Oros controlled-release formulations of metoprolol: an approach to the development of a system for once daily administration

W. GOOD¹, L. J. LEESON¹, S. L. ZAK¹, W. E. WAGNER¹, J. B. MEEKER¹ & J. D. ARNOLD²

¹Ciba-Geigy Corporation, Development Department, Pharmaceuticals Division, Summit, New Jersey, and

²Quincy Research Center, Kansas City, Missouri, USA.

1 A combined biopharmaceutical and haemodynamic approach to the development of a metoprolol Oros controlled-release delivery system for once daily administration is reported.

2 Two studies, each involving 18 healthy volunteers, were performed in which twice daily administration of 100 mg conventional metoprolol tartrate tablets was compared with once daily administration of Oros systems containing 190 mg metoprolol fumarate but with different drug release rates. Plasma drug concentrations and β -adrenoceptor blocking effects were measured over 24 h on days 1 and 5 of each treatment, and pre-dose in the interval between the main study days.

3 The results of the first study with a 19 mg/h Oros system indicated that this rate was too rapid to provide the required response under steady-state dosing conditions. Theoretical calculations based on a one-compartment pharmacokinetic model and input functions for hypothetical Oros systems were then performed to define the optimal release rate for a once daily preparation.

4 The results of the second study confirmed that a 14 mg/h system possessed the required characteristics in that it maintained more uniform β -adrenoceptor blockade throughout 24 h, and produced pre-dosing plasma concentrations and haemodynamic effects which were identical to those for the conventional tablet twice daily regimen.

Keywords metoprolol Oros formulation plasma concentrations repeated dosing

Introduction

Metoprolol is a β_1 -selective adrenoceptor antagonist which exhibits a moderately short plasma elimination half-life of 2–4 h (Regårdh *et al.*, 1974). Its biopharmaceutical behaviour is fairly complex in that it undergoes substantial first-pass metabolism after oral dosing yielding mainly a ring hydroxylated compound which has little β -adrenoceptor blocking activity (Johnsson & Regårdh, 1976). Absorption of the drug throughout most of the gastrointestinal tract is rapid and complete (Johnsson *et al.*, 1975; Regårdh *et al.*, 1975). Although single-dose proportionality has been demonstrated in the range 50–200 mg (Kendall *et al.*, 1977), higher

bioavailability is obtained after multiple compared with single oral dosing, and changes in clearance may occur as a result of altered elimination and distribution volume (Kendall *et al.*, 1980). Interindividual differences in plasma concentrations, clearance and area under the plasma concentration-time curve can also be substantial within a given population (Quarterman *et al.*, 1979), apparently due to genetically-determined metabolic differences (Lennard *et al.*, 1982).

All of these factors are challenges to the rational development of a controlled-release metoprolol formulation. Fortunately, a well-defined relationship between plasma concentra-

tion and attenuation of exercise tachycardia (as a measure of β -adrenoceptor blockade) exists for this drug (Kendall *et al.*, 1977; McDevitt, 1977; Harron *et al.*, 1981). We have, therefore, approached the development of an Oros controlled-rate delivery system for metoprolol on haemodynamic as well as direct biopharmaceutical principles. The objective of the work described here was to design a system for once daily administration which would provide a degree of β -adrenoceptor blockade, at the dosing points, equivalent to that produced by 100 mg rapid-release conventional tablets administered twice daily.

Methods

Dosage forms

Commercially available tablets containing 100 mg metoprolol tartrate were used as control formulations in the studies reported here. Oros systems were prepared by air-suspension coating and laser drilling techniques. General descriptions of the design and mechanism of drug release have been given elsewhere (Theeuwes, 1975). Each Oros system contained 190 mg of metoprolol fumarate (equivalent to 200 mg metoprolol tartrate) and was designed to deliver either 19 mg/h (19/190 Oros) or 14 mg/h (14/190 Oros) during its steady-state release phase.

In vitro release rates

The dissolution of conventional tablets, and release rates for Oros systems, were determined in a standard USP rotating basket apparatus in simulated gastric fluid at 37.5°C and 50 rev/min, using ultraviolet spectrophotometry as the detection method. The *in vitro* release rates for the 19/190 and 14/190 Oros systems are compared in Figure 6.

Plasma analysis

Plasma samples were extracted with ethyl acetate/toluene, derivatized, and metoprolol concentration determined by gas chromatography using propranolol as internal standard. Calibration of the assay method was accomplished during the course of the analysis by running a series of spiked plasma standards along with the study samples. The assay was capable of detecting drug at concentrations below 5 ng/ml, and the calibration curves were linear in the range 10–200 ng/ml.

Clinical methods

A total of 36 healthy male volunteers aged 18–45 years gave informed consent, and participated in one of two studies. Before being accepted, each subject underwent a physical examination, the medical history was updated, an electrocardiogram was recorded, pulmonary function was evaluated using a Wright peak flow meter, and clinical laboratory parameters were measured. A urine sample was also tested for drugs of abuse.

In each study, 18 subjects were randomized into a crossover design and were subjected to an initial 3 day conditioning period during which time they exercised on a bicycle ergometer three times daily to determine the loads necessary to produce an exercise tachycardia equal to 85% of a theoretical maximum at the end of a 3 min test procedure. These individual workloads were then used during the rest of the study. All heart rates were estimated from electrocardiographic tracings.

In study 1, each subject received 5 days' treatment with a 100 mg conventional metoprolol tablet twice daily, and a 19/190 Oros preparation once daily, on separate occasions. A 9 day drug-free interval elapsed between treatments which were administered in random order according to a pre-determined sequence. Plasma drug concentrations and β -adrenoceptor blocking effects were measured over 24 h on days 1 and 5, and immediately before dosing on day 4 of each treatment.

On the morning of the study day, a blood sample was drawn and an exercise test performed following which each subject received his medication according to the treatment sequence. No food or liquid other than water was permitted for 12 h before drug administration. Breakfast was provided immediately after the morning dose, lunch at 5 h, dinner at 10 h and a snack at 15 h. All meals were caffeine-free and standardized throughout the course of the study. Caffeine-free drinks were permitted at any time during the study period. The volunteers were not allowed to rest supine for 4 h after dosing.

Blood samples were collected into 7 ml heparinized vacuum tubes at 1, 2, 3, 4, 6, 8, 10, 12, 13, 14, 16, 20 and 24 h on days 1 and 5, and immediately before dosing on day 4. The samples were centrifuged, and the plasma separated and frozen until analysed.

The standardized exercise tests were performed at 2, 4, 6, 12, 16 and 24 h on days 1 and 5, and at 0 h on day 4 using the appropriate individual workloads.

Study 2 with the 14/190 Oros system was performed in a similar manner, except that a

placebo period was added to the protocol, and the study was conducted as a double-blind, double-dummy crossover. An additional assessment at 0 h on day 3 was also included. The same conventional tablet regimen was used as in the first study.

Since the results of the first study led directly to the development of the 14 mg/h Oros system, the procedure for defining the optimal release rate for a once daily preparation will be described after the results from this study are presented.

Results from study 1 (metoprolol Oros 19/190)

Plasma concentrations

The mean plasma concentration/time profiles for the Oros and conventional tablet regimens on days 1 and 5 are shown in Figure 1. The plasma concentrations showed considerable intersubject variability on both study days regardless of the dosage form administered.

Figure 1 Mean plasma concentrations ($\pm$ s.e. mean) of metoprolol during days 1 and 5 of dosing with 100 mg conventional metoprolol tartrate tablets every 12 h (●) and 190 mg metoprolol fumarate (equivalent to 200 mg tartrate) once daily in the form of a 19/190 Oros system designed to release drug initially at 19 mg/h (○).

Analysis of the conventional tablet data using the Wagner-Nelson method (Wagner, 1974) indicated that metoprolol pharmacokinetics could be described by a single compartment model for virtually all subjects, irrespective of whether they exhibited large or small areas under the curve. In all but four cases, total clearance on day 1 increased for the second compared with the first conventional dose. Interestingly, the elimination rate constants determined from the terminal phases of the two plasma profiles showed only a slight reduction, suggesting a significant increase in apparent volume of distribution between the morning and evening dose. The steady-state clearance values on day 5 were only slightly smaller than those for the first dose on day 1, but no differences between the two daily doses were observed. Elimination rate constants on day 5 showed only marginal differences between doses, and in contrast to day 1, volumes of distribution were unchanged. Clearance values and pharmacokinetic parameters on both study days are given in Table 1.

The mean plasma concentration-time profiles after once-daily dosing with the 19/190 Oros system (Figure 1) were as expected for a dosage form with an extended *in vitro* drug delivery. Deconvoluting the Oros plasma concentration data on days 1 and 5 according to the equation:

$$F = \frac{[C_t + (k_a + k_e)C_t]}{A k_a k_e} + \frac{1}{A} C_0 C_t dt$$

gave the mean apparent cumulative *in vivo* delivery profiles shown in Figure 2. In this expression, F is the fraction of drug reaching the systemic circulation and A is area under the plasma curve, while C_t and C'_t are plasma concentration and rate of change of plasma concentration, respectively. The rate constants, k_a and k_e , were determined from individual data for the first conventional dose on the respective treatment days. Areas under the plasma concentration curves, calculated by the trapezoidal method, are given in Table 2.

Exercise tachycardia

The reductions in exercise tachycardia due to metoprolol were generally in the range 10–15% of baseline values. Figure 3 shows the exercise heart rate profiles for the conventional and 19/190 Oros regimens on days 1 and 5. In both cases, haemodynamic effects closely mirrored the plasma concentrations. A comparison of the heart rate reductions at 24 h after dosing on days 1, 3, 4 and 5 (Figure 4), revealed that once daily dosing with 19/190 Oros just failed to produce comparable effects to those for the conventional tablet regimen. Significantly greater β -adreno-

Table 1 Pharmacokinetic parameters calculated for 18 subjects in study 1 given metoprolol 100 mg in conventional tablets twice daily for 5 days

	Dose 1 (morning)				Dose 2 (evening)			
	k_a (h^{-1})	k_e (h^{-1})	V_d (l)	CL (l/h)	k_a (h^{-1})	k_e (h^{-1})	V_d (l)	CL (l/h)
<i>Day 1</i>								
Mean	1.90	0.252	495	130	1.51	0.200	835	174
s.e. mean	0.67	0.018	73	23	0.33	0.019	124	33
Range								
Max	>10	0.473	1366	369	>10	0.451	2293	478
Min	0.82	0.106	230	27	0.23	0.062	344	35
<i>Day 5</i>								
Mean	1.34	0.215	453	103	1.07	0.172	591	107
s.e. mean	0.26	0.012	51	16	0.11	0.009	72	16
Range								
Max	5.26	0.274	979	270	>10	0.250	1218	227
Min	0.41	0.096	203	32	0.37	0.087	210	28

Figure 2 Apparent *in vivo* delivery profiles for metoprolol Oros 19/190 system on day 1 (●) and day 5 (○). Data obtained by deconvolution of mean plasma concentrations from study 1.

ceptor blockade ($P < 0.05$) was achieved with the latter treatment on days 3 and 4; on day 5, the differences between regimens were just below the level of significance ($P < 0.12$). These results indicate that release from the 19/190 Oros system is too rapid to provide the required haemodynamic and plasma level responses during repeated dosing.

Optimization of Oros release rate

Optimizing the performance of a once-daily Oros system for metoprolol requires the selection of a release rate which is sufficiently slow to produce the necessary plasma concentrations and haemodynamic effects at 24 h after dosing, while not significantly reducing the amount of drug reaching the circulation as a result of increased metabolic clearance with low rates of drug delivery. The procedure adopted in the

Table 2 Comparison of areas under the plasma time-concentration curve ($ng\ ml^{-1}\ h$) for conventional 100 mg tablets administered twice daily and for the metoprolol Oros 19/190 system given once daily for 5 days

	Day 1		Day 5	
	Conventional 100 mg tablet	19/190 metoprolol Oros	Conventional 100 mg tablet	19/190 metoprolol Oros
Mean	2031	1159	2758	1979
s.e. mean	319	196	401	411
Range				
Max	5699	3983	7173	7418
Min	462	297	957	309
Ratio ($\pm$ s.e. mean)				
Oros: conventional	$60.1 \pm 4.4\%$		$68.2 \pm 5.9\%$

Figure 3 Comparison of heart rate ($\pm$ s.e. mean) in response to standardized exercise during days 1 and 5 for 100 mg conventional metoprolol tablets administered every 12 h ($\bullet$) and for the Oros 19/190 systems ($\circ$) administered once daily. The broken lines show baseline rates found during the conditioning period.

Figure 4 Comparison of change in exercise tachycardia at the 24 h dosing points between 100 mg metoprolol tartrate every 12 h in conventional tablets (hatched) and the Oros system (solid) designed to deliver 19 mg/h and 14 mg/h metoprolol fumarate once daily. Significant differences ($P < 0.05$) are indicated by an asterisk.

present investigation is described in the following sections.

The release rate profile for the Oros system was characterized by two rate equations; a theoretical treatment has been published elsewhere (Theeuwes, 1975), but a more pragmatic approach was followed in our analysis. The *in vitro* release profile was considered to consist of several phases: first, a phase of increasing release rate after a time lag associated with water initially penetrating the semipermeable membrane; second, an extended period of constant-rate drug delivery once water flux has achieved equilibrium; and, third, a phase of decreasing rate as the core concentration falls below saturation. In the case of metoprolol Oros, the initial time delay can be ignored, and for times such that $0 \leq t \leq t_z$, the drug delivery rate is constant. For times $t \geq t_z$, the release rate can be adequately characterized as a decreasing first-order process. The overall release function can therefore be expressed as:

$$Q_t = kt, \quad Q \leq t \leq t_z$$

$$Q_t = Q_\infty - (Q_\infty - kt_z)e^{-k_1(t-t_z)}, \quad t \geq t_z$$

where Q_t and Q_∞ represent the amount of drug delivered at time t and infinity, respectively, k characterizes the constant release phase, and t_z is the time at which saturation in the core is lost (i.e. after approximately 70% of the drug content has been delivered). The rate constant k_1 characterizes the first-order release phase beyond time t_z , and $\tau = t - t_z$.

The above equations were then used as input functions to a one-compartment pharmacokinetic model and theoretical concentrations at steady-state dosing points were calculated for hypothetical Oros systems having nominal release rates of 10–20 mg/h of the tartrate salt. These values were compared with the measured concentrations for the conventional tablet twice-daily regimen, and the most appropriate release rate for an Oros system selected. The parameters

Table 3 Pharmacokinetic parameters calculated from the mean plasma concentrations on the fifth day of dosing with the 100 mg conventional tablet

	Dose 1 (morning)	Dose 2 (evening)
k_a (h^{-1})	1.421	1.086
k_e (h^{-1})	0.1858	0.1439
V_d (l)	393.5	492.2

of the pharmacokinetic model used in this analysis were estimated from the mean plasma concentration data for the conventional doses on day 5 of study 1; k_a , k_e and V_d values were calculated for each dose separately and then averaged. These constants are given in Table 3.

Figure 5 presents the outcome of this optimization procedure. The arrow on the curve indicates the release rate for Oros which should produce pre-dosing plasma concentrations at steady-state equivalent to those for the conventional tablet regimen. This value corresponded to 14.1 mg/h for metoprolol tartrate or 13.4 mg/h for metoprolol fumarate. A release rate of 14 mg/h metoprolol fumarate was finally selected, and the drug delivery characteristics of the 190 mg Oros system modified accordingly. The *in vitro* release profile for the 14/190 Oros system is compared with that for the original 19/190 form in Figure 6.

Results of study 2 (metoprolol Oros 14/190)

Plasma concentrations

The 18 subjects in this study exhibited the same

Figure 5 Calculated plasma concentrations expected at the once daily dosing points for Oros systems with the nominal linear delivery rates shown. The arrow indicates the release rate expected to provide foot-point concentrations equivalent to conventional tablet dosing at 100 mg every 12 h. **Figure 6** *In vitro* release profiles ($\pm$ s.e. mean) for Oros systems designed to deliver 19 mg/h ($\bullet$) and 14 mg/h ($\circ$) of metoprolol fumarate. Total dose in both cases is 190 mg.

pattern of pharmacokinetic behaviour with respect to metoprolol as the subjects in study 1. Clearance differences between single-dose and steady-state conditions, and changes in elimination rate constants between two doses on the same day, were again observed in this second study.

In Figure 7, mean plasma concentrations for the conventional and 14/190 Oros regimens on days 1 and 5 are compared. The mean concentrations for both dosage forms were slightly smaller in this study compared with study 1, indicating a somewhat larger clearance in the second group of subjects. However, a comparison of the relative profiles for the conventional and Oros regimens in the two studies indicated a longer duration of constant-rate drug delivery for the 14/190 compared with the 19/190 Oros preparation. In Figure 8 the results of deconvoluting the mean plasma concentration profile for 14/190 Oros, using the same analytical procedure as in study 1, is compared with that obtained for the 19 mg/h system. The slopes of the linear portions of these curves are in a 1.33:1 ratio, closely reflecting the 19:14 ratio for *in vitro* rates of release from the two systems. In each case, the durations of *in vivo* and *in vitro* constant-rate delivery were also similar. There was a short *in vivo* time lag associated with both dosage forms, the mean durations being 0.5 and 1.0 h for the 19 and 14 mg/h systems, respectively.

Areas under the curves at steady-state were determined for the conventional tablet and 14/190 Oros system from the plasma concentration data on day 5 (Table 4). The mean apparent systemic availability of metoprolol from the 14/190 system was estimated to be 62.3% of that from the conventional tablet. This was smaller

Figure 7 Comparison of metoprolol plasma concentrations ($\pm$ s.e. mean) produced by conventional tablets, 100 mg every 12 h ($\bullet$), and by the Oros 14 mg/h system ($\circ$), once daily, on days 1 and 5 of dosing in study 2.

than that found for the 19 mg/h system in study 1 (68.2%), but a statistical analysis using the mean t test comparison failed to identify any significant differences between Oros dosage forms ($P = 0.14$). Even a comparison of individual relative

Figure 8 Comparison of apparent day 1 *in vivo* delivery profiles for the Oros 14 mg/h system ($\circ$) with the 19 mg/h system ($\bullet$). The former data represent a deconvolution calculation from mean plasma concentrations obtained in study 2 while the latter data came from study 1. The linear portions are drawn as the best linear regression fit to the data.

bioavailabilities in the separate studies did not produce a statistically significant result ($P = 0.20$). While drug delivery rate may be a significant factor with regard to overall systemic availability, interindividual variability in the present studies was too great to permit confirmation of such a delivery-rate effect. Despite this possible limitation on the availability of the drug, once-daily dosing with the 14 mg/h system produced pre-dosing plasma concentrations at steady state which were equivalent to those for twice daily administration of 100 mg conventional tablets.

Exercise tachycardia

As in study 1, heart rate responses to exercise mirrored the plasma concentrations of the drug.

Table 4 Comparison of areas under the curve ($\text{ng ml}^{-1} \text{ h}$) on the fifth day of dosing with either 100 mg conventional metoprolol tablets twice daily or metoprolol Oros 14/190 once daily

	Conventional tablet (0–12 h)	14/190 Oros (0–24 h)
Mean	2345	1459
	(n = 16)	(n = 17)
s.e. mean	333	211
Range		
Max	5630	2863
Min	843	301
Ratio (s.e. mean)		
Oros: conventional	62.3 $\pm$ 4.6%

Figure 9 Comparison of heart rates ($\pm$ s.e. mean) in response to standardized exercise during days 1 and 5 of study 2. $\bullet$ = data from 100 mg tablets administered every 12 h; $\circ$ = data from administration of the Oros 14 mg/h system once daily. The broken lines represent baseline rates during the placebo period.

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Exercise heart rates for the conventional tablet and Oros dosage regimens on days 1 and 5, are compared in Figure 9. As expected, the longer duration of drug delivery from the 14/190 system produced a more uniform level of β -adrenoceptor blockade over its dosing interval. A comparison of heart rate reductions at the 24 h dosing points (Figure 4) also showed that the differences between Oros and conventional dosage regimens were minor, and not statistically significant.

Conclusion

In conclusion, despite the highly variable behaviour of metoprolol with respect to its pharmacokinetics in different individuals, it has been possible to design a controlled-release system which has a sound basis in terms of pharmacodynamic needs. Because the release characteristics of an Oros system can be finely adjusted to provide specific and reproducible drug delivery profiles, we have gained confidence in our ability to predict the biopharmaceutical and haemodynamic outcome of appropriately designed systems. Therefore, it is possible to construct therapeutically rational dosing regimens with minimal repetition during the development process. This approach to the design of new dosage forms will probably become more routine for many drugs in the future.