parent drug. However when CL_H is high the terminal phase is reached only after the metabolite concentrations have declined to a small fraction of the maximum attained. Formation rate limited metabolite kinetics are maintained in all simulations due to the large difference between the volumes of distribution for metabolite and drug, $V(m)$ is approximately 10% of the drug volume hence the metabolite half-life (0.4 h) is always less than the drug half-life (3–19 h).

Although the rate of formation (CL_H) is of prime importance in defining the metabolite concentration-time profile the metabolite's own elimination and the parent drug's absorption and distribution characteristics can modify the curve. The simulations in Figures 3, 4 and 5 illustrate these effects for the case of the high clearance drug (half-life 3 h).

A decrease in the renal clearance of metabolite (see Figure 3) results in corresponding increases in AUC(m) and metabolite half-life. When CL_R (m) (54 l/h) is reduced by 50% and 33% a progressive loss in the degree of curvature occurs. However, only when $CL_R(m)$ is lowered to 9 l/h and the metabolite and drug half-lives approach a similar value is the curvature lost (curve d). A further reduction in $CL_R(m)$ to 3 l/h results in a metabolite half-life of 7 h. Hence the metabolite kinetics become elimination rate limited.

A loss in the degree of curvature in the metabolite concentration decline occurs when the rate of absorption of drug into the body is decreased (Figure 4). As noted in the previous simulations the maintenance of formation rate limited metabolite kinetics is a requirement for this curvature to be apparent. Hence in curve **d** the absorption and disposition half-lives for the drug are similar and the decline in the metabolite concentrations appears monoexponential within the time span of the simulation. Subsequent simulations over a time period equivalent to 15 drug half-lives show a gentle curvature and a terminal phase parallel to curves **a**–**c**. In the extreme case for slow absorption (curve **e**, absorption half-life 5.4 h) the absorption rate constant rate limits drug disposition and consequently metabolite kinetics also.

Comparison of Figures 1 and 5 allow the influence of drug distribution dynamics on drug and metabolite concentration-time profiles to be assessed. Panels **a** and **b** refer to time profiles for a highly cleared drug and panels **c** and **d** to those

for the lowly cleared drug. In contrast to Figure 1, a multiexponential decline is observed for the drug after both oral and intravenous administration when distribution dynamics are slow (see Figure 5). The kinetic behaviour of the drug is reflected in the metabolite time profile and all four curves in panels **b** and **d** are multiexponential. However when the routes of administration are compared, the consequences of first-pass metabolite formation become apparent. A marked divergence between the metabolite curves is observed for the high clearance drug yet the metabolite curves are virtually superimposable for the low clearance drug.

In the simulations presented where $CL_R(m)$ is constant (that is Figures 1, 2, 4 and 5), AUC(m) is independent of the route of drug administration. A condition imposed for all simulations is that CL_H is the only mechanism for drug elimination. Recently Pang (1981) demonstrated the relationship between AUC(m) following intravenous and oral administration of drugs subject to both hepatic and renal elimination. The following relationship was derived

$$\frac{AUC(m)_{po}}{AUC(m)_{iv}} = 1 + \frac{CL_R}{Q_H} \qquad (4)$$

The above equation may be rewritten in terms of the model in scheme 1 by using the relationship $CL_H = Q_H (1 - F_H)$ and defining the fraction of the dose of drug undergoing renal excretion (fe) as the ratio of CL_R to $(CL_R + CL_H)$.

$$\frac{AUC(m)_{po}}{AUC(m)_{iv}} = F_H + \frac{(1 - F_H)}{1 - fe} \qquad (5)$$

Figure 6 illustrates the relationship between the AUC(m) ratio and fe for different $(1 - F_H)$ values. When the extent of metabolism is greater than 99% ($fe < 0.01$) the AUC(m) ratio is unity regardless of $(1 - F_H)$. The AUC(m) ratio does not exceed 1.1 provided that fe is below 0.1. Ratios significantly greater than one only occur if the drug is highly cleared by metabolism (low F_H) and undergoes appreciable renal excretion ($fe < 0.1$). Since these two properties tend to be mutually exclusive it would appear that AUC(m) will be independent of route of administration for the vast majority of drugs.

Discussion

It is widely appreciated that following oral absorption a drug enters the splanchnic circulation and crosses the liver prior to reaching the general circulation and undergoing distribution to the various organs of the body. The role of hepatic first-pass metabolism in explaining the low oral bioavailability of numerous drugs is well known (Rowland, 1973; Gibaldi & Perrier, 1974; Routledge & Shand, 1979). In addition the phenomenon of first-pass metabolism has been exploited in the development of methods of assessing hepatic blood flow and drug intrinsic clearance (Routledge & Shand, 1979).

In contrast little attention has been paid to the first-pass formation of metabolites which may contribute to the pharmacological response observed following oral drug administration. Intuitively one might expect the shape of a metabolite concentration-time profile, and hence any pharmacological response associated with this metabolite, to be dependent upon the route of drug administration. In accord with this premise recent studies on concentration-effect relationship with quinidine (Holford *et al.*, 1981), propranolol (Bai & Abramson, 1983) and alprenolol (Collste *et al.*, 1979) have shown the importance of active metabolites following oral but not intravenous drug administration. The simulations reported above illustrate systematically the consequence of first-pass metabolite formation on metabolite concentration-time profiles and identify those factors which influence the magnitude of the route dependent effect.

In all the metabolite simulations route dependence is readily apparent when the parent drug is moderately or highly cleared ($CL_H > 25$ l/h, $F_H < 0.7$). The magnitude of the difference in maximum metabolite concentration following oral and intravenous drug administration is directly proportional to drug clearance. Under conditions where the absorption and distribution of drug and the elimination of metabolite are rapid, the metabolite concentration-time profile is triphasic with a biphasic decline, after oral drug administration. In contrast a biphasic profile is obtained when the same drug is given intravenously. This behaviour may be rationalised in the following manner. After oral administration only a certain fraction of the dose escapes first-pass metabolism (F_H) and is metabolised subsequently in an analogous manner to an intravenous drug dose. The remaining fraction of the oral dose $(1 - F_H)$ appears in the systemic circulation as the metabolite. Viewed from the systemic circulation the metabolite formed during the first-pass will behave kinetically as if the metabolite *per se* had been administered. Thus when there is substantial first-pass metabolism, the initial decay in metabolite concentrations is influenced largely by the metabolite's own half-life. In the situation where formation rate limited metabolite kinetics apply to systemic biotransformation, a biphasic decline in the metabolite concentration-time profile results.

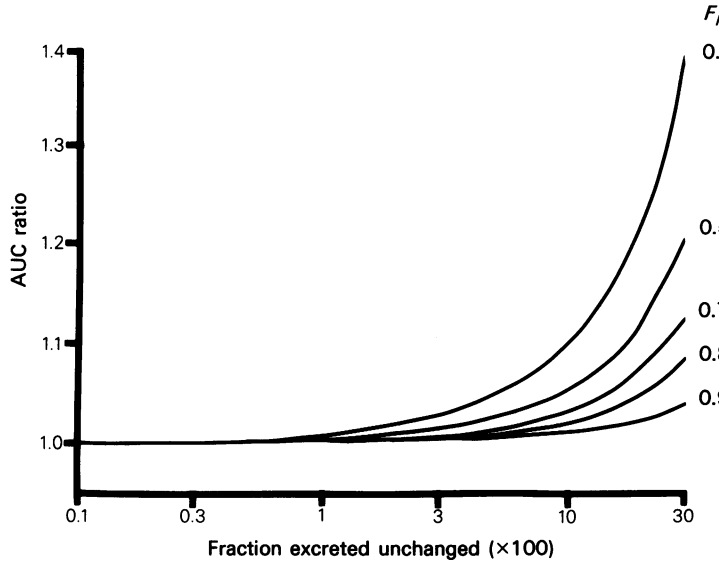


Figure 6 Relationship between the ratio of AUC(m) after oral and intravenous drug administration and the fraction of drug dose eliminated unchanged. Equation (5) was used to generate curves for drugs with different systemic availabilities.

A classic example of the biphasic metabolite decline following oral administration of drug would appear to be 4-hydroxypropranolol (Walle *et al.*, 1980). Earlier studies with propranolol (Paterson *et al.*, 1970) were unable to detect this metabolite after intravenous drug administration and reported that following oral administration 4-hydroxypropranolol plasma concentrations declined faster than propranolol concentrations. Using more sensitive analytical techniques, Walle and coworkers (1980) were able to characterise the 4-hydroxypropranolol concentration-time profile after both oral and intravenous administration of parent drug.

An analogous situation may occur with alprenolol (Collste *et al.*, 1979), chlorpromazine (Dahl & Strandjord, 1977) and methotrimeprazine (Dahl, 1976). In each case metabolites were only detectable after oral drug administration and the decline in metabolite concentrations was faster than the decline in parent drug. Probably an increased analytical sensitivity would have revealed a second phase with a half-life similar to the parent compound. Other data consistent with this interpretation of the phenothiazine metabolite concentration-time profiles have been discussed by Taylor *et al.* (1983).

Other examples of highly cleared drugs whose metabolite concentration-time profiles show route dependence include nortriptyline (Alvan *et al.*, 1977), amitriptyline (Mellstrom *et al.*, 1982), imipramine (Gram & Christiansen, 1975) and promethazine (Taylor *et al.*, 1983). However, the degree to which these drugs' metabolites show the biphasic metabolite decline is variable. The simulations indicate that although drug clearance is the prime determinant of the shape of the metabolite concentration-time profile both the drug's absorption characteristics and the metabolite's own clearance are also important in defining the observed profile. It should be noted that although decreased rates of drug absorption and metabolite elimination reduce the maximum difference between the peak metabolite concentration for the two routes of administration, the time period over which the metabolite concentrations after oral drug administration exceed that after intravenous drug administration is prolonged. Hence even when metabolite elimination is slower than drug elimination and an elimination rate limitation occurs a route dependent effect can be observed. This is exemplified by the kinetic behaviour of the nor-metabolites of propoxyphene (Gram *et al.*, 1979) and pethidine (Pond *et al.*, 1981; Verbeeck *et al.*, 1981b).

A recent study (Drummer *et al.*, 1981) comparing conventional and slow release propranolol dosage forms provide an excellent example of how the absorption rate of a drug may markedly influence the metabolite concentration-time profile. The plasma concentration-time profile of 4-hydroxypropranolol was triphasic following administration of a conventional tablet. However when a slow release propranolol preparation was administered to the same subjects the metabolite concentration-time curve was biphasic. In each case the terminal phase of the

metabolite curve paralleled that of propranolol and there was a marked increase in the terminal half-life when the slow release dosage form was employed. This is indicative of an absorption rate limitation in both the kinetics of the drug and the metabolite.

The simulations described were generated using a model where the entire dose of drug undergoes biotransformation to a single metabolite. However, similar qualitative results are obtained when several primary metabolites are formed by parallel pathways. Indeed the specific metabolite examples discussed relate to the latter situation. Similarly the introduction of an additional clearance mechanism (for example renal clearance) in the elimination of a drug does not alter the shape of the metabolite time profile. If renal excretion is responsible for the elimination of more than 10% of the drug dose then the AUC(m) may show appreciable route dependence. Examples of metabolites where AUC(m) is not route dependent include 10-hydroxynortriptyline following nortriptyline administration (Alvan *et al.*, 1977), nortriptyline following amitriptyline administration (Mellstrom *et al.*, 1982) and promethazine sulphoxide (Taylor *et al.*, 1983) following promethazine administration.

For simplicity the case of primary metabolites only has been considered. It is unlikely that route dependence will be quite so marked for secondary or higher orders of metabolites. The more steps in the catenary sequence preceding metabolite formation the more blurred any first-pass effect will be come. A case in point is propranolol, since neither naphthoxylactic acid (Walle *et al.*, 1979) nor 4-hydroxypropranolol glucuronide (Walle *et al.*, 1980), two secondary metabolites, show the well defined triphasic plasma concentration-time profile exhibited by 4-hydroxypropranolol after oral drug administration.

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