The Effect of Dosage Release Formulations on the Pharmacokinetics of Propranolol Stereoisomers in Humans

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Recent studies in dogs have suggested that the disposition of S- and R-propranolol may depend on the input rate of drug delivered to the liver. Therefore, this study was designed to determine whether differences in the disposition of S- and R-propranolol occur in humans when altering the input rate of propranolol by giving different dosage forms of the drug. Twelve healthy subjects were enrolled in a single-dose, 4-way crossover pharmacokinetic study in which racemic propranolol was given according to 1 of 4 treatments: one 80-mg immediate-release (IR) tablet, phase A; two 80-mg IR tablets, phase B; a 160-mg controlled-release capsule, phase C; or a 10-mg IV bolus, phase D. The results showed no significant differences in the ratios of S/R-propranolol for AUC, clearance, or overall mean concentration among the oral dosage groups. Significant differences in these parameters including C_{max} S/R ratio were seen between the oral phases and the IV phase. These differences appear to be related more to the route of administration than to the low input rate. However, at high concentrations there may be input-rate alteration in S/R ratios. Specifically, for phase B, which had the highest C_{max} concentrations, the C_{max} S/R ratio was significantly lower than the other oral dosage groups A and C (C_{max} S/R ratios: 1.44 versus 1.54 and 1.54, respectively; $P < .05$). These results suggest, as shown by the C_{max} S/R ratio, that at high concentrations as seen after 160-mg IR propranolol, the disposition of S- and R-enantiomers may be different (i.e., input-rate dependent) compared with dosage forms that result in lower drug concentrations. This may have important clinical implications, because the pharmacodynamic response may be altered.

Propranolol, a β-adrenergic antagonist, is given as a racemic mixture that undergoes extensive hepatic metabolism and has a high extraction ratio. There are significant pharmacokinetic and pharmacodynamic differences between the two propranolol enantiomers.[1-6] Specifically, studies have shown that after oral administration, S-propranolol plasma concentrations may be greater, by 20% or more, than R-propranolol plasma concentrations.[1-6] The difference in enantiomer concentrations is due to stereoselective metabolism with higher clearance for the R-isomer. This results in an S/R-enantiomer clearance ratio of less than one and S/R plasma concentration ratios greater than one. Because the S-isomer contains the majority of the β-blocking activity in humans, variability in the S/R ratio may have important clinical consequences, such as altered blood pressure and heart rate effect of the drug.[7]

Recent data in dogs suggest that the metabolism of S- and R-propranolol may be input-rate dependent, which when extrapolated to humans suggests that the metabolism of these enantiomers and the resultant S/R ratios may be dosage-form dependent.[8] Theoretically, differences in the rate of drug release between immediate- and controlled-release (IR and CR) formulations may alter the disposition of S- and R-isomers. For example, IR dosage formulations may

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lead to sufficiently high drug concentrations for hepatic enzymes to become saturated, resulting in a different rate of metabolism for the S- and R-enantiomers, as compared with formulations that lead to lower concentrations that do not saturate the hepatic enzymes, i.e., sustained-release and intravenous (IV) dosage forms. Because alterations in the S/R ratios may have clinical consequences, it is important to determine whether propranolol enantiomer ratios are input-rate dependent in humans. Therefore, this study was designed to determine the effects of different dosage formulations, and thus input rate, on the disposition of propranolol enantiomers.

METHODS

Twelve healthy subjects (11 men; 1 woman) participated in this single-dose, four-way crossover study, designed to evaluate the effect of drug input rate on plasma enantiomer concentrations. After approval from the hospital's Institutional Review Board and before study entry, informed consent was obtained from each subject. The subjects ranged in age from 20 to 32 years (26 ± 4 years), and all were within 25% of their ideal body weight. Health status for each subject was determined by a prestudy physical exam and laboratory evaluation. Subjects were excluded if they had a history of tobacco use, consumption of any medications (including over-the-counter products), or xanthine-containing foods (including caffeine) within 48 hours before each treatment phase.

After an overnight fast, propranolol (Inderal; Ayerst Laboratories Inc., New York, NY) was given to the subjects according to 1 of 4 treatments: a single 80-mg IR tablet, phase A; two 80-mg IR tablets, phase B; a single 160-mg CR capsule, phase C; or a 10-mg IV injection, phase D. The infusion was given at a rate of 1 mg/min using an infusion syringe pump (model 2001; Medfusion, Duluth, GA). The oral doses were given with 240 mL of water. There was a one-week washout period between each treatment phase. A standard meal was provided at four and nine hours after dosing.

During treatment phases A, B, and C, 5-mL blood samples were collected from a forearm venous catheter into heparinized vacutainer tubes (Becton Dickinson, Rutherford, NJ) at 0 (predose), 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, and 12.0 hours after drug administration. During phase C, blood samples were also obtained at 16 and 24 hours after drug administration. During treatment phase D, 5-mL blood samples were collected from a forearm venous catheter placed in the opposite arm in which drug was being infused at 0 (predose), 0.083, 0.18, 0.22, 0.25, 0.33, 0.5, 0.6, 0.83, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after the initiation of the infusion. Blood samples were centrifuged at 2000 rpm for 10 minutes. The plasma was then harvested and frozen at −20°C until it was assayed.

DRUG ANALYSIS

For determination of R- and S-propranolol, sodium hydroxide with 3 mL of methyl-t-butyl ether was added to the 0.5-mL plasma samples.[9] After drying the organic layer, the residue was reconstituted with equal parts of 0.4% v/v triethylamine in acetonitrile and 0.025% w/v 2,3,4,5-tetra-o-acetyl-α-d-glucopyranosyl isothiocyanate in acetonitrile. After evaporating this mixture to dryness, 0.5 mL of mobile phase was added (50% acetonitrile in 75 mmol/L ammonium phosphate, pH = 3). After reconstitution a 100-μL aliquot was injected onto a reverse phase, C-18 column. The flow rate of the mobile phase was 1.4 mL/min. The R- and S-enantiomers were detected using a fluorometer at 216 nm excitation and 340 nm emission. Assay sensitivity was between 2.5 ng/mL and 150 ng/mL with a coefficient of variation of less than 10% for each enantiomer.

DATA ANALYSIS

The area under the plasma concentration-time curve from zero to infinity (AUC) and from zero to the last measured time point (AUC_{0-t}) was determined by the linear trapezoidal method. The elimination half-life ($t_{1/2}$) was determined by linear regression analysis of the terminal phase of the log concentration-time profile. The apparent oral clearance (CL/f) for each isomer was calculated by dividing one-half the administered dose by the AUC. The mean maximal plasma concentrations (C_{max}) and time to C_{max} (t_{max}) were determined by visual inspection of the available data points. Overall mean concentration ratios were determined by averaging the concentrations at each time point for each patient within each phase. Secondary to the sustained-release pattern of the CR formulation, no estimation of elimination rate was possible; therefore, no calculation of AUC (zero to infinity) or oral clearance was possible. In addition, the AUC_{0-t} as reported in Table I should also be interpreted with caution for the CR formulation again owing to the variable absorption pattern. These limitations do not greatly affect the study, because the primary objective was to evaluate enantiomer ratios and not necessarily absolute numbers.

Statistical comparisons of the pharmacokinetic parameters for each isomer as well as the S/R ratios for each of these parameters among the four groups were

TABLE I

Mean Pharmacokinetic Parameters for R and S Isomers of Propranolol

Group	Ke (hr^{-1}) R	Ke (hr^{-1}) S	AUC 0-T (μcg·hr/L) R	AUC 0-T (μcg·hr/L) S	AUC 0-INF (μg·hr/L) R	AUC 0-INF (μg·hr/L) S	CL/F (L/hr) R	CL/F (L/hr) S	C_{max} (μg/L) R	C_{max} (μg/L) S	T_{max} (min) R	T_{max} (min) S
A	0.19 ± 0.05	0.22 ± 0.06	137 ± 94	196 ± 129	157 ± 107	224 ± 146	436 ± 366	270 ± 192	34 ± 23	47 ± 29	91 ± 28	90 ± 27
B	0.18 ± 0.04	0.18 ± 0.04	291 ± 180*	420 ± 243*	350 ± 222*	490 ± 294*	360 ± 252	234 ± 138	68 ± 40‡	93 ± 52‡	86 ± 23	86 ± 23
C	—	—	124 ± 120	165 ± 175	—	—	—	—	8 ± 9‡	12 ± 13‡	560 ± 207§	690 ± 212§
D	0.21 ± 0.04	0.21 ± 0.05	62 ± 14	73 ± 15	69 ± 14	82 ± 15	76 ± 16†	63 ± 14†	46 ± 30	52 ± 34	15 ± 8	15 ± 8

— = not calculated; A = 80 mg immediate release; B = 160 mg immediate release; C = 160 mg controlled release; D = 10 mg intravenous infusion; INF = infinity.

** B > ACD; P < .05.*

†D < AB; P < .05.

‡B > AD > C; P < .05.

§ C > ABD; P < .05.

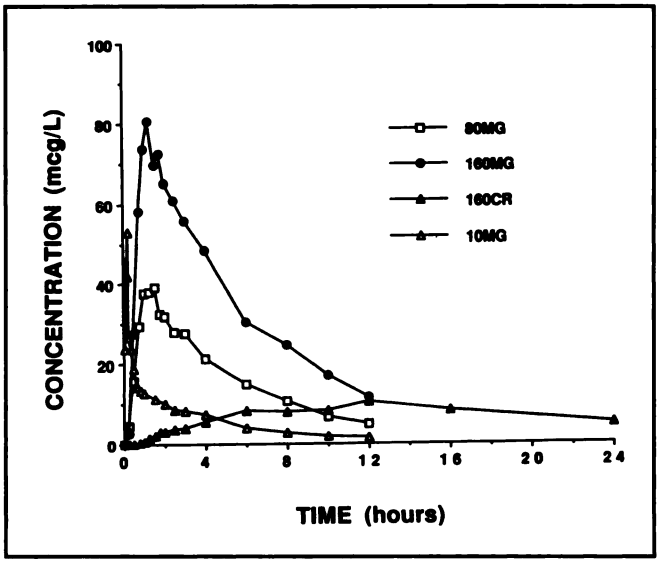

Figure 1. Mean plasma concentration-time curves for S-propranolol.

done using two-way analysis of variance. Repeated measures analysis of variance was used to evaluate S/R concentration ratios at each time point. Differences between means were evaluated using Tukey's multiple range test. A $P \leq .05$ was considered the critical probability level. The reported data are represented as the mean and standard deviation.

RESULTS

All 12 subjects completed each phase of the study. The mean pharmacokinetic parameters for propranolol isomers during each phase are shown in Table I, and the mean concentration-time curves are shown in Figures 1 and 2. The AUC values and C_{max} values were significantly higher in phase B (IR 160 mg) as compared with the other phases. Additionally, phase D (IV) showed a significantly lower clearance than phase A (IR 80 mg) and B. No significant difference was seen in bioavailability between phase A and phase B. Specifically, bioavailability for the S isomer was 34 ± 21% versus 39 ± 24% for phase A and B, respectively ($P = .44$), and 29 ± 23% versus 33 ± 24% for the R-isomer, respectively ($P = .39$).

When the S/R-isomer ratios were evaluated, no significant differences in overall mean concentration, AUC, or clearance ratios were seen among the oral dosage routes (Table II). However, significant differences were seen with these parameters when compared with the IV phase. Additionally, the S/R ratio for C_{max} was also significantly lower in phase B and D as compared with A and C (CR). Specifically,

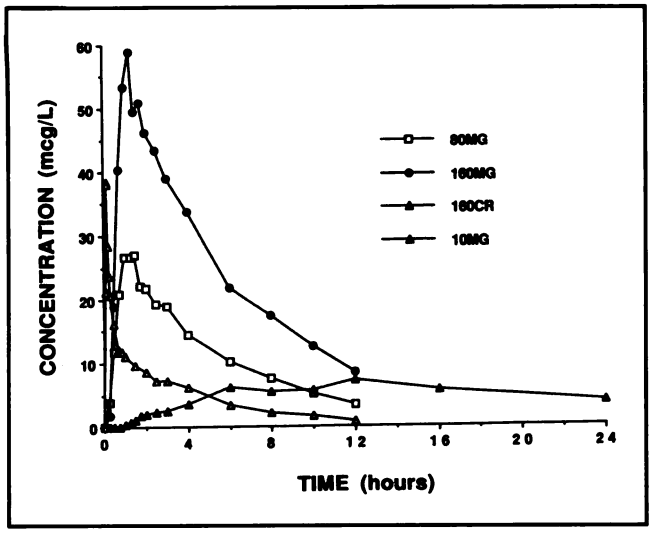

Figure 2. Mean plasma concentration-time curves for R-propranolol.

among the oral dosage groups 9 of the 12 subjects had a lower S/R ratio for C_{max} in phase B as compared with phase A and C.

In addition to evaluating overall mean concentration enantiomer ratios, individual ratios at each concentration-time point were also evaluated. Similar to the overall mean concentration ratio, significant differences were seen only between the oral and IV phases. Specifically, S/R concentration ratios during phase A were significantly higher than those during phase D at the 2, 4, and 6 hour times points. Phases A and B S/R concentration ratios were significantly higher than that of phase D at the 1 hour time point. Phases A, B, and C S/R concentration ratios were significantly higher than those of phase D at the 3 and 10 hour time points. No significant differences were seen among the oral treatment phases.

DISCUSSION

In evaluating the effect of different dosage formulations (and thus input rate) on enantiomer disposition, this study showed no significant differences among the oral dosage forms for concentration, AUC, or clearance enantiomer ratios. However, significant differences were seen between IV and oral routes. Significant differences were also observed among the oral dosage groups and to the IV group for C_{max} enantiomer ratios.

The differences in enantiomer ratios between IV and oral dosage forms can be explained in part by the finding that R-propranolol is cleared to a higher degree than S-propranolol in humans.[1-6] Like previous studies, our study showed that the R-isomer was cleared more rapidly than the S-isomer (Table I). Because clearance of the R-isomer was greater for the oral groups as compared with the IV group, this suggests that the preferential removal of the R-isomer probably occurs primarily during the first pass through the liver, which occurs after oral administration.[2] This results in differences not only for isomer ratios but also for individual pharmacokinetic parameters between the oral and IV phases. To prove this explanation, however, evaluation of individual extraction ratios of the isomers *in vivo* are required.

Another potential explanation for the difference between the oral and IV groups as postulated by Rose et al. suggests that when portal/hepatic concentrations of drug are low, the isomers are metabolized to nearly the same extent.[8] This contrasts with a situation where the rate of isomer presentation to the liver is high (such as after IR dosing), in which hepatic enzymes may become saturated. Saturation of specific isoenzymes for R and S metabolism probably occurs at different concentrations depending on the isoenzyme's respective K_m. This will result in varying plasma concentrations of the S- and R-isomers. Our data initially suggests that this may be another possibility to explain the discrepancy in S/R ratios between the IV and oral groups based on the low concentrations (C_{max}) seen after IV dosing. However, because the CR dosage group also had low concentrations (lower than those of the IV phase) and had significantly different enantiomer ratios from the IV phase, this suggests that low drug delivery to the liver in the concentrations observed does not affect isomer metabolism and that presystemic clearance accounts for the differences between oral and IV phases. Therefore, it may be hypothesized that low drug input rate does not affect S- and R-isomer disposition.

Though our findings show that the degree of ste-

TABLE II

Mean S/R Propranolol Isomer Ratios

Group	Concentration	AUC 0-T	C_{max}	CL/F
A	1.53 ± 0.05	1.55 ± 0.29	1.54 ± 0.33	0.68 ± 0.11
B	1.48 ± 0.02	1.51 ± 0.21	1.44 ± 0.23†	0.70 ± 0.11
C	1.44 ± 0.08	1.52 ± 0.36	1.54 ± 0.43	—
D	1.23 ± 0.09*	1.20 ± 0.17*	1.14 ± 0.17†	0.88 ± 0.13‡

— = not calculated; A = 80 mg immediate release; B = 160 mg immediate release; C = 160 mg controlled release; D = 10 mg intravenous infusion.

** D < ABC; P < .05.*

† D < B < AC; P < .05.

‡ D > ABC; P < .05.

reoselective metabolism is not altered at low concentrations, this may not be the case at higher concentrations. From our data, the S/R C_{max} ratio for the 160-mg IR dose (phase with the highest drug concentration) suggests that alteration in stereoselective metabolism may be occurring as compared with the other oral dosage forms. One hypothesis for this, as alluded to previously, is that a sufficiently high rate of drug delivered to the hepatic system (i.e., after high-dose IR formulation) will result in saturation of the metabolizing enzymes. If the isoenzyme responsible for metabolism is saturated, it may metabolize S- and R-isomers to a different degree, as compared with when one or neither isomer is fully saturated. Further elucidation of this finding and the exact mechanism (i.e., K_m for specific isoenzymes) needs to be addressed, especially because alteration in the S/R ratio may result in alteration in pharmacodynamic effects.

A factor in this study that partly limits our conclusions is that additional doses providing higher concentrations as well as assessment at steady-state must be done to determine whether alterations in S/R ratios occur secondarily to the amount of drug delivered over time to the liver. The doses chosen for this study were based on animal data and clinical experience. However, results in animals may not be similar to those in humans, and higher doses may also be used in the clinical setting. Therefore, as suggested, other doses and regimens need to be studied. Another potential limitation is that we may not be able to detect a difference in bioavailability between phase A and B owing to the variability observed (type II error). However, we feel that clinically the small difference in bioavailability between the groups is probably not important.

In conclusion, the significant differences found in the S- to R-isomer ratios for plasma propranolol concentration, AUC, and clearance in the current study are most probably due to the route of administration and not to dose or dosage form. The ability of the IV form to bypass the first-pass effect of the liver probably contributed to the lower clearance values and alteration in S/R ratio as compared with the oral dosage form. However, with the oral dosage forms, decrease in S/R ratio for C_{max} in the 160-mg IR phase as compared with the other 2 oral phases suggests that at sufficiently high concentrations alterations in propranolol's stereoselective metabolism may occur.

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REFERENCES

1. Hunt BA, Bottorff MB, Herring VL, Self TH, Lalonde RL: Effects of calcium channel blockers on the pharmacokinetics of propranolol stereoisomers. *Clin Pharmacol Ther* 1990;47:584–591.

2. Walle T, Webb JG, Bagwell EE, Walle UK, Daniell HB, Gaffney TE: Stereoselective delivery and actions of beta receptor antagonists. *Biochem Pharmacol* 1988;37:115–124.

3. Ward SA, Walle T, Walle UK, Wilkinson GR, Branch RA: Propranolol's metabolism is determined by both mephenytoin and debrisoquin hydroxylase activities. *Clin Pharmacol Ther* 1989;45:72–79.

4. Olanoff LS, Walle T, Walle UK, Cowart TD, Gaffney TE: Stereoselective clearance and distribution of intravenous propranolol. *Clin Pharmacol Ther* 1984;35:755–761.

5. Von Bahr C, Hermansson J, Tawara K: Plasma levels of (+) and (−) propranolol and 4-hydroxypropranolol after administration of racemic (±)-propranolol in man. *Br J Clin Pharmacol* 1982;14:79–82.

6. Lalonde RL, Bottorff MB, Straka RJ, Tenero DM, Pieper JA, Wainer IW: Nonlinear accumulation of propranolol enantiomers. *Br J Clin Pharmacol* 1988;26:100–102.

7. Barrett AM, Cullum VA: The biological properties of the optical isomers of propranolol and their effects on cardiac arrhythmias. *Br J Pharmacol* 1968;34:43–55.

8. Rose SE, Leesman GD, Amidon GL: A model for predicting drug isomer plasma levels from oral controlled release dosage forms: Application to (+) and (−) propranolol. *Proc Intern Symp Control Rel Bioact Mater* 1990:17.

9. Rose SE, Randinitis EJ: A high-performance liquid chromatographic assay for the enantiomers of bevantolol in human plasma. *Pharm Res* 1991;8:758–762.