Pharmacokinetic investigation of the absorption of oxprenolol from Oros delivery systems in healthy volunteers: comparison of *in vivo* and *in vitro* drug release

I. D. BRADBROOK¹, V. A. JOHN³, P. J. MORRISON², H. J. ROGERS² & R. G. SPECTOR²

Departments of ¹Forensic Medicine and ²Pharmacology and Clinical Pharmacology, Guy's Hospital Medical School, London, and ³Clinical Research Department, Ciba-Geigy Pharmaceuticals, Horsham, West Sussex, UK

1 The absorption kinetics of oxprenolol have been investigated in eight healthy volunteers after single dosing with 16/260 Oros drug delivery systems. Oxprenolol disposition kinetics in individual subjects were estimated from intravenous dose data.

2 Loo-Riegelman analysis of the plasma concentration data indicated an extended duration of drug absorption for the Oros system. Initially, the *in vivo* absorption rate was similar to the *in vitro* release rate but after 5–6 h it slowed perceptibly. However, at later times similar *in vivo* and *in vitro* rates were again observed.

3 The absolute bioavailabilities for prototype and clinical trial systems were shown to be similar, at approximately 42%, and no significant differences in plasma profiles or pharmacokinetic constants were detected between the two Oros forms.

4 A comparison of plasma concentration data in seven subjects who received the prototype system on two occasions in separate studies indicated a consistent level of drug absorption from this preparation.

5 Approximately 10–15% of the administered dose was found in Oros systems recovered from faeces. The quantity of drug remaining was poorly correlated with the observed areas under the plasma concentration-time curve.

Keywords oxprenolol Oros delivery systems drug release

Introduction

Conventional slow-release formulations may exhibit variable *in vivo* absorption because dissolution is influenced by physiological factors within the gut. Oros dosage forms are specifically designed to overcome this problem in that the semipermeable membrane surrounding the core permits only the passage of water into the system, effectively isolating the dissolution process from the luminal environment. The only physiological factors likely to influence *in vivo* release from Oros are osmolarity and temperature within the gut, both of which show little within- or between-subject variability.

The release characteristics of Oros systems can be readily modified by varying the physical dimensions of the system, the permeability of the membrane, or the solubility of the drug (Eckenhoff *et al.*, 1981). Any modification in *in vitro* release should produce a corresponding change in the *in vivo* absorption rate.

Previous studies in healthy volunteers have shown that a prototype Oros system produced more uniformly sustained plasma oxprenolol concentrations and β -adrenoceptor blocking effects over 24 h than the existing polymer-matrix slow-release formulation (Woods *et al.*,

1985; Bennett *et al.*, 1985). However, manufacture of systems for clinical trial use necessitated the inclusion of an inner microporous film to provide additional support for the semi-permeable membrane, but the *in vitro* release characteristics were not affected.

This study investigated the kinetics of absorption of oxprenolol from both systems, and sought to determine whether their *in vivo* release rates were comparable, and related to those measured *in vitro*. Seven of the eight volunteers who participated in this study had received the prototype system on a previous occasion (Bennett *et al.*, 1985). The opportunity was therefore taken to examine the reproducibility of oxprenolol absorption from the Oros system. Since the two studies were separated by an interval of approximately 11 months, caution was exercised in interpreting the outcome of this comparison. However, in the intervening period the subjects had not been exposed to chronic drug therapy or other factors likely to modify oxprenolol kinetics, and a comparison between studies was considered justifiable.

Methods

Subjects

Eight healthy male volunteers aged 21–23 years, and weighing 72–90 (mean 78.6) kg, participated in the study. All had regular bowel habits, were normotensive with normal electrocardiograms, and had no history of asthma, respiratory disease, or contra-indications to the administration of β -adrenoceptor blocking drugs. Biochemical and haematological screening before the study yielded normal findings. After full explanation, all subjects gave their written consent to participate in the study, the protocol of which had been approved by the Guy's Hospital Ethics Committee.

Materials

The study was of an open crossover design in which oral and intravenous (i.v.) doses of the drug were administered in predetermined random order on three separate occasions. The treatments administered were: 260 mg oxprenolol succinate given orally in the form of prototype and clinical trial 16/260 Oros systems; and 20 mg oxprenolol hydrochloride (Trasicor Injection) dissolved in 20 ml physiological saline, and given i.v. over 2 min.

Procedure

The volunteers attended at weekly intervals having fasted for at least 12 h overnight. They were requested to empty their bowels at the beginning of each study day. The drug was administered at approximately 9 a.m. and, in the case of the Oros system, taken with 100 ml water. Blood samples (7 ml) for oxprenolol estimation were drawn from a butterfly needle and heparin lock inserted into a forearm vein, before drug administration and at: 1, 2, 3, 4, 6, 8, 12, 15, 20, 24, 28 and 34 h after the oral dose; and at 5, 10, 20 and 30 min, and 1, 2, 3, 4, 6, 8 and 12 h after the i.v. dose. Blood samples were taken into lithium heparin tubes and centrifuged. The separated plasma was stored at -20°C .

Subjects remained in hospital overnight during Oros treatments. They were permitted non-alcoholic drinks at 2 and 6 h, and were given light standardized meals at 4 and 10 h after dosing. No other medication was taken during the study.

After Oros administration, subjects collected their faeces for a period of up to 3 days in an attempt to recover the systems in order to estimate the total amount of drug released in the gut.

Analytical techniques

Plasma samples were analysed by a modification of the method of Kinney (1981) in which trifluoroacetylated derivatives of oxprenolol and metoprolol, the internal standard, were estimated by gas-liquid chromatography on a 3% OV 225 column with alkali flame ionization detection. The limit of detection of this method was 2 ng/ml with a within-batch coefficient of variation of 6.6% at 100 ng/ml. The detector response was linear up to 500 ng/ml. Measured concentrations were reported as the hydrochloride salt.

Pharmacokinetic analysis

The plasma concentration-time data following i.v. bolus dosing were analysed on the basis of an open two-compartment pharmacokinetic model, and a biexponential rate equation of the form:

$$C(t) = A e^{-\alpha t} + B e^{-\beta t}$$

where $C(t)$ = concentration at time t , A and B are coefficients, and α and β are apparent first order distribution and elimination rate con-

stants, respectively. This equation was fitted to the data by a digital computer program employing a non-linear least-squares simplex algorithm (Nelder & Mead, 1965).

The microconstants of the model were found from:

$$k_{21} = \frac{A\beta + B\alpha}{A + B}; k_{10} = \frac{\alpha\beta}{k_{21}};$$

$$k_{12} = \alpha + \beta - k_{21} - k_{10}$$

Areas under the plasma concentration-time curve (AUC) were estimated by the linear trapezoidal approximation with addition of a correction for the part of the curve beyond the last measured concentration, $C(t')$, at time t' ($= C(t')/\beta$). The areas under the first moment of the curve (AUMC) were obtained by similar methods, the correction factor being obtained by the approximation:

$$\int_{t'}^{\infty} t C dt = \frac{t' C(t')}{\beta} + \frac{C(t')}{\beta^2}$$

The apparent volume of the central compartment, V_1 , was found from: $V_1 = \text{Dose}/(A + B)$. The apparent volume of distribution at steady-state, V_{ss} , was estimated by the non-compartmental method of Benet & Galeazzi (1979) from:

$$V_{ss} = \frac{\text{Dose} \left(\int_0^{\infty} t C dt \right)}{\left(\int_0^{\infty} C dt \right)^2}$$

Systemic clearance, CL, was given by: $CL = \text{Dose}/\text{AUC}$, and was normalized to the individual's weight in kg.

Absorption rates were determined using the microconstants obtained from the i.v. data in mass balance calculations, as described by Loo & Riegelman (1968), to yield the amounts absorbed to time t . The original Loo-Riegelman method was modified to avoid possible errors which result from the use of the two-term Taylor expansion (Boxenbaum & Kaplan, 1975). Absorption rate constants, k_a , were estimated by linear regression of the initial phase of each Loo-Riegelman plot.

The mean absorption time, MAT, (the mean time which a drug molecule spends in the input compartment before being absorbed) was estimated as proposed by Riegelman & Collier (1980):

$$\text{MAT} = \frac{\int_0^{\infty} t C dt}{\int_0^{\infty} C dt} - \frac{1}{\beta} + \frac{1}{\alpha} - \frac{1}{k_{21}}$$

The total systemic availability of oxprenolol (F) from the Oros systems was calculated by the area ratio method taking into account the different molecular weights of the oxprenolol salts which were administered by the oral and i.v. routes:

$$F = \frac{(\text{AUC})}{242} \times \frac{20}{(\text{AUC})^{\text{i.v.}}}$$

(260 mg of the tartrate salt in Oros is equivalent to 242 mg of the hydrochloride salt in the i.v. preparation).

In vitro dissolution studies

These were carried out under standard conditions in a laminar-flow apparatus at 37°C (Langenbucher & Rettig, 1977). Simulated gastric fluid USP (pH 1.3) was used as the dissolution medium for the first 2 h followed by simulated intestinal fluid (pH 7.5) for the remainder of the experiment. The flow rate was 16 ml/min and the total cell volume 20 ml.

Statistical methods

Comparisons of variates were made using Student's t -test (paired or unpaired case as appropriate).

Results

Table 1 shows the mean parameter estimates for the two-compartment open pharmacokinetic model used to describe the i.v. bolus dose kinetics.

The mean plasma concentration-time profiles after administration of the two Oros systems are shown in Figure 1. Plasma concentrations increased gradually to reach a peak value of approximately 220 ng/ml at 5–6 h after dosing. The subsequent decline from peak was slow and measurable plasma concentrations were still observed in individual profiles on 11 out of a possible 16 occasions at 28 h after dosing. By 34 h levels had fallen to below the detection limit of the assay on all but two occasions. The mean total areas under the plasma concentration

Table 1 Pharmacokinetic parameters derived from plasma oxprenolol concentrations following intravenous injection

	<i>Mean</i> (n = 8)	<i>s.d.</i>
A (ng/ml)	1175	961
α (h ⁻¹)	17.4	8.0
B (ng/ml)	371	90
β (h ⁻¹)	0.641	0.098
$t_{1/2,z}$	1.09	0.24
k_{10} (h ⁻¹)	2.40	1.35
k_{12} (h ⁻¹)	10.63	7.00
k_{21} (h ⁻¹)	5.05	1.66
V_1 (l/kg)	0.24	0.15
V_{ss} (l/kg)	0.72	0.16
CL (l h ⁻¹ kg ⁻¹)	0.46	0.09

curve were 3008 and 2927 ng ml⁻¹ h for the prototype and clinical trial systems, respectively. Secondary peaks were detected after administration of both Oros systems in different subjects. The timing of these effects corresponded approximately to the intake of food at 4 and 10 h after dosing.

The plasma profiles after administration of the prototype and clinical trial systems were similar throughout the 34 h study period. No statistically significant differences were identified in the pharmacokinetic constants determined for the two Oros preparations (Table 2). The systems differed in one respect, however, in that plasma concentrations showed a greater

Figure 1 Plasma oxprenolol concentrations following administration of prototype (○—○) and clinical trial (●—●) 16/260 Oros systems. Points are means of eight observations; bars represent standard deviations.

Table 2 Summary of bioavailability comparisons between prototype and clinical-trial oxprenolol Oros formulations

	Prototype formulation			Clinical trial formulation			P for difference
	Mean (n = 8)	s.d.	CV (%)	Mean (n = 8)	s.d.	CV (%)	
(AUC) ₀ [∞] (ng ml ⁻¹ h)	3008	976	32.4	2979	1108	37.2	0.95
F (%)	42.0	10.0	23.8	43.7	20.1	46.0	0.74
C _{max} (ng/ml)	214.3	53.7	25.1	239.4	85.0	35.5	0.44
t _{max} (h)	5.3	3.0	56.5	6.1	3.9	63.2	0.56
MAT (h)	10.1	2.94	29.4	9.15	2.84	31.0	0.54
k _e (%/h)	6.6	4.5	68.1	6.8	3.7	55.4	0.94

s.d. = standard deviation

CV = coefficient of variance

percentage coefficient of variation (CV) for the clinical trial than for the prototype preparation; a similar though less pronounced effect was also observed in the *in vitro* drug release profiles.

Some significant differences were also observed in individual profiles. In two volunteers, on separate occasions when the prototype or clinical trial system was administered, plasma concentrations showed an unexpectedly rapid fall from roughly 6 h onwards at a rate similar to that after i.v. dosing. On one of these occasions the spent system was recovered from faeces. The recovery time (25.4 h after dosing), and the amount of drug remaining in the system (10.7% of the administered dose) showed that this effect was not due to rapid expulsion of the dosage form or to a failure of the drug delivery mechanism. A possible explanation would appear to be that drug was released in the gut but not absorbed into the circulation, although no direct evidence is available to support this conclusion.

The results of the Loo-Riegelman analysis of the plasma concentration data are shown in Figure 2, in which the mean percentage remaining to be absorbed is plotted against time. The corresponding *in vitro* release profile is also included in this figure for comparison. Initially the *in vivo* and *in vitro* profiles were similar but at 5–6 h the apparent *in vivo* rate slowed. However, at later times the two profiles converge and at 20 h the calculated amounts remaining to be absorbed or released were again similar. The initial absorption rates, estimated from the first phase of each plot, averaged 6.6 and 6.8 %/h for the prototype and clinical trial systems, respectively, and were

consistent with the initial *in vitro* release rate of 16 mg/h (= 6.15 %/h) for the 16/260 Oros systems.

The estimated mean absorption times ranged from 3.80 to 13.85 (mean 9.63) h for the prototype system, and from 3.22 to 12.06 (mean 8.78) h for the clinical trial form. The mean dissolution time, calculated in a similar manner from the *in vitro* data, was 8.52 h.

Oros systems were recovered from the faeces on 11 out of the possible 16 occasions. The mean recovery times were 26.3 h (s.d. 2.1 h) for the prototype, and 29.3 h (s.d. 6 h) for the clinical trial system. The mean residual amounts of drug (as a percentage of the original dose) were significantly different ($P = 0.03$) for the two dosage forms, being 9.6% (s.d. 1.9%) and 14.1% (s.d. 3.6%) for the prototype and clinical trial systems, respectively. There was a poor inverse correlation ($r = -0.37$) between the amount of drug remaining in the system and the measured plasma AUC.

No changes were noted in biochemical or haematological parameters after completion of the study and no clinical effects or sequelae were noted in any volunteer which were attributable to participation in the study.

Discussion

The pharmacokinetic constants calculated from the i.v. oxprenolol data in the present study were similar to those reported in other studies (Kendall *et al.*, 1976; Mason & Winer, 1976), although the former authors considered their mean data for a 4 mg i.v. dose to be better fitted

Figure 2 Mean Loo-Riegelman plot of percentage remaining to be absorbed against time for the 16/260 Oros system (solid line); the vertical bars represent standard deviations of the mean. The *in vitro* release rate profile, expressed in terms of the amount remaining to be released, is shown as a dashed line.

by a linear three-compartment pharmacokinetic model. The apparent volumes of distribution and systemic clearances estimated for our subjects are also similar to those reported elsewhere (Mason & Winer, 1976).

Plasma oxprenolol concentrations after administration of the Oros system reached measurable levels within 1 h of dosing and were well sustained over most of the study period. The rate of decline from the peak concentration was considerably slower than the drug's elimination half-life of approximately 1 h would suggest, and was consistent with an extended duration of *in vivo* release from both Oros systems. In a previous study (Bennett *et al.*, 1985) involving the same subjects, it was shown that a 15% reduction in sub-maximal exercise tachycardia was achieved with plasma concentrations of approximately 70 ng/ml. In the present study this level was reached within 1–2 h and was maintained on average for a further 18–20 h.

The absolute bioavailabilities for both Oros systems were similar at 42 and 43.7%, and comparable to those reported by Mason & Winer (1976) for conventional rapid-release tablets in various doses. This suggests that the low rate of drug delivery from either Oros system does not result in a substantial increase in first-pass elimination of the drug. The number of subjects investigated in the respective studies, however, is too small to allow any definite conclusions to be drawn from this comparison.

A Loo-Riegelman analysis of the plasma concentration/time data indicated that *in vivo* absorption reflected *in vitro* release although there was some indication that the *in vivo* rate slowed between 4 and 8 h before reverting to the expected value. The total durations of release and absorption also appeared to be in reasonable agreement as were the mean absorption and dissolution times calculated by statistical moment analysis. These results indicate that absorption is determined by drug release from the Oros system, which in turn provides some justification for the use of *in vitro* procedures for evaluating *in vivo* drug release.

The mean total gut transit times for both prototype and clinical trial systems were greater than 24 h, and the amounts recovered from spent systems agreed closely with the theoretical values predicted from the *in vitro* drug release profiles. There was no indication from a visual inspection of the systems that the semi-permeable membrane was damaged in any way during transit through the gut. Some of the prototype systems, however, appeared to have been slightly compressed and twisted, which

may explain the smaller amount of drug recovered from these Oros forms. The differences in systemic drug availability between the prototype and clinical trial systems, however, could not be explained in terms of the relative amounts of drug remaining in the systems after transit through the gut.

Table 3 summarizes the bioavailability comparisons made on the prototype system when this was administered on two separate occasions to seven of the eight subjects who participated in this study. No statistically significant differences were found in these estimates despite the

Table 3 Summary of bioavailability comparisons of the prototype oxprenolol Oros formulation administered on two separate occasions to seven normal subjects

	First occasion Mean (n = 7) s.d.		Second occasion Mean (n = 7) s.d.		CV (%)	P for difference
(AUC) ₀ [∞] (ng ml ⁻¹ h)	2792	957	3088	1026	33.2	0.50
F (%)	29.6	14.7	30.5	7.9	25.9	0.80
C _{max} (ng/ml)	199.3	67.6	219.3	48.9	22.3	0.34
t _{max} (h)	4.0	1.0	4.0	1.0	25.0	1.00
MAT (h)	9.55	2.57	9.84	3.14	31.9	0.85
k _a (%/h)	6.3	3.7	6.9	4.8	69.6	0.79

s.d. = standard deviation
CV = coefficient of variance

fact that the respective studies were separated by an interval of 11 months. The significance of this observation, however, should not be overstated since the i.v. data from the present study were used to estimate constants from both sets of oral data. With this proviso, the results indicate consistent absorption from the prototype system on both occasions.

The results of this study indicate that transit times for the Oros system through the gut are sufficiently long to permit once-daily dosing in most individuals. The absolute systemic availability of oxprenolol from Oros systems also

appears to be comparable to published values for the conventional rapid-release tablet, suggesting that slow delivery of the drug is not associated with a greater first-pass loss. The comparison with previous data in the same individuals, and the analysis of the Oros plasma profiles by the Loo-Riegelman method, indicate that the 16/260 system functions in a predictable and reproducible manner.

We are grateful to Jillian Robinson, SRN, for her expert nursing assistance during the conduct of these studies.

References

- Benet, L. Z. & Galeazzi, R. L. (1979). Non-compartmental determination of the steady-state volume of distribution. *J. pharm. Sci.*, **68**, 1071–1074.
- Bennett, P. N., Bennett, J., Bradbrook, I., Francis, J., John, V. A., Rogers, H., Turner, P. & Warrington, S. J. (1985). Single-dose pharmacokinetic and pharmacodynamic comparison of polymer-matrix (Slow Trasicor) and Oros dosage forms in healthy volunteers. *Br. J. clin. Pharmacol.*, **19**, 171S–175S.
- Boxenbaum, H. G. & Kaplan, S. A. (1975). Potential source of error in absorption rate calculations. *J. Pharmacokinet. Biopharm.*, **3**, 257–264.
- Eckenhoff, B., Theeuwes, F. & Urquhart, J. (1981). Osmotically actuated dosage forms for rate-controlled drug delivery. *Pharmac. Technol.*, **5**, 35–44.
- Kendall, M. J., Mitchard, M., West, M., John, V. A. & Ebbutt, A. F. (1976). Factors influencing the absorption of oxprenolol. A pharmacokinetic study. *Eur. J. Drug Metab. Dispos.*, **3**, 155–160.
- Kinney, C. D. (1981). Determination of metoprolol in plasma and urine by gas-liquid chromatography with electron capture detection. *J. Chromatogr.*, **225**, 213–218.
- Langenbucher, F. & Rettig, H. (1977). Dissolution rate testing with the column method: Methodology and results. *Drug Develop. Ind. Pharm.*, **3**, 241–263.
- Loo, J. C. K. & Riegelman, S. (1968). New method for calculating the intrinsic absorption rate of drugs. *J. pharm. Sci.*, **57**, 918–928.
- Mason, W. D. & Winer, N. (1976). Pharmacokinetics of oxprenolol in normal subjects. *Clin. Pharmac. Ther.*, **20**, 401–402.
- Nelder, J. A. & Mead, R. (1965). A simplex method for function minimisation. *Computer J.*, **7**, 308–313.
- Riegelman, S. & Collier, P. (1980). The application of statistical moment theory to the evaluation of *in vivo* dissolution time and absorption time. *J. Pharmacokinet. Biopharm.*, **8**, 509–534.
- Woods, K. L., Jack, D. B., Kendall, M. J., Halsey, A., O'Donnell, M. L., Warrington, S. J. & John, V. A. (1985). A multiple-dose comparative study of the pharmacodynamic and pharmacokinetic behaviour of polymer-matrix and Oros dosage forms of oxprenolol in healthy volunteers. *Br. J. clin. Pharmacol.*, **19**, 177S–184S.