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The pharmacokinetics and dynamics of oxprenolol: a simulation study with six subjects

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Experimental results of plasma concentration determinations and lowering of exercise heart rate for six subjects taking a conventional tablet and a sustained release preparation of oxprenolol have been analysed by a comprehensive computer simulation model. Individual plasma values were simulated using a least squares procedure and the results were applied to evaluate individual release patterns following dosage with the sustained release preparation. Application of the model to the lowering of exercise heart rate indicated that the response is in a steady state with the plasma values and that the response-concentration relation is of the saturable, E_{max}, type. The parameters for this were evaluated for each subject for the results after a dose of a conventional tablet. These parameters were applicable to the results after dosage with a sustained release preparation. The method should be applicable to other sustained release preparations.

The plasma concentration-response relation for oxprenolol has been discussed in general terms by Brunner et al (1975) and by Davidson et al (1976). Mason & Winer (1976) noted that responses to oxprenolol showed a limiting maximum value as the dose was increased, indicating that the concentration-response relation was of the E_{max} type (Holford & Sheiner 1981).

In this paper, plasma levels and exercise heart rate lowering after oral dosing with conventional oxprenolol tablets and with a sustained release preparation are described and discussed. Plasma levels have been simulated by least squares fitting using the computer model Macdopex (Bloch et al 1980). Release patterns for the sustained release preparation have been evolved from these fittings. The method should be applicable to other sustained release products.

METHODS

The results used in this paper were taken from a broader study of different preparations of oxprenolol (Woods et al 1985). Six healthy volunteers participated; their demographic details are shown in Table 1.

Each subject was exercised on a Siemens-Elema bicycle to determine the work load necessary to produce a heart rate greater than 150 beats min^{-1} during the last 10 s of a fixed 3 min exercise period. These individually determined work loads were then used in the study which was a double-blind within subject comparison using a double-dummy technique. Subjects were randomly allocated to three treatments each involving taking a conventional tablet and a sustained release preparation (Oros); there were at least six days between treatments. The tablets were placebo or contained 80 mg of oxprenolol and the sustained release preparation was either placebo or contained 170 mg oxprenolol. The treatments were: (1) 80 mg oxprenolol tablet plus placebo sustained release preparation; (2) placebo tablet plus 170 mg oxprenolol in the sustained release preparation; (3) placebo tablet plus placebo sustained release preparation. At the end of the study each subject had received each of the three treatments.

The subjects took the appropriate preparations after an overnight fast and 10 ml venous blood samples were taken into lithium heparin tubes before and at set times after the dose. Samples were immediately separated and stored at −20 °C until analysed by gas chromatography (Degen & Riess 1976). The standardized exercise tests were performed before and at set times after dosing.

The sustained release preparation functions by an osmotically controlled mechanism designed to extend the period of drug release compared with other slow release forms. It had a nominal release rate of 10 mg h^{-1} and a content of 170 mg of oxprenolol as hydrochloride. The conventional tablet contained 80 mg of oxprenolol as hydrochloride in an inert base.

The computer model used has been described by Bloch et al (1980) and its application by Saunders et al (1982).

The model is provided with a least squares fitting

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procedure in which a set of experimental plasma level-time data for a drug are compared with the simulated values. A sum of squared deviations, Q, between observed and simulated plasma levels is evaluated. A drug or subject parameter is altered and the effect on Q is assessed. Alterations are then continued manually or automatically until a minimum value of Q is attained.

The output used for this work was in the form of tables giving amounts distributed and plasma and urine concentrations of drug and metabolites at set times after dosing.

The details of each subject were set up in the model from the data in Table 1. The standard parameters for the drug were used to give a first value of Q for the results following dose with the 80 mg tablet. A limited set of parameters which mainly governed the plasma levels of oxprenolol were then varied in turn, manually at first and then automatically so as to give a minimum Q.

Table 1. Details of subjects.

Subject	Sex	Height (cm)	Weight (kg)	Age
1	M	173	69	27
2	M	173	64	19
3	M	183	71	22
4	M	188	97	22
5	M	170	73	31
6	F	151	52	30

The least squares parameters for the 80 mg dose for each subject were maintained for the least squares fitting to the sustained release plasma data. With these data the minimization was carried out in terms of four further parameters. In the model, sustained release is described in terms of two concurrent zero order release processes. The amount of drug absorbed from the preparation, ED (effective dose), is considered to be partitioned between a zero order process of duration T_1 hours and one of duration T_2 hours, with a fraction F of ED going to the second process. Starting values for these four parameters were assessed from the data as follows: T_1 was taken as the time at which plasma concentrations first began to decrease, T_2 was taken as the subsequent time at which plasma concentrations started to decrease sharply, ED was taken as the nominal dose and F was taken as 0·5. With these starting values rounds of minimization of Q were made until a final minimum was reached.

RESULTS

Plasma levels of total oxprenolol following an 80 mg tablet dose (treatment 1) are summarized in Table 2 and values for the sustained release preparation in Table 3. Values for the fall in exercise heart rate for the two treatments are shown in Tables 4 and 5. The baseline for estimating the fall for each subject was taken as the simple mean of the zero time (before dose) exercise heart rate and the mean of all the placebo exercise heart rate values for that subject.

Table 2. Plasma concentrations of subjects (S) in ng ml^{-1} after dose with an 80 mg tablet of oxprenolol.

S	1 h	2 h	3 h	4 h	6 h	9 h
1	542	507	342	234	74	22
2	325	578	430	365	121	30
3	184	305	84	100	26	7
4	432	280	157	79	22	11
5	348	263	157	79	16	5
6	1168	1229	689	427	209	37

Table 3. Plasma concentrations of subjects (S) in ng ml^{-1} after dose with sustained release preparation.

S	1 h	2 h	3 h	4 h	6 h	9 h	12 h	14 h	20 h	24 h
1	16	181	258	296	258	174	149	135	55	63
2	21	90	197	259	251	215	191	189	181	129
3	12	70	102	94	69	73	29	11	6	5
4	6	31	65	76	64	46	55	62	47	32
5	33	73	152	149	121	71	72	59	42	33
6	13	170	233	255	235	208	191	151	88	58

The results of the least squares fittings to the tablet results are shown in Table 6. The five parameters which mainly affected plasma concentrations of oxprenolol were those which controlled metabolic

Table 4. Exercise heart rate fall in beats min^{-1} following dose with an 80 mg tablet of oxprenolol.

S	Baseline	1 h	2 h	4 h	6 h	9 h
1	155·7	49·7	36·7	27·7	15·7	4·7
2	145 4	29·4	34·4	30·4	20·4	4·4
3	147·0	29·0	30·0	23·0	6·0	-ve
4	146·1	36·1	29·1	22·1	5·1	10·1
5	158·1	35·1	29·1	16·1	2·1	-ve
6	158·5	35·5	40·5	35·5	27·5	22·5

Table 5. Exercise heart rate fall in beats min^{-1} after dose with sustained release preparation.

S	Base line	1 h	2 h	4 h	6 h	9 h	12 h	14 h	24 h
1	157·2	9·2	26·2	29·2	25·2	24·2	21·2	21·2	10·2
2	146·4	18·4	26·4	29·4	24·4	28·4	25·4	25·4	29·4
3	146·0	16·0	20·0	21·0	16·0	17·0	10·0	8·0	8·0
4	144·6	9·6	14·6	18·6	13·6	14·6	15·6	15·6	11·6
5	153·6	16·6	23·6	27·6	24·6	22·6	18·6	20·6	15·6
6	155·5	14·5	31·5	34·5	31·5	34·5	28·5	29·5	20·5

rate, dissolution time for the tablet, distribution rate and ratio and stomach emptying time. The least squares values for these parameters are given in Table 6.

Table 6. Parameters for least squares fits to plasma levels after 80 mg tablet.

S	(i)	(ii)	(iii)	(iv)	(v)	Q	$T\frac{1}{2}$
1	1·2	1·3	1·0	0·85	1·3	508	1·2
2	1·0	1·7	1·1	1·3	0·8	3665	1·3
3	2·5	2·4	0·3	0·7	0·9	940	1·0
4	2·1	0·0	0·3	2·0	1·3	42	1·1
5	2·3	0·0	0·2	0·4	1·0	1760	0·9
6	0·5	1·5	1·0	0·7	1·6	4772	1·9

(i), The ratio to the standard value for rate of metabolism; (ii), tablet dissolution time in hours; (iii), (iv), ratios to standard for distribution coefficient and rate; (v) ratio to normal of stomach emptying rate; Q, minimized sum of squared differences between simulated and observed plasma concentration; $T\frac{1}{2}$ the plasma half life.

Table 7. Least squares sustained release parameters following sustained release preparation.

S	ED	T_1	T_2	F	Q
1	164·0	4·7	22·2	0·81	2155
2	152·0	3·9	23·0	0·86	937
3	67·0	3·0	11·1	0·73	862
4	82·5	4·3	22·9	0·95	329
5	137·0	5·8	23·2	0·78	2406
6	71·0	4·5	18·7	0·89	4581

ED, effective dose in mg; T_1, T_2, durations of first and second releases in hours; F, fraction of ED going to the second release; Q, minimized sum of squared differences between simulated and observed plasma concentrations.

Table 7 shows the least squares values for the four sustained release variables. The data of Table 3 indicate that there is a lag period before release starts. This was assessed graphically and was found to vary between 0·5 and 0·8 h. The lag time was taken as the zero time for the Macdopex runs.

DISCUSSION

Plasma levels

The results in Table 6 show that subjects with shorter plasma half lives for the drug (3,4,5) required an increase in the metabolism factor coupled with a decrease in distribution for the least squares fit to the data. Subjects with a relatively high plasma concentration at 2 h (Table 2: 1,2,3,6) required a non zero value for the tablet dissolution time. Subject 6, the only female, with the lowest weight in the group, had much the highest oxprenolol plasma concentrations and required a substantial reduction in the metabolic factor, to half the standard value.

The results in Table 7 for the fitting of the sustained release preparation show that the first release period varies between 3 and 5·8 h while the second period continues for over 18 h for all subjects except 3 who showed a sharp drop in plasma value between 9 and 12 h (Table 3).

Release patterns for the subjects were calculated from the values in Table 7 and are shown in Figs 1 and 2. In the first period when both release processes

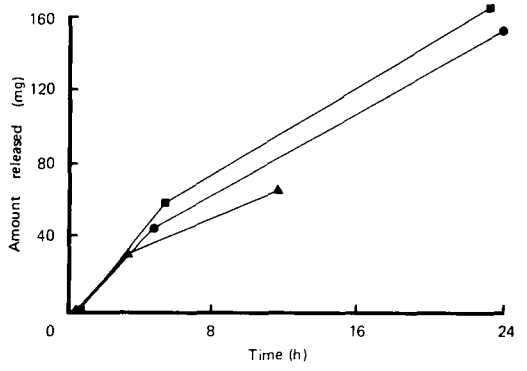

FIG. 1. Release patterns for subjects 1 ■, 2 ●, 3 ▲, based on the results in Table 7.

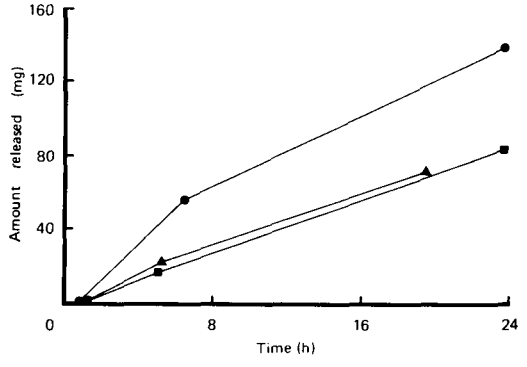

FIG. 2. Release patterns for subjects 4 ■, 5 ●, 6 ▲, based on the results in Table 7.

are running together, subjects 1, 2, 3 and 5 gave estimated rates near to the nominal 10 mg h^{-1} for the sustained release preparation; subjects 4 and 6 were below this. The total release, i.e. the effective dose (ED), is near to the nominal 170 mg for subjects 1 and 2, but is less than half this value for 3, 4 and 6. With the last two subjects, the low value of ED is due to a low overall release rate while with subject 3, it is due to a short second release period.

Pharmacodynamics

The relation between heart rate lowering and plasma concentration for oxprenolol was confirmed to be of

a saturable, E_{max} type by Ingram et al (1983). The data in Table 4 for heart rate fall following the 80 mg tablet, were examined together with the plasma data of Table 2, using simulation, to see if there was any detectable lag between response and plasma level. None was found and it was concluded that the response was in a steady state with plasma levels over the time of the study.

The steady state equation for E_{max} type response

$$E = E_{max}/(1 + K/C_p) \quad (1)$$

was therefore applied directly to the results to evaluate the parameters, E_{max}, the maximum effect and K, the concentration at which the effect is half the maximum value. E is the response (effect), i.e. heart rate fall, in beats min^{-1} and C_p is the plasma concentration in ng ml^{-1}.

The parameters were first evaluated by arranging equation (1) in the reciprocal form,

$$1/E = 1/E_{max} + (K/E_{max})\cdot(1/C_p) \quad (2)$$

and evaluating the linear regression of 1/E on $1/C_p$. With some of the subjects, the points were scattered about the regression line. Therefore a direct least squares calculation was made using equation (1) with the reciprocal regression parameters as starting values.

In Table 8 the direct least squares values of E_{max} and K are given. The values of Q, the sum of squared differences between observed and calculated responses, are for these direct least squares results. The calculations were made with the data from Tables 2 and 4.

Table 8. Pharmacodynamic parameters, 80 mg tablet.

S	Baseline	E_{max}	K	Q
1	155·7	68·5	309·9	80·6
2	145·4	41·5	128·7	0·5
3	147·0	41·8	96·8	16·8
4	146·1	40·9	80·7	16·0
5	158·1	52·2	186·1	3·6
6	158·5	37·4	30·1	47·7
Mean		47·1	138·7	
S.d.		11·6	92·7	

E_{max}, direct least squares values for the estimated maximum heart rate fall in beats min^{-1}; K, direct least squares values for the estimated plasma concentration in ng ml^{-1} at which the response is $E_{max}/2$; Q, sum of squared differences between calculated and observed responses.

For subjects 1, 2, 3 and 4, the results were calculated from the four C_p, E results at 1, 2, 4 and 6 h. With subject 5, inclusion of the 6 h point resulted in a negative intercept in the reciprocal regression, only three points were therefore used in the calculation. With subject 6 the values of C_p and E were relatively high at 9 h and therefore 5 points including this one were used.

The values of E_{max} show a 24·6% inter-individual coefficient of variation while the K values have a coefficient of 71%. The value of K for subject 6 (female) is much less than the others indicating a more rapid onset of saturation. When this value of K is excluded, the coefficient of variation of K for the 5 males is reduced to 57·8%.

The values of E_{max} and K in this study compare with those which we have calculated from the mean data on five subjects reported by Tuckman et al (1977). They determined exercise heart rate fall after dosage with a 160 mg conventional tablet of oxprenolol and with a 160 mg slow release tablet which had a shorter release period than the preparation we have used. The heart rate baseline of Tuckman et al was 140–145 beat min^{-1}, which was lower than the mean baseline in the present study (152). The conventional tablet results gave E_{max} 41·8 beats min^{-1} and K 166 ng ml^{-1}; the slow release tablet gave E_{max} as 42·6 and K as 182. These values compare with the mean for E_{max} in this study of 47·1 and the mean for K of 138·7.

The sustained release preparation gave comparatively uniform responses over a long period (Table 5). When equations (1) and (2) were applied to the results, the apparent E_{max} values were all low and it was concluded that the maximum response was governed by the zero order release process rather than by the saturation of response. The response results of the preparation were therefore examined by using the E_{max} and K values for each subject derived from the 80 mg tablet data. The mean plasma concentrations and mean response values of the preparation over a central time of 2 to 14 h after

Table 9. Pharmacodynamic results after the sustained release preparation.

S	C_m	E_{obs}	E_{cal}	Diff
1	205·6	24·4	27·3	2·9
2	211·6	26·7	25·8	−0·9
3	61·2	15·3	16·2	0·9
4	56·7	15·4	16·9	1·5
5	92·5	22·9	17·3	−5·6
6	205·5	31·7	32·6	0·9
Mean	138·9	22·8	21·9	−0·05
S.d.	76·3	5·8	8·0	2·72
t				−0·05

C_m, mean plasma concentration, 2 to 14 h, in ng ml^{-1}; E_{obs}, mean heart rate lowering, 2 to 14 h, in beat min^{-1}; E_{cal}, mean 2 to 14 h response calculated from C_m and the values of E_{max} and K from Table 8; diff, the difference between E_{cal} and E_{obs}; t is the normal distribution statistic estimated for the difference between the values of diff and zero.

dosing were calculated for each individual. A mean response was then estimated using equation (1), the mean concentration and the E_{max} and K values for each subject from Table 8. The results are summarized in Table 9.

The mean concentration values have a coefficient of variation of 55%. The mean responses follow these concentration variations so that the responses calculated from the concentrations are in reasonably good agreement with the observed mean responses. A paired t-test for the difference between calculated and observed values gives a t value of $-0{\cdot}05$ which is not significant at the $P = 0{\cdot}05$ level ($t = 2{\cdot}57$), consequently it is concluded that the parameters for the response-plasma concentration relation derived from the 80 mg tablet data are applicable to the results for the sustained release preparation.

CONCLUSIONS

Release patterns for oxprenolol from the sustained release preparation may be evaluated, using the conventional tablet data, for each individual by means of the computer simulation model, Macdopex. This method should also be applicable to other drugs and to other sustained release preparations.

The pharmacodynamic results clearly indicate that the response-plasma concentration relation is of the saturable, E_{max} type. The response parameters derived from the conventional tablet results may be used to interpret time mean responses and plasma concentrations following dosing with the prolonged release preparation.

There was no significant correlation between the individual time mean response following the sustained release dose and the maximum observed response of each subject following the 80 mg tablet dose. The inter-individual variation in time mean response to the former dose is therefore due to differences in the uptake of the drug from this preparation.

Three of the six subjects showed a high total absorption of oxprenolol from the Oros preparation spread over 20 h. One subject ceased to absorb after 11 h and the other two subjects showed a low initial rate of uptake giving totals absorbed of less than half the nominal dose. The values of the effective dose absorbed were derived in the least squares fitting; however these results are inherent in the plasma concentration, time data as may be shown by estimating areas under the curves from the results in Tables 2 and 3. The ratios of total AUC for the slow release preparation to total AUC for the tablet with the same subject gave values of 1·75, 2·02, 1·09, 1·16, 1·84 and 0·86 for subjects 1 to 6. The area ratios are relatively high for subjects 1, 2 and 5 while subjects 3, 4 and 6 give lower ratios, in agreement with the effective dose values in Table 7.

The correlation of responses with plasma levels supports the view that the plasma level of oxprenolol is a main factor in determining the effect of the drug.

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