Reproducibility of oxprenolol plasma concentrations in young female volunteers following oral administration of an oxprenolol Oros dosage form

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1 Plasma oxprenolol concentrations were measured in six young healthy female volunteers after single oral dosing with a 16/260 oxprenolol Oros system on three separate occasions. Reproducibility was assessed by comparing individual plasma profiles, areas under the curve, peak concentrations and times to peak.

2 Plasma concentration-time profiles were consistent with an extended duration of drug release from the Oros system. Individual and mean profiles on the three occasions were similar, and no significant differences in mean plasma levels, or derived pharmacokinetic parameters, were detected.

3 The mean amount of drug in eight systems recovered from faeces corresponded to 11% of the dose. Individual amounts were related to the total transit time of the system through the body.

4 The 16/260 Oros system functioned reproducibly within the gastrointestinal tract, and *in vivo* absorption mirrored *in vitro* drug release.

Keywords oxprenolol Oros dosage form plasma concentration reproducibility

Introduction

Studies in healthy volunteers have shown that once-daily dosing with an oxprenolol Oros system (Theeuwes *et al.*, 1985) produces satisfactory plasma concentrations over most of the 24-h period (Woods *et al.*, 1985). The reproducibility of *in vivo* release, however, has not been assessed for these formulations.

The transit times of solid dosage forms such as Oros through the small intestine are relatively short, and most of the drug is released in the colon. Some drugs exhibit poor and unpredictable colonic absorption (Schanker, 1959) while others undergo extensive metabolism by bacteria within the lumen. Drug availability in such situations will be determined by the transit times of the system in each gut segment. Of the many physiological factors affecting absorption, transit times probably represent the greatest single source of variation (Cummings *et al.*, 1976).

For some formulations *in vivo* drug dissolution is influenced by physiological factors within the gut, although this is unlikely to occur with Oros since the semipermeable membrane surrounding the core permits only the passage of water into the unit, effectively isolating the dissolution process from the luminal environment. Identical *in vitro* dissolution rates have been obtained in simulated gastric and intestinal fluid with Oros systems (Theeuwes *et al.*, 1985), but the possibility of *in vivo* differences cannot be excluded.

In view of these potential difficulties it is obviously important to know if the plasma concentration-time profile after Oros administration can be regularly reproduced. It has recently been shown that significant within-subject variability occurs even with the conventional rapid-release formulation of oxprenolol (Jack *et al.*, 1982); both the duration and

location of drug release within the gut may be contributing factors to greater variability with the Oros dosage form.

Methods

Subjects

Six healthy young female volunteers were recruited and all were shown to have normal haematological and biochemical profiles immediately before starting the study. The nature and purpose of the investigation was explained to each, and written consent obtained. The protocol described to them had been approved by the Central Birmingham Health District Research Committee. None of the volunteers smoked but two (subjects 2 and 4) were regularly taking a low-dose combined oestrogen-ethinyloestradiol oral contraceptive pill and continued to do so throughout the study. With this exception, no drugs other than oxprenolol were taken. The volunteers had a mean age of 21.7 (s.d. 1.0 years), weight of 61.8 (s.d. 2.8) kg and body surface area of 1.71 (s.d. 0.07) m².

Procedure

The volunteers attended on three occasions separated by intervals of at least 1 week. Single doses of oxprenolol in the form of a 16/260 Oros system were administered and an identical procedure was followed on each occasion. The volunteers were required to fast overnight and to empty their bowels before arriving at the unit. A cannula was then inserted into a suitable forearm vein and connected via a three-way tap to an intravenous giving set, kept patent by slow infusion of physiological saline. At approximately 9 a.m. a 10 ml blood sample was taken before the Oros preparation was administered orally with 100 ml of water. Further blood samples were withdrawn 0.5, 1, 2, 3, 4, 6, 8, 13, 20, 24, 28 and 32 h after dosing. Plasma was separated by centrifugation and stored at -20°C until analysed. The subjects remained supine for the first 8 h, the intravenous cannula was then removed and the subjects were allowed up; subsequent blood samples were collected by venepuncture. Non-alcoholic drinks were allowed at 2 and 4 h, and lunch was given 4 h after dosing. All subjects were required to maintain their normal dietary habits throughout the study period.

Subjects were requested to examine their stools and several were able to retrieve the excreted Oros system; this was then analysed to determine the amount of drug retained.

Oxprenolol plasma concentrations were measured by a gas-chromatographic method (Jack *et al.*, 1982). The assay was estimated to have a lower limit of quantitation of 10 ng/ml and a coefficient of variation of 7% at a concentration of 100 ng/ml. Plasma concentrations were reported as the hydrochloride salt.

Data analysis

The areas under the plasma concentration-time curves between 0 and 32 h (AUC) were estimated using the trapezoidal rule; total areas were not calculated since the terminal elimination rates could not be determined from the available data. Coefficients of variation (CV) were calculated by using the relationship: $CV = 100 \times \text{s.d.}/\text{mean}$.

Within-subject variability was assessed by calculating the CV of the AUC and peak concentration ($C_{\max}$) values obtained on each of the three study days. Between-subject variability was assessed by calculating the corresponding CV values for the data on the first study day only. Individual differences in the plasma oxprenolol profiles were examined for statistical significance by using a repeated-measures analysis of variance approach. Differences between AUC, $C_{\max}$, and times to peak ($t_{\max}$) were examined by Friedman's rank sum test with tied ranks.

Results

Individual oxprenolol plasma concentrations and AUC values derived from these data are presented in Table 1. Mean concentrations and their s.d. and CV, together with the minimum and maximum values at each time point, are given in Table 2.

Individual plasma profiles exhibited a short initial delay of approximately 1 h before plasma concentrations gradually increased to reach a peak at around 6 h after dosing. The decline from peak was slow, and mean plasma concentrations of 114, 173 and 173 ng/ml, respectively, were observed at 24 h after dosing on the three study days. Measurable plasma concentrations of the drug were maintained for at least 32 h in all but one case (subject 1, day 3).

Individual profiles generally followed the same time course even to the extent of exhibiting secondary peaks at roughly similar times (12 h) after dosing. No statistically significant differences between Oros profiles on the three days were identified in the repeated-measures analysis of variance, the *F*-probability value being 0.288.

Table 1 Plasma oxprenolol concentrations (ng/ml), calculated as the hydrochloride, and AUC values (ng ml⁻¹ h) following separate oral administration of 16/260 oxprenolol Oros to six female volunteers on three occasions (a, b and c).

Subject	0	0.5	1	2	3	4	6	8	13	20	24	28	32	AUC ³²	Mean _{AUC}	CV _(AUC)
a	< 10	< 10	10	133	184	207	247	200	231	122	64	42	50	4410		
1 b	< 10	< 10	19	128	229	302	268	297	422	69	58	50	33	5809	4829	17.6
c	< 10	< 10	< 10	138	228	293	278	191	280	39	39	47	< 10	4268		
a	< 10	< 10	18	62	420	530	220	302	428	261	218	NS	91	8465		
2 b	< 10	< 10	< 10	240	475	516	650	443	463	NS	351	NS	66	11647	9759	17.1
c	< 10	< 10	18	283	320	402	435	272	261	NS	337	NS	191	9166		
a	< 10	< 10	36	315	572	680	392	480	476	228	173	122	70	9828		
3 b	< 10	< 10	28	133	464	628	450	317	345	NS	207	134	80	8593	8699	12.4
c	< 10	< 10	17	74	318	418	330	300	416	200	156	138	82	7677		
a	< 10	< 10	25	157	395	450	325	390	228	197	88	NS	11	6286		
4 b	< 10	< 10	29	193	229	319	385	413	227	NS	105	NS	64	6212	6630	10.0
c	< 10	< 10	15	64	259	233	259	330	299	NS	248	NS	70	7391		
a	< 10	< 10	24	91	155	203	100	113	120	83	65	NS	35	2870		
5 b	< 10	12	18	42	153	205	257	130	390	NS	132	NS	22	5948	3892	45.8
c	< 10	< 10	38	NS	78	169	182	129	78	66	107	NS	39	2857		
a	< 10	< 10	23	149	187	375	238	161	188	106	78	93	59	4468		
6 b	< 10	< 10	10	77	140	295	263	178	279	138	187	129	96	5705	5621	19.8
c	< 10	< 10	20	68	245	428	231	168	427	156	153	117	85	6690		

NS = No sample

Table 2 Comparison of plasma concentration-time data after single dosing with 16/260 oxprenolol Oros on three separate occasions

		Time after dosing (h)												
		0	0.5	1	2	3	4	6	8	13	20	24	28	32
First occasion	Mean	0	0	23	151	319	408	254	278	279	166	114	85	53
	s.d.	0	0	9	88	169	187	99	142	141	72	65	46	28
	CV%	—	—	39	58	53	46	39	52	51	43	57	54	53
	Max	0	0	36	315	572	680	392	480	476	261	218	155	91
	Min	0	0	10	62	155	203	100	113	120	83	64	42	11
Second occasion	Mean	0	2	17	136	282	378	380	296	354	205	173	114	60
	s.d.	0	5	11	73	150	160	155	124	89	114	103	56	28
	CV%	—	250	65	54	53	42	41	42	25	56	60	49	47
	Max	0	12	29	240	475	628	650	443	463	393	351	208	96
	Min	0	0	0	42	140	205	257	130	227	69	58	50	22
Third occasion	Mean	0	0	18	114	241	324	286	232	294	175	173	133	78
	s.d.	0	0	12	88	89	109	88	80	127	111	105	76	64
	CV%	—	—	67	77	37	34	31	34	43	63	61	57	82
	Max	0	0	38	283	320	428	435	330	427	267	337	263	191
	Min	0	0	0	57	78	169	182	129	78	39	39	47	0

Values below limit of quantitation (10 ng/ml) taken as 0.

The mean AUC values on the three occasions were 6054, 7319 and 6341 ng ml⁻¹ h respectively. Individual areas covered a similar range and the differences between study days were not statistically different ($P = 0.740$). With one exception, the within-subject CVs over the 3 days were less than 20%; individual CVs ranged from 10–45.8% with a mean of 20.5%. Only in the case of subject 5 was a clear difference between the single-dose profiles observed but this was almost entirely due to a single high plasma concentration 13 h after dosing on the second occasion.

There was an approximately 3.5-fold difference between the lowest and highest AUCs for

the six individuals on the first occasion, and the mean between-subject CV was 44%.

Similar $C_{\max}$ values were obtained on each of the three occasions when Oros was administered, the mean values being 414, 466 and 347 ng/ml, respectively. These differences were not statistically significant ($P = 0.430$). The within-subject CVs ranged from 15.5–44.3% with a mean of 25.1%. Peak values on the first study day showed an approximately 3.5-fold variation in individual values, and higher between- than within-subject CVs were again observed (43% compared with 25.1%).

$t_{\max}$ values showed greater variability than AUC or $C_{\max}$ values largely because minor fluctuations in plasma concentrations between 5 and 15 h after dosing produce considerable differences in $t_{\max}$ values. The medians on the three occasions were 4, 7 and 5 h, respectively. The greater value on the second occasion resulted from secondary peaks at 13 h after dosing in two individuals (subjects 1 and 5). The differences between study days were not statistically significant.

The total gut transit times of the eight systems recovered from faeces ranged from 23 to 37.5 h with a median time of 30 h (Table 3). The variations in the amounts of drug recovered, and in transit times, were similar on the three study days.

All the volunteers successfully completed the study and there were no significant deviations from the study protocol. Oros treatment was well tolerated and no side-effects were reported.

Table 3 Actual and theoretical percentages of administered doses recovered in expelled systems, and total transit times (h)

Subjects	Days	Percentage of dose		Transit time (h)
		Actual	Theoretical*	
1	1	12.8	8.6	27.5
	2	5.4	4.8	37.5
	3	13.2	8.0	26.5
2	2	4.5	4.3	36.3
	3	12.4	8.5	28.0
3	2	6.2	5.0	34.7
	3	14.9	11.3	23.0
4	3	13.2	6.0	32.0

*Estimated by extrapolation of the *in vitro* release profile for 16/260 Oros.

Discussion

The plasma concentration-time profiles in this study showed a time dependency which was consistent with an extended duration of drug release from the Oros system. Plasma concentrations were maintained above the detection limit of the assay for 32 h after dosing in all but one case. There was no indication from the rate of decline in plasma levels after the peak that drug delivery from any of the Oros systems ceased prematurely.

Individual plasma levels in this study were generally higher than those previously reported (Woods *et al.*, 1985; Bennett *et al.*, 1985) for reasons which are not immediately apparent. The only difference between this and other studies was that female rather than male volunteers were investigated, but existing data on oxprenolol do not suggest any sex differences in the drug's pharmacokinetics (Jack *et al.*, 1982) or that related factors such as body weight influence plasma concentrations. No significant differences were observed between plasma profiles for the volunteers taking the oral contraceptive pill compared with those who were drug-free.

Within-subject variability

The mean plasma profiles for the six subjects after single dosing with the Oros system on three occasions were similar, and no statistically significant differences in any pharmacokinetic parameters were observed. Individual profiles showed little within-subject variability, although some irregularities in profile shape were noted. For both AUC and $C_{\max}$ values, the variability within subjects was considerably smaller than that between subjects, the CVs being, respectively, 20.5 and 25.1% (within) compared with 44 and 43% (between).

The small within-subject differences in oxprenolol AUC values in the present study compare favourably with those reported for conventional 80 mg film-coated tablet (Jack *et*

al., 1982). In that study three female subjects taking oral contraceptives had CVs of 12.7, 31.3 and 39.4%, while a control group of three drug-free female subjects had values of 6.4, 9.8 and 11.0%. In the same study the range of individual CVs for other β -adrenoceptor blockers was: 9–24%, metoprolol; 14–41%, propranolol; and 2–14%, acebutolol.

Between-subject variability

The between-subject CV for AUC values in the present study (44%) was marginally greater than that previously reported for conventional 80 mg tablets but similar to that for Slow Trasicor, the polymer-matrix slow-release formulation (Woods *et al.*, 1985). The small numbers of subjects involved in these studies, however, do not permit any conclusions to be drawn concerning differences between oxprenolol formulations.

In vivo drug release

The fraction of the dose remaining in the eight recovered Oros systems showed that the percentage released was consistently high, the mean being 89.7%. Where systems were recovered on more than one occasion by individual volunteers, a clear relationship existed between the amount of drug remaining and the total transit (residence) time of the system in the body. Generally, there was reasonable agreement between actual amounts recovered and those predicted from the *in vitro* release profile.

In conclusion, the 16/260 oxprenolol Oros system performed reproducibly and maintained plasma concentrations over 24 h sufficient to provide significant levels of β -adrenoceptor blockade. Within-subject variability was low, and between-subject variability compared well with that for existing oxprenolol formulations.

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