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Research Article

Pharmacokinetic Analysis of the Enantiomeric Inversion of Chiral Nonsteroidal Antiinflammatory Drugs[1]

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Equations describing plasma concentration–time courses of the individual enantiomers of chiral 2-arylpropionic acid nonsteroidal antiinflammatory drugs were derived from a general model. The model assumes first-order absorption and elimination of the enantiomers with presystemic and/or systemic R-to-S enantiomeric inversion. Utilizing reported pharmacokinetic parameters, plasma concentrations of the enantiomers of ibuprofen (IB) were simulated. In the case of presystemic inversion, S:R plasma concentration ratios remained constant after an initial rise; the ratio progressively increased with time, however, when systemic inversion was assumed. Under the assumption of simultaneous systemic and presystemic inversion, the increase in the ratio in the postabsorptive phase was preceded by a steeper increase during absorption. Furthermore, it was shown that purturbation of IB absorption from the gastrointestinal tract may serve as an important discriminative measure for identification of the inversion site. For systemic and presystemic inversions, negative and positive sigmoidal relationships, respectively, were observed between the S:R concentration ratio 5 hr after drug administration and the time to reach the maximum plasma concentration. The applicability of the model to previously reported IB data is discussed.

KEY WORDS: chiral drugs; enantiomeric inversion; first-pass metabolism; nonsteroidal antiinflammatory drugs; ibuprofen.

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) of the 2-arylpropionic acid (2-APA) group are usually marketed and administered as a racemate. The pharmacologic activity of the racemate, however, has been attributed mainly to the S antipode (1). In the rat, generally, most of the 2-APA derivatives undergo R-to-S isomeric inversion (2). In man, however, there are exceptions from this generality, as thus far only fenoprofen (3), ibuprofen (IB) (4,5), and benoxaprofen (6) are shown to undergo significant isomeric inversion. Inversion in man seems to be minimal or nonexistent for tiaprofenic acid (7), ketoprofen (8), and carprofen (9). The enzyme system(s) responsible for this unique inversion has not yet been studied. However, in different investigations, presystemic inversion in the gastrointestinal (GI) tract (6,10) and systemic inversion in the liver (11) have been proposed as the major mechanism for this metabolism.

In the presence of enantiomeric bioinversion, the plasma concentration–time course of the S enantiomer is analogous to that of a metabolite following simultaneous administration of the metabolite and the parent drug. The objectives of this article are threefold: (i) to derive equations describing plasma time courses of the enantiomers of 2-APA derivatives undergoing presystemic GI tract and/or systemic R-to-S inversion; (ii) to establish discriminative measures for identification of the site of inversion, utilizing only oral data; and (iii) to compare the obtained theoretical results with those reported in the literature for IB enantiomers.

THEORY

Based on the model depicted in Fig. 1, the following general equations were derived for the R and S isomers (*Appendix* 1):

$$C_R = A'[e^{-(k_{ip}+k_{aR})t} - e^{-K_R t}] \quad (1)$$

$$C_S = A\, e^{-(k_{ip}+k_{aR})t} + B\, e^{-K_{aS} t} + C\, e^{-K_S t} + D\, e^{-K_R t} \quad (2)$$

A one-compartment disposition model with first-order absorption and disposition kinetics was assumed for both enantiomers. The systemic and presystemic inversion rate constants were also assumed to be of first-order kinetics. Simulated plasma concentration–time curves were generated using an IBM PC-AT computer utilizing the Lotus 123 program.

Values close to those reported in the literature (4) were used for the simulation (D_i, 400 mg; V_i, 10 liters; k_{aR}, 1 hr^{-1}; k_{aS}, 1.0001 hr^{-1}; K_{iR}, 0.34 hr^{-1}; K_{iS}, 0.340001 hr^{-1}). After administration of the individual enantiomers of IB, pharmacokinetic parameters of the R and S isomers have been shown to be very close (4). However, implementation of

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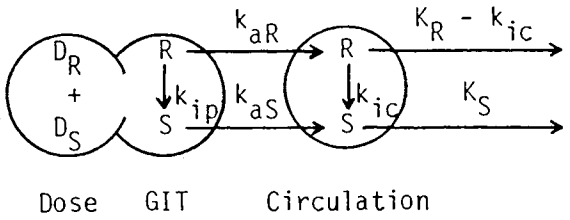

Fig. 1. A general model depicting R-to-S presystemic and/or systemic enatiomeric inversion following oral administration of the enantiomers.

some insignificant differences between the enantiomers' rate constants were necessary, as substitution of identical values renders Eq. (2) unsolvable.

To be comparable with the available experimental data (4,10), time courses of the enantiomers in plasma were simulated up to 12 hr following oral administrations of either racemate or pure isomers of the NSAID.

Simulations were carried out for four different cases assuming systemic and/or presystemic GI tract inversion (Fig. 2) after racemic IB administrations. Equations (1) and (2); however, may be applied to other cases when different ratios of R and S or pure isomers are administered. In all of the cases, the magnitude of k_{ip} and k_{ic} was selected in such a way as to cause 60% (4) R-to-S bioinversion. The percentage inversion was calculated as $AUC_S^R/AUC_S^S \times 100$. AUC values were calculated by the linear trapezoidal rule up to 12 hr. The S:R concentration ratios were plotted vs time. Discriminative measures were sought for identification of the site of the inversion as discussed below.

RESULTS AND DISCUSSION

The bioinversion of R to S enantiomers of orally administered NSAIDs may take place presystemically in the GI tract and/or liver or systemically after the drug reaches systemic circulation. *In vitro* studies utilizing everted rat intestinal sac preparation and *in vivo* results after oral and iv administration of *R*-benoxaprofen suggest that the site of isomeric inversion of benoxaprofen is in the GI tract, rather than the liver (6). For IB, *in vitro* studies with isolated rat liver have shown that limited inversion may take place in this organ upon each pass (11). In man, however, a substantial formation of the S enantiomer during the absorption of an orally administered dose of R isomer was followed by parallel (4) or superimposable (12) time courses for both isomers. This coupled with the observation that the S isomer has a similar elimination half-life when given alone or with the R isomer (12) indicates insignificant inversion during the postabsorptive phase. A recent study in human subjects (10) suggests that the degree of inversion for IB is related to the residence time of the drug product in the GI tract, the suggested site of inversion. The presystemic inversion of R to S enantiomer in the liver, on the other hand, seems unlikely, as the calculated inversion clearance from the reported data by Lee *et al.* (4) was 43 ml/min. Assuming a hepatic blood flow of 1.5 liters/min in a normal, healthy subject (13), we calculated a liver extraction ratio of 0.029 for the inversion, which is not sufficient for substantial first-pass metabolism in the liver. Consequently, we based our models on the systemic and/or presystemic GI tract inversion, as available data on NSAIDs indicate that presystemic inversion in the liver, if any, cannot be significant.

Simulated plasma concentration–time courses of the individual enantiomers of IB and the S:R concentration ratios after the administration of racemic IB for the aforementioned cases are depicted in Fig. 2. While the S:R concentration ratios in case 1 (presystemic inversion only) remains constant after an initial rise, it increases with time in case 4 (systemic inversion only). This, however, is valid if K_S is

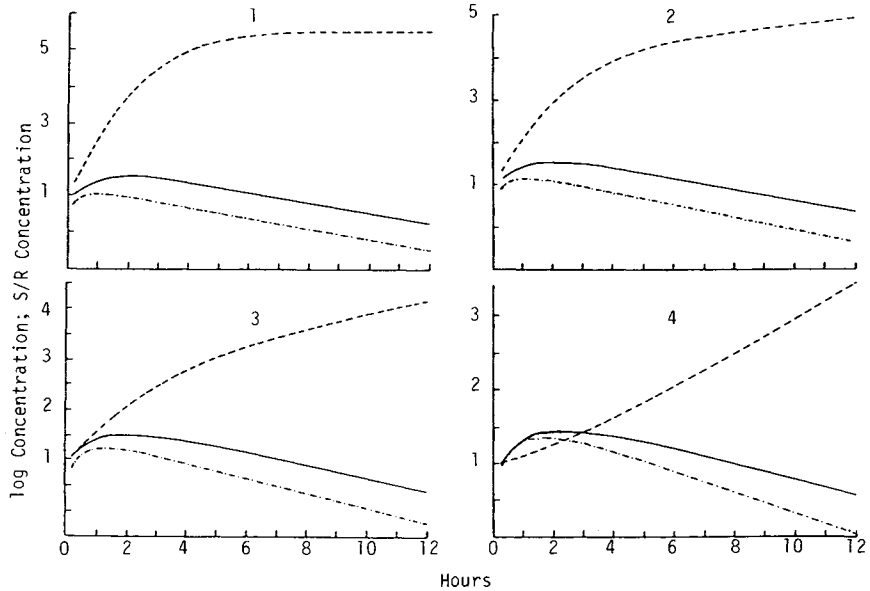

Fig. 2. Simulated log plasma concentration–time curves of S (——) and R(– · – · –) and corresponding S:R ratios (— – – –) following administration of single racemic doses. 1 (k_{ip}, 1.5 hr^{-1}; k_{ic}, 0), presystemic inversion only; 2 (k_{ip}, 1.0 hr^{-1}; k_{ic}, 0.08 hr^{-1}) and 3 (k_{ip}, 0.5 hr^{-1}; k_{ic}, 0.15 hr^{-1}), presystemic and systemic inversions; 4 (k_{ip}, 0; k_{ic}, 0.225 hr^{-1}), systemic inversion only.

equal to K_R; the reported values are in agreement with this assumption (4,10,12). If $K_S < K_R$, the S:R ratio will progressively increase, irrespective of the site of inversion. On the other hand, when $K_S > K_R$ and the inversion takes place systemically, constant S:R ratios will be observed. In the case of presystemic inversion, a faster elimination of S gives rise to a progressive decline of the ratio during the postabsorption phase; the ratio during the absorption phase will depend on the magnitude of K_S as compared to K_{ip}.

In the case of presystemic inversion in the GI tract, a plateau in the ratio is indicative of the completion of absorption and, consequently, inversion. The time to reach the plateau, therefore, is dependent upon the absorption rate constant for the R isomer (k_{aR}). When presystemic and systemic inversions take place simultaneously (cases 2 and 3), a progressive increase in the S:R ratio is seen. However, the increase in the ratio in the postabsorptive phase is preceded by a steeper increase during absorption (Fig. 2). Nevertheless, in the presence of systemic inversion, the ratio increases as long as the R enantiomer exists in the body.

Discriminative Measures. The plot of the S:R concentration ratio vs time may serve as a relatively reliable measure for identification of the site of inversion, provided that the underlying assumption of K_S being equal to K_R holds valid. Furthermore, perturbation of the absorption of IB from the GI tract has a very strong discriminative power, which is not based on any assumption with regard to the relative values of K_R and K_S: if the site of inversion is in the GI tract, a delay in the absorption can result in a greater ratio of S:R concentration at any time after absorption. On the other hand, if inversion takes place systemically, a delay in absorption causes a delay in inversion, and therefore, relatively lower ratios will be attained. To demonstrate the power of this measure, simulations were made for cases 1 and 4, where either presystemic or systemic inversion takes place, with different absorption rate constants. The latter parameter was selected to result in t_{max} values of 0.25–7 hr for the S isomer. Plots of S:R concentration ratios 5 hr after administration of the drug [S:R(5)] vs t_{max} of the S isomer for the two cases are shown in Fig. 3. While the S:R(5) ratio increased with t_{max} for case 1 (presystemic inversion), it decreased in case 4 (systemic inversion). Both relationships, nevertheless, were sigmoidal. This discriminative measure can be applied to the experimental data when the same dosage form is given to different subjects, as well as when dosage forms with different k_{ai} are administered to the same subject. However, when data from more than one subject are used, it is assumed that the site and rates of systemic or presystemic inversions are consistent among the subjects, regardless of the extent of inversion.

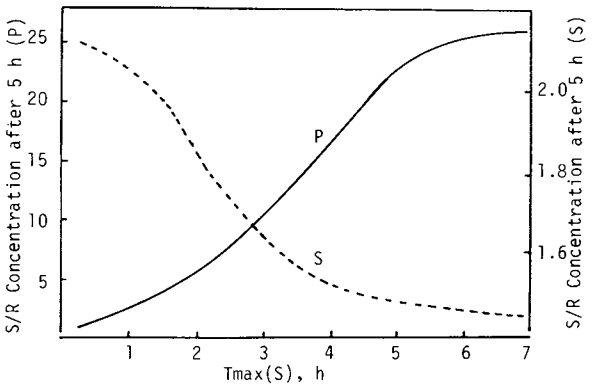

Fig. 3. Simulated S:R plasma concentration ratios 5 hr after the administration of single racemic doses with different rates of absorption vs the T_{max} of the S enantiomer. P, presystemic inversion (k_{ip}, 1.5 hr^{-1}); S, systemic inversion (k_{ic}, 0.225 hr^{-1}).

The data reported by Lee *et al.* (4) do not include the t_{max} or k_{ai}. Further, detailed plasma concentration levels in the individual subjects are also absent. Consequently, evaluation of their findings by our models was not possible. Jamali *et al.* (10), on the other hand, reported the effects of changing absorption rate constant on the S:R ratio at t_{max}. To do this, they administered different IB products known to have different absorption characteristics. Their finding is in agreement with our model when there is only presystemic inversion. They reported plots of S:R concentration ratios vs time which could be best described by our model provided that a lag inversion time is incorporated (*Appendix 2*); the rise in the S:R concentration ratios is preceded by a constant ratio close to unity, its duration being dependent upon the lag time (Fig. 1, Ref. 10). Interestingly, positive relationships are also reported between S:R concentration ratios and the peak time (10).

In conclusion, based on the derived equations with or without the incorporation of a lag time in the inversion (*Appendices 1 and 2*), time courses of the individual isomers of IB were predicted. The predicted time courses were comparable to those reported after administration of the drug (10). Powerful discriminative measures were found which enable the investigators to differentiate between presystemic (in the GI tract) and systemic inversion for NSAIDs which undergo R-to-S bioinversion. Thus far, reports on the stereoselective pharmacokinetics of NSAIDs are scarce. Further experimental data are needed to confirm the validity and power of our model.

APPENDIX 1

The rate equations describing the amounts of the R and S enantiomers in the GI tract and body according to model 1 are as follows:

$$dR_g/dt = -(k_{ip} + k_{aR})R_g \quad (1)$$

$$dR/dt = (k_{aR} \cdot R_g) - (K_R \cdot R) \quad (2)$$

$$dS_g/dt = (k_{ip} \cdot R_g) - (k_{aS} \cdot S_g) \quad (3)$$

$$dS/dt = (k_{aS} \cdot S_g) + (k_{ic} \cdot R) - (K_S \cdot S) \quad (4)$$

Using Laplace transformation and the partial integration method (13), the plasma concentrations of the R and S enantiomers are described by Eqs. (5) and (6):

$$C_R = A'[e^{-(k_{iP} + k_{aR})t} - e^{-K_R t}] \quad (5)$$

where $A' = k_{aR}D_R/[V_R(K_R - k_{ip} - k_{aR})]$;

$$C_S = Ae^{-(k_{iP} + k_{aR})t} + Be^{-k_{aS}t} + De^{-K_R t} \quad (6)$$

where $A = [(k_{aS}k_{iP}D_R)(K_R - k_{iP} - k_{aR}) + (k_{iC}k_{aR}D_R)(k_{aS} - k_{iP} - k_{aR})]/[V_S(K_S - k_{iP} - k_{aR})(k_{aS} - k_{iP} - k_{aR})(K_R - k_{iP} - k_{aR})]$, $B = k_{aS}(K_R - k_{aS})[D_S(k_{ip} + k_{aR} - k_{aS}) +$

$(k_{iP}D_R)]/[V_S(K_S - k_{aS})(k_{iP} + k_{aR} - k_{aS})(K_R - k_{aS})]$, $C = \{k_{aS}(K_R - k_S)[D_S(k_{iP} + k_{aR} - K_S) + (k_{iP}D_R)] + [(k_{aS} - K_S)k_{iC}k_{aR}D_R]\}/[V_S(k_{iP} + k_{aR} - K_S)(k_{aS} - K_S)(K_R - K_S)]$, and $D = [(k_{aS} - K_R)k_{iC}k_{aR}D_R]/[V_S(K_S - K_R)(k_{iP} + k_{aR} - K_R)(k_{aS} - K_R)]$.

APPENDIX 2

Introducing a lag time in the presystemic GI tract inversion, the plasma concentrations of the R isomer at any time after administration of the drug can be described by Eq. (1).

$$C_R = C_R^1 + C_R^2 \tag{1}$$

where C_S^1 and C_S^2 are described by the following equations: at $t \leq T_L$,

$$C_R^1 = \{k_{aR}D_R/[V_R(K_R - k_{aR})]\}[e^{-k_{aR}t} - e^{-K_Rt}] \tag{2}$$

and at $t \geq T_L$,

$$C_R^1 = C_R(T_L) \cdot e^{-K_R(t - T_L)} \tag{3}$$

while

$$C_R^2 = \{[k_{aR}D_R(T_L)]/[V_R(K_R - k_{iP} - k_{aR})]\} [e^{-(k_{iP}+k_{aR})(t-T_L)} - e^{-K_R(t-T_L)}] \tag{4}$$

Similarly plasma concentrations of the S isomer may be described by Eq. (5).

$$C_S = C_S^1 + C_S^2 \tag{5}$$

where C_S^1 and C_S^2 are described by the following equations: at $t \leq T_L$,

$$C_S^1 = A'e^{-K_{AR}t} + B'e^{-k_{aS}t} + C'e^{-K_St} + D'e^{-K_Rt} \tag{6}$$

and at $t \geq T_L$,

$$C_S^1 = C_S(T_L)\, e^{-K_S(t - T_L)} + C'_S \tag{7}$$

while

$$C_S^2 = A''e^{-(k_{iP} + k_{aR})(t - T_L)} + B''e^{-k_{aS}(t-T_L)} + C''e^{-K_S(t - T_L)} + D''e^{-K_R(t - T_L)} \tag{8}$$

where A', B', C', and D' are the same as A, B, C, and D in Appendix 1, respectively, when $k_{ip} = 0$. Equation (9) describes C'_S as

$$C'_S = \{[k_{ic} \cdot R(T_L)/[V_S(K_R - K_S)]\} [e^{-K_S(t-T_L)} - e^{-K_R(t-T_L)}] \tag{9}$$

The values of A'', B'', C'', and D'' can be obtained by replacing D_R and D_S with $D_R(T_L)$ and $D_S(T_L)$, respectively, in the equations describing A, B, C, and D in Appendix 1.

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NOMENCLATURE

AUC	Area under plasma concentration—time curve
AUC_S^R	AUC of S after administration of R
AUC_S^S	AUC of S after administration of S
C_i	Plasma concentration
C_i^1	Plasma concentration of the isomer absorbed in the absence of presystemic inversion
C_i^2	Plasma concentration of the isomer absorbed in the presence of presystemic inversion
$C_i(T_L)$	Plasma concentration of the isomer at T_L
C'_S	Plasma concentration of the S isomer generated from the systemic R isomer absorbed prior to the T_L
D_i	Dose
$D_i(T_L)$	Amount of the isomer in the GIT at T_L
GIT	Gastrointestinal tract
k_{ai}	First-order absorption rate contant
K_i	First-order elimination rate constant
k_{ic}	First-order systemic inversion rate constant
k_{ip}	First-order presystemic inversion rate constant
R	Amount of R isomer in the body
R_g	Amount of R isomer in the GI tract
$R(T_L)$	Amount of R isomer in the body at T_L
S	Amount of S isomer in the body
S_g	Amount of S isomer in the GI tract
T_L	Lag time of inversion
V_i	Volume of distribution
Subscript i	S or R isomer

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