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Stereoselective drug disposition: potential for misinterpretation of drug disposition data

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1 Although it is well recognised that the enantiomers of a chiral drug may possess different pharmacokinetic and pharmacodynamic properties, many studies dealing with chiral drugs which are administered as their racemates rely on non-stereoselective analytical techniques.

2 We present a theoretical analysis to illustrate the potential which exists for misinterpretation of drug disposition and plasma drug concentration-effect data generated for a racemic drug using a non-stereoselective assay.

3 It was shown that the use of such an analytical method can lead to the collection of data which may be both quantitatively and qualitatively inaccurate with respect to the individual enantiomers. For example, the clearance of the unresolved drug may indicate concentration- and time-dependence even though this pharmacokinetic process is concentration- and time-independent for each of the enantiomers.

4 The problems discussed emphasise the need to consider stereoselectivity in clinical pharmacological studies involving racemic drugs.

Keywords stereoselectivity enantiomers drug disposition data interpretation

Introduction

A drug possessing a single chiral carbon atom can exist as two non-superimposable mirror image forms, or enantiomers. The majority of such drugs, in particular those synthesized by chemical rather than biological processes, are employed clinically in their racemic form; that is, as an equal mixture of each enantiomer. Although enantiomers have essentially identical physico-chemical properties in a non-chiral environment, they may behave differently when exposed to an optically discriminating environment such as the human body. Consequently, they may differ in their pharmacodynamics, pharmacokinetics or both.

Pharmacodynamic differences between enantiomers result from the intricate structural requirements of drug-receptor interactions, and generally one enantiomer will be more potent than the other in eliciting a specific therapeutic or non-therapeutic response. Pharmacokinetic differences between enantiomers arise because the processes of drug absorption, distribution, metabolism and excretion all involve close interactions between the drug molecule and various chiral biological macromolecules. For example, the stereoselective pharmacodynamics and pharmacokinetics of the racemic anticoagulant RS-warfarin have been well documented. The anticoagulant potency of the S(−)-enantiomer of warfarin has been estimated to be about five times that of the R(+)-enantiomer (Eble *et al.*, 1966; Hewick & McEwen, 1973), a difference which cannot be attributed to stereoselective plasma protein binding (Yacobi & Levy, 1977).

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In addition, it has been demonstrated that the metabolism of warfarin exhibits stereoselectivity both quantitatively and qualitatively (Hewick & McEwen, 1973; Toon *et al.*, 1986). Further examples of stereoselectivity in the pharmacokinetic and pharmacodynamic properties of chiral drugs can be found in recent reviews (Ariens, 1984; Drayer, 1986; Williams & Lee, 1985).

Because of the difficulties involved in the resolution of enantiomers, the majority of analytical techniques used for measuring chiral drugs in biological fluids, following the administration of the racemate, are non-stereoselective. The ensuing interpretation of the concentration data generated for unresolved drug is usually based upon the assumption that one compound only was administered, an assumption which may have important implications in pharmacokinetic and concentration-effect studies and in therapeutic drug monitoring. A recent survey of research articles appearing in a clinical pharmacology journal (Ariens & Wuis, 1987) indicates the need for an increased appreciation of stereoselectivity in the field of clinical pharmacology.

The present paper examines some limitations of using non-stereoselective methods for analysing chiral drugs when they are administered in their racemic form. We emphasize three main aspects and will provide evidence for each by analysis of simulated plasma concentration-time data generated using a model chiral drug. Firstly, it will be demonstrated that the pharmacokinetic properties of a chiral drug, determined using the results of non-stereoselective drug analysis, may not reflect the true pharmacokinetic characteristics of the individual enantiomers. For example, the pharmacokinetics of a chiral drug may demonstrate concentration and/or time-dependence even though for each enantiomer the drug disposition processes are concentration- and time-independent. Secondly, the limited value of non-stereoselective methods, in particular certain radiochemical techniques used for determining the plasma binding of chiral drugs will be illustrated. Finally, some of the limitations associated with the use of non-stereoselective analysis in concentration-effect correlations and in therapeutic drug monitoring will be considered.

Methods

Pharmacokinetic properties of model chiral drug

The model chiral drug X, possesses a single chiral carbon atom and exists as two enantiomers, R and S. Clinically X is employed as an equal mixture of R and S (i.e. as the racemate).

X undergoes stereoselective disposition which originates solely from the stereoselective binding of R and S to both plasma and tissue proteins. The fraction unbound in plasma (fu) of R (fu^R) is 0.100 while that of S (fu^S) is 0.200. The ratio of the unbound fraction in plasma to the unbound fraction in tissue (fu/fu_T) is identical for both R and S. Accordingly, given that plasma volume (V_p) and tissue volume (V_T) are the same for R and S, equation 1 (Rowland & Tozer, 1980) predicts that the volume of distribution (V) of R and S will be identical.

$$V = V_p + V_T \cdot fu/fu_T \quad (1)$$

For the purposes of this investigation V^R and V^S have been arbitrarily set at 20.8 l. Both R and S are cleared from the body by glomerular filtration, with no tubular secretion or reabsorption, and so the total clearance (CL) of each enantiomer is given by equation 2,

$$CL = fu \cdot GFR \quad (2)$$

Assuming a glomerular filtration rate (GFR) of 120 ml min^{-1}, the total clearance of R (CL^R) is 12.0 ml min^{-1} and that of S (CL^S) is 24.0 ml min^{-1}. The elimination half-lives ($t_{1/2}$) of R (20.0 h) and S (10.0 h) have been calculated using equation 3.

$$t_{1/2} = 0.693\ V/CL \quad (3)$$

Accordingly, the elimination rate constant (k) of R (k^R) is 0.0347 h^{-1} and that of S (k^S) is 0.0693 h^{-1}. Following intravenous administration of the racemate each enantiomer undergoes instantaneous distribution and mono-exponential disposition which is both time- and concentration-independent.

Dosage

This paper will discuss the consequences of administering racemic X in two ways.

Single dose Racemic X is administered as a rapid intravenous (i.v.) bolus dose of 208 mg (i.e. 104 mg of each enantiomer).

Chronic dose Racemic X is again administered as a rapid i.v. bolus dose of 208 mg but, in addition, an i.v. infusion of racemic X is administered at a rate of 9.61 mg h^{-1}. The infusion is commenced at the same time as the bolus dose is administered and is continued for 160 h. This dosage regimen was designed to achieve and maintain a total concentration of X in plasma of

10 mg l^{-1}. The infusion rate was calculated using a clearance value for X of 16.0 ml min^{-1} (see later).

Simulations

The disposition data for R, S and X resulting from the two dosage regimens were generated using the pharmacokinetic parameters of R and S and standard pharmacokinetic equations.

Single dose In the single dose simulation, the total, that is bound plus unbound, plasma concentration(C)-time(t) data for R and S were calculated by substituting their respective parameters into the equation

$$C = \frac{\text{Dose} \cdot e^{-k \cdot t}}{V} \quad (4)$$

The concentrations of unbound R and S in plasma were determined by multiplying the total plasma concentrations by their respective unbound fractions. The total and unbound concentrations of unresolved X in plasma were determined by summing the corresponding plasma levels of R and S. These data for unresolved drug represent those which would be determined if non-stereoselective techniques were used for measuring X in plasma.

Chronic dose In this case, the plasma concentration-time data of total R and total S were simulated using equation 5.

$$C = \frac{\text{i.v. bolus dose } e^{-k \cdot t}}{V} + \frac{\text{infusion rate } (1 - e^{-k \cdot t})}{\text{CL}} \quad (5)$$

The plasma concentrations of unbound R and S were determined as described previously. The total and unbound plasma concentrations for X were determined by summing the corresponding values for R and S.

Results and discussion

Single i.v. dose

The simulated log plasma concentration-time profiles of total (bound + unbound) R and total S following single dose i.v. administration of racemic X are presented in Figure 1. The profile of total unresolved X is presented on the same plot. The volume of distribution of both enantiomers is the same (20.8 l) and accordingly, following the administration of 208 mg of racemic X, both R and S attain the same initial plasma concentration ($C^R(0)$ and $C^S(0)$, respectively) of 5 mg l^{-1}. Subsequently, the plasma concentrations of R and S decline mono-exponentially, but at different rates. Accordingly, the plasma concentration of X (C^X) delines bi-exponentially, in accordance with equation 6.

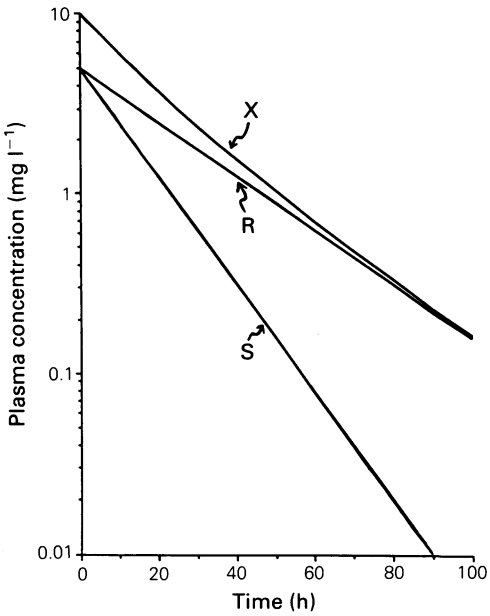

Figure 1 Plasma concentration-time profiles of total R, total S and total X following the single i.v. bolus administration of racemic X (208 mg).

$$C^X = C^R(0)e^{-kR \cdot t} + C^S(0)e^{-kS \cdot t} \quad (6)$$

This differential disposition of R and S results in a noticeable curvature of the log concentration-time profile for total unresolved X (Figure 1).

The disposition of X at any time-point is dependent upon the disposition of R and S, and, accordingly, as the enantiomeric composition in plasma changes with time, so too will the pharmacokinetic behaviour of X. For example, at any time following the administration of racemic X the unbound fraction of X in plasma (fu^X) is dependent upon the unbound fractions of the individual enantiomers and their relative plasma concentrations, in accordance with equation 7.

$$fu^X = \frac{C^R}{C^S + C^R} fu^R + \frac{C^S}{C^S + C^R} fu^S \quad (7)$$

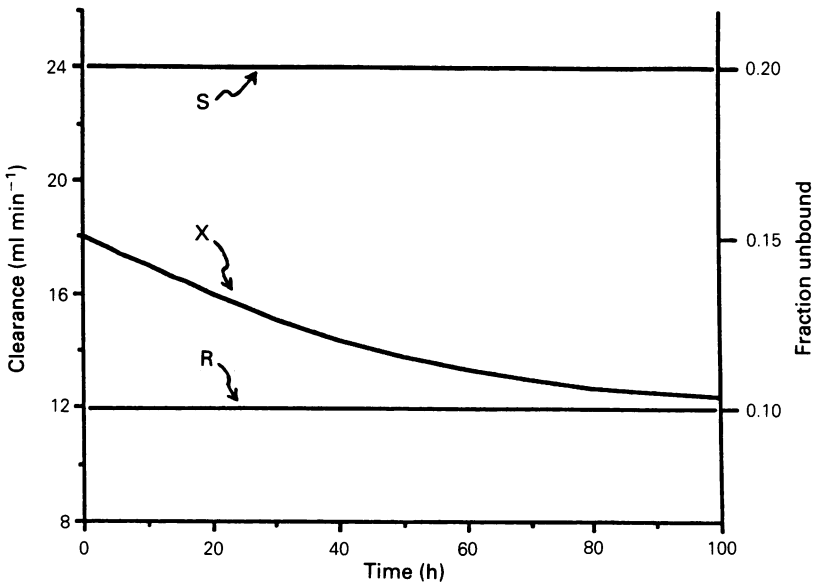

Figure 2 The clearance and unbound fraction of R, S and X plotted against time following the single i.v. bolus administration of racemic X.

Hence, although fu^R and fu^S remain constant, as the enantiomeric composition of X in plasma changes so too does its unbound fraction. Because the clearance of X is directly proportional to its unbound fraction ($CL^X = fu^X \cdot GFR$) the change with time in fu^X is reflected in corresponding changes in CL^X. These changes are presented graphically in Figure 2 which shows that the unbound fraction and clearance of X change from 0.150 and 18.0 ml min^{-1}, respectively (the arithmetic means of the corresponding values for the two enantiomers), and approach 0.100 and 12.0 ml min^{-1}, respectively (the values of the more slowly cleared enantiomer). It should be noted that if the total clearance of X is calculated by dividing the i.v. dose by the area under the plasma concentration-time curve from zero to infinite time, a value of 16.02 ml min^{-1} is obtained which represents a weighted average of CL^R (12.0 ml min^{-1}) and CL^S (24.0 ml min^{-1}).

Mathematically, such a clearance estimate is given by the following term, $(2CL^R \cdot CL^S)/(CL^R + CL^S)$. The plasma concentration-time profiles of unbound R, unbound S and unbound X are presented in Figure 3. In contrast to that which occurs with total drug, the initial plasma concentration of unbound R is half that of unbound S. This difference arises because of the difference between the enantiomers in their volumes of distribution with respect to unbound drug. As with total X, the plasma concentration-time profile of unbound X displays a distinct curvature (Figure 3) which reflects, in this case, a change with time in the volume of distribution of unbound X. The unbound clearances of R and S are identical and so the unbound clearance of X is independent of its enantiomeric composition and remains constant at 120 ml min^{-1}. However, it should be emphasized that for some chiral

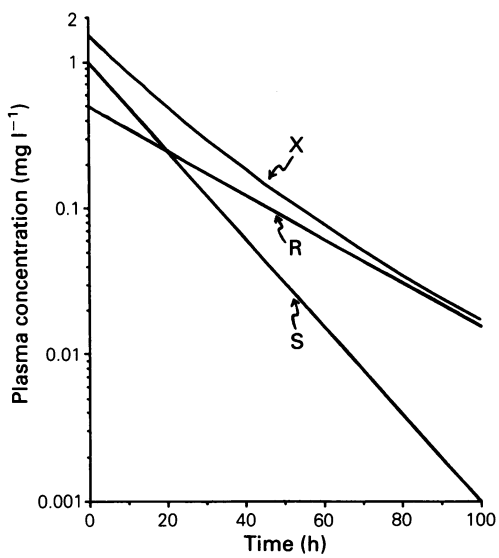

Figure 3 Plasma concentration-time profiles of unbound R, unbound S and unbound X following the single i.v. bolus administration of racemic X (208 mg).

drugs, the possibility exists that the unbound clearances of the individual enantiomers may differ significantly (e.g. as a result of stereoselective hepatic metabolism or renal secretion). In such a case, in contrast to that which occurs for X, there exists a potential for both the total and unbound clearance of the unresolved species to change with time.

Potential limitations of non-stereoselective analysis of total X The use of non-stereoselective analytical techniques for studying the disposition of X may lead to a number of erroneous conclusions regarding its pharmacokinetic behaviour. The curvature of the total plasma concentration-time profile (Figure 1) may be interpreted as 'multicompartmental' disposition. Indeed for a drug such as X which undergoes stereoselective disposition, data generated for unresolved drug alone add additional complications to the application and interpretation of compartmental model analysis (Ariens, 1984). The estimation of a half-life for X would also prove difficult because of the constant curvature of the profile.

The accepted method for determining the renal clearance of a drug is to relate the total amount of unchanged drug eliminated in the urine over a discrete time interval to the levels of the drug in the plasma over that same period of time. If this method was used to determine serial estimates of the total renal clearance of X, the values would be found to decrease with time (Figure 2). For example, the value obtained over the time interval 0 to 4 h would be about 17.8 ml min^{-1} while that obtained over the interval 78 to 82 h would be about 12.7 ml min^{-1}. Purely on the basis of the data for total X, a variety of postulates, such as concentration dependent plasma protein binding, may be proposed to explain such a change.

There are a number of examples in the literature where potentially erroneous conclusions regarding the renal clearance of racemic drugs have been reached on the basis of disposition data for unresolved drug only. When the renal excretion rate of the β-adrenoceptor antagonist, RS-pindolol, was plotted against plasma concentration (Balant *et al.*, 1981), the slope of the resulting line (renal clearance) decreased as the pindolol concentrations decreased. To explain this phenomenon a saturable tubular reabsorption process was postulated. A similar mechanism was proposed to explain the decrease with time in the renal clearance of hydroxychloroquine (Cutler *et al.*, 1987), another chiral compound which is administered as its racemate. However, in both of these cases the mechanism was proposed by the authors solely on the basis of disposition data for unresolved drug. Clearly, for a racemic drug the possibility must not be overlooked that a change with time in the renal clearance of unresolved drug may be due to changes in enantiomeric composition, as shown for drug X (Figure 2).

Potential limitations of non-stereoselective analysis of unbound X Because the unbound fraction of X in plasma changes with time (Figure 2) one may falsely conclude, purely on the basis of unresolved disposition data, that the plasma binding of X demonstrates concentration-dependence, possibly as a result of saturation of protein binding sites. In addition, the reason for the decrease with time in the renal clearance of X may be attributed to this proposed concentration-dependent binding.

There are a large number of methods available for studying the plasma protein binding of drugs. However these approaches have important potential limitations when applied non-stereoselectively to racemic drugs. One of the most common and convenient methods for measuring the unbound fraction of a drug in a post-dose *ex vivo* plasma sample involves radiochemical analysis. In general, this methodology involves the addition of a tracer quantity of the radiolabelled form of the drug to the sample under investigation. Following a suitable separation technique such as equilibrium dialysis or ultrafiltration, radiochemical analysis is used to obtain an estimate of the unbound fraction of the drug. In many cases this approach has been utilised for investigating the plasma protein binding of drugs which are administered as their racemates. However, if the plasma binding of the two enantiomers differs, then for a binding estimate obtained in such a manner to be accurate the enantiomeric composition of the spiked radiolabelled drug must be identical to that of the unlabelled drug present within the plasma sample. Generally, the radiolabelled material used in such studies is racemic and the radiochemical analysis is performed non-stereoselectively. Accordingly, if the plasma binding of the individual enantiomers differs and the drug undergoes stereoselective disposition such that the enantiomers are not present in the plasma sample in equal concentrations, then the result obtained will be inaccurate.

Evidence of such inaccuracies is exemplified in the case of the model drug. Consider a sample collected 80 h after the single dose i.v. administration of X. The true unbound fraction of unresolved X is 0.106. If racemic radiolabelled X is added to the sample and the unbound fraction determined using non-stereoselective radio-

chemical analysis, the result obtained would be 0.150, which is the arithmetic mean of fu^R (0.100) and fu^S (0.200). The difference between the true unbound fraction of X and the unbound fraction determined radiochemically arises because the spiked material is racemic while the unlabelled X present within the plasma sample consists predominantly of R. If this methodology was used to monitor the plasma protein binding of X following its single dose administration, no time-dependence would be detected and quantitative errors of up to 50% would be made. Furthermore, it would not be possible to explain the decreasing renal clearance of X in terms of a changing unbound fraction. Thus the use of racemic radiolabelled drug added into post-dose plasma samples for determining plasma protein binding is potentially misleading. This factor should be considered when assessing the results and conclusions of studies which have used such techniques, for example, in the case of the non-steroidal anti-inflammatory agent ibuprofen (Aarons *et al.*, 1983; Albert *et al.*, 1984; Gallo *et al.*, 1986; Lockwood *et al.*, 1983a,b; Wagner *et al.*, 1984) a racemic drug which undergoes stereoselective disposition (Lee *et al.*, 1985) and plasma protein binding (Hansen *et al.*, 1985; Nation *et al.*, 1987).

Another approach commonly used in examining plasma protein binding in drug disposition studies is to generate a binding curve by spiking varying concentrations of the drug under investigation into drug-free plasma. Such binding curves are used to infer the unbound fraction of the drug in post-dose plasma samples where the total drug concentration is known. In the case of racemic drugs there are potential problems associated with this approach. For example, if the plasma protein binding of X was determined using this method the results would indicate that the unbound fraction is constant (0.150). This result does not take into account the stereoselective disposition of X and once again may lead to confusion as to the cause of its changing renal clearance. Such a technique should not be used to determine the unbound concentration of X in post-dose plasma samples. A binding curve approach has been used by a number of workers for studying the disposition of the racemic anti-arrhythmic drug RS-disopyramide (Cunningham *et al.*, 1977; Giacomini *et al.*, 1982; Meffin *et al.*, 1979). The results of these studies may be in-

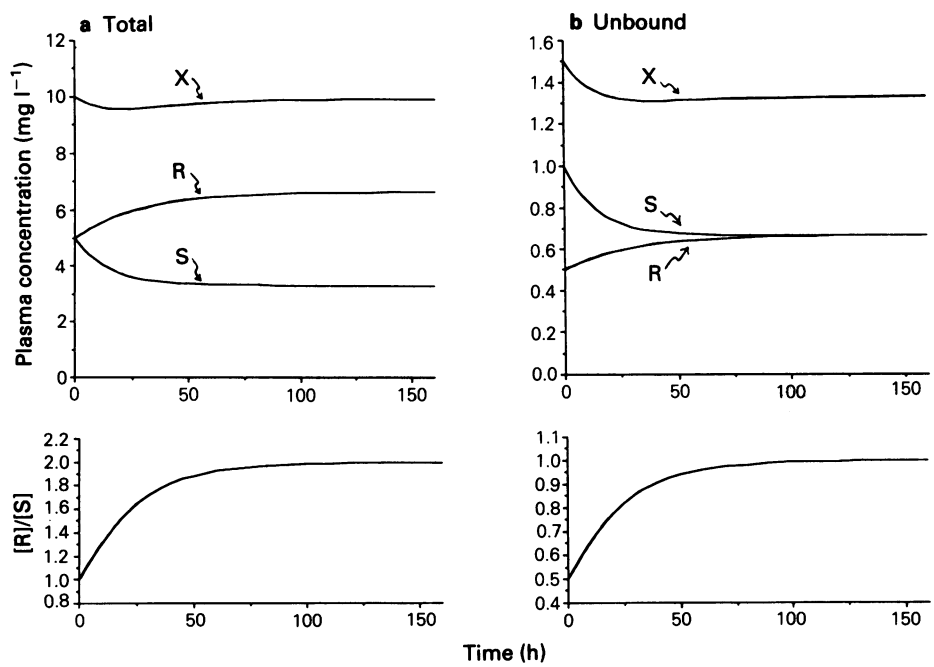

Figure 4 a) Upper panel: Plasma concentration-time profiles of total R, total S and total X following chronic i.v. dosing (bolus + infusion) with racemic X. Lower panel: The enantiomeric composition of total X *vs* time following chronic i.v. dosing with racemic X. b) Upper panel: Plasma concentration-time profiles of unbound R, unbound S and unbound X following chronic i.v. dosing (bolus + infusion) with racemic X. Lower panel: The enantiomeric composition of unbound X *vs* time following chronic i.v. dosing with racemic X.

accurate if the disposition and binding of disopyramide enantiomers in the populations studied were stereoselective.

Chronic i.v. dose

The simulated plasma concentration-time profiles of total X, total R and total S over the time interval 0 to 160 h are presented in the upper panel of Figure 4a. Because R and S have identical volumes of distribution their initial plasma concentrations are the same. However, because of the two-fold difference between the enantiomers in their half-lives and clearances, their rates of approach to steady state and steady state concentrations, respectively, differ by a factor of two. In this particular case the total plasma concentration of S changes with time from 5.00 mg l^{-1}, immediately after the bolus loading dose to 3.33 mg l^{-1} at steady state, while that of R changes from 5.00 mg l^{-1} to 6.67 mg l^{-1}. Over the same time period the concentration of unresolved X remains virtually constant. The transient fall in the total plasma concentration of unresolved X, a phenomenon usually associated with drugs which display multicompartmental characteristics (Gibaldi & Perrier, 1982) results from the differential disposition of R and S. Because of the change in its enantiomeric composition, the unbound fraction of X and consequently its renal clearance, decrease from 0.150 to 0.133 and 18.0 ml min^{-1} to 16.0 ml min^{-1}, respectively.

The plasma concentration-time profiles of unbound X, unbound R and unbound S are presented in the upper panel of Figure 4b. In contrast to that which occurs for total R and S, the initial concentrations of unbound R and S differ by a factor of two (because of the difference in the volume of distribution of R and S with respect to unbound drug) while their steady state concentrations are identical (because of identical clearances of unbound R and unbound S). The unbound concentrations of R and S change from 0.500 mg l^{-1} to 0.667 mg l^{-1} and 1.00 mg l^{-1} to 0.667 mg l^{-1}, respectively, and the unbound concentration of X changes from 1.50 mg l^{-1} to 1.33 mg l^{-1}. It should be noted that if non-stereoselective radiochemical analysis was used to determine the unbound fraction of unresolved X in a steady state plasma sample, a value of 0.150 would be obtained. A similar result would be obtained if the binding was investigated using a binding curve approach. In either case, if the unbound fraction was multiplied by the total plasma concentration of X an incorrect answer of 1.50 mg l^{-1} for the unbound concentration would result.

The enantiomeric composition (expressed as the concentration of R divided by the concentration of S) of total and unbound X in plasma *vs* time are presented in the lower panels of Figure 4. The enantiomeric composition of total X increases from 1.00 at the commencement of therapy to 2.00 at steady-state, while that of unbound X increases from 0.500 to 1.00. A change similar to that which occurs for total X has been documented for the antiarrhythmic drug tocainide (Thompson *et al.*, 1986). Following an infusion of racemic tocainide to twelve patients, the ratio of total S(+)-tocainide to total R(−)-tocainide in plasma increased steadily from an average of 1.03 shortly after the commencement of the infusion to an average of 1.76 at 48.5 h.

Potential limitations of non-stereoselective analysis of X The enantiomeric composition of a chiral drug in plasma can differ between routes of administration, as in the case of verapamil (Vogelsang *et al.*, 1984) and between individuals, as with metoprolol (Lennard *et al.*, 1983) and tocainide (Sedman *et al.*, 1984). Although some of the potential problems associated with such differences with respect to therapeutic drug monitoring have been discussed (Drayer, 1986) very little attention has been focused on the consequences of intra-individual variability in enantiomeric composition. Lima *et al.* (1985) postulated that the stereoselective clearance of disopyramide may lead to a change with time in its enantiomeric composition in plasma upon chronic administration and that this change may be important clinically. Although changes in the enantiomeric composition of chiral drugs in plasma with respect to time have been described for other drugs such as tocainide (Thompson *et al.*, 1986) the theoretical aspects relating to such changes occurring during concentration-effect studies and therapeutic drug monitoring do not appear to have been considered.

For drug X, depending on the relative pharmacological properties of R and S, there are a variety of pharmacological outcomes which may result from a chronic dosage schedule such as that described. Many chiral drugs used clinically as the racemate derive the majority of their primary pharmacological activity from one enantiomer only. Examples include the 2-phenylpropionic acid NSAIDs such as ibuprofen (Adams *et al.*, 1976) and the β-adrenoceptor antagonists (Ariens *et al.*, 1983). In the case of the model drug X, if unbound R alone correlates with therapeutic and/or toxic effects then the increase in the plasma concentration of unbound R over the period of chronic dosing may result in an

enhanced response. Such an enhancement could not logically be explained on the basis of results from non-stereoselective analysis, because not only does the total plasma concentration of unresolved X remain almost constant (Figure 4a), but the unbound plasma concentration of unresolved X actually decreases (Figure 4b).

Conversely, if unbound S alone is the active entity, then a significant reduction in the response may occur over the period of dosing, since the unbound concentration of S decreases by 33.3% (Figure 4b). On the basis of non-stereoselective analysis of total X in plasma such a decrease could not be explained and one may erroneously conclude that a degree of tolerance to the effect of X develops upon chronic administration. Alternatively a decrease in the clinical response may be interpreted as a reflection of the reduced unbound concentration of unresolved X (assuming that the binding of X was not measured using one of the problematical approaches outlined previously).

With many racemic drugs, both enantiomers contribute significantly to the overall pharmacological profile of the drug. In some cases, as with ketamine (White *et al.*, 1980), and the optically active barbiturates (Ho & Harris, 1981), the individual enantiomers may elicit qualitatively different responses. If such was the case with drug X, then the alteration in the enantiomeric composition of the unbound drug with time may result in a change in the nature of the pharmacological response which again would be difficult to explain on the basis of unresolved plasma concentration data.

The chiral antiarrhythmic agents RS-disopyramide, RS-tocainide, and RS-mexiletine are all administered in their racemic form and are subject to therapeutic drug monitoring. For all three drugs there is evidence of stereoselective pharmacokinetics (Giacomini *et al.*, 1986; Edgar *et al.*, 1984; Grech-Belanger *et al.*, 1986) and for disopyramide (Giacomini *et al.*, 1980) and tocainide (Byrnes *et al.*, 1979) there is also evidence of stereoselective pharmacodynamics. However non-stereoselective analytical techniques are used in routine therapeutic drug monitoring to measure the concentrations of these drugs in plasma. For both old and new drugs where therapeutic drug monitoring is indicated, one would anticipate that the use of stereoselective drug analysis may enable the establishment of a more relevant and clinically useful relationship between concentration and effect.

Conclusion

This paper has highlighted limitations arising from non-stereoselective analysis of racemic drugs in pharmacokinetic studies, concentration- effect correlations and therapeutic drug monitoring. Additionally the limitations of some plasma protein binding techniques in dealing with racemic drugs have been outlined.

The properties of the model drug used in this paper were selected so as to simplify its theoretical analysis. However the two-fold difference between R and S in their unbound fractions and clearances is in accordance with enantiomeric differences reported for drugs used clinically. Although the unbound clearances of R and S were identical, more complex scenarios may result when the unbound clearances differ, as for example in the case of a racemic drug which undergoes stereoselective hepatic metabolism or renal secretion. Finally, although the paper addresses primarily chiral drugs which are administered in their racemic form, in some cases the biotransformation of a non-chiral drug may result in the generation of a metabolite with a chiral centre (Testa & Trager, 1983). In such cases, where one is interested in measuring metabolite levels in biological fluids, the interpretation of results obtained using non-stereoselective analysis should be approached cautiously.

We hope that this paper will contribute to the recent move within the literature to promote awareness in clinical pharmacology of stereoselectivity. This awareness should be applied to re-evaluate the results of previous studies on chiral drugs which have failed to consider stereoselective drug disposition, and to anticipate potential complications of using non-stereoselective drug analysis in future studies.

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