Br. J. clin. Pharmac. (1985), **20**, 387–391

Comparison of two slow-release formulations of metoprolol with conventional metoprolol and atenolol in hypertensive patients

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1 We have compared the β-adrenoceptor blocking and antihypertensive effects of chronic once daily treatment with conventional metoprolol 200 mg, two 'long-acting' formulations of metoprolol 200 mg and atenolol 100 mg in a cross-over study in 12 hypertensive patients concurrently receiving diuretic therapy.

2 The peak effects of all compounds were similar, with significant reductions in exercise heart rate and blood pressure.

3 Twenty-four hours after dosing only atenolol treatment was consistently associated with a reduction in both exercise heart rate ($P < 0.001$) and blood pressure ($P < 0.02$) when compared with placebo.

4 Once daily treatment of hypertension with metoprolol, even in 'long-acting' formulations, cannot be recommended because of waning antihypertensive effect which would be missed at routine clinic attendance. Metoprolol should be prescribed twice daily in hypertension. So-called long-acting formulations do not always confer benefits over conventional dose forms.

Keywords metoprolol long-acting metoprolol atenolol β-adrenoceptor blockade hypertension

Introduction

Metoprolol is usually prescribed twice daily because its β-adrenoceptor-blocking effect may not be sustained over 24 h after once daily dosing (Reybrouck *et al.*, 1978; Quarterman *et al.*, 1979). This is in keeping with a short plasma half-life of 3 h (Johnsson *et al.*, 1975). Two slow-release formulations of metoprolol are now available, namely film-coated metoprolol SR (Lopressor, Geigy) and metoprolol SA durules (Betaloc, Astra). These once daily preparations might be valuable if their β-adrenoceptor blocking or antihypertensive profiles are superior to those of the same dose of conventional metoprolol administered once daily. However, previous studies in healthy volunteers have shown that at 24 h metoprolol SR may not confer greater β-adrenoceptor blockade than conventional metoprolol (Quarterman *et al.*, 1979; Freestone *et al.*, 1982a). In contrast metoprolol SA has been evaluated in hypertensive patients and was shown to exert significant β-adrenocepter blocking and antihypertensive effects 24 h after dosing (Wilcox & Hampton, 1981). Unfortunately, the effects of the same dose of conventional metoprolol were not compared. In this chronic dosing study we have compared the β-adrenoceptor blocking and antihypertensive effects of once daily treatment with each of the three formulations of metoprolol (200 mg) and atenolol (100 mg). The β-adrenoceptor blocking

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and antihypertensive effects of the latter are known to last for at least 24 h (Petrie *et al.*, 1980).

Methods

Patients and protocol

Twelve patients with hypertension controlled by atenolol and a diuretic (bendrofluazide 5 mg daily (n = 9), cyclopenthiazide 0.25 mg daily (n = 2) or spironolactone 50 mg daily) were studied. There were 9 men and 3 women, mean age 54 years (range 35–66 years), mean (s.d.) weight 69.9 (11.3) kg and all had normal renal function (serum creatinine 83–150 μmol l^{-1}). They were randomised to receive first placebo and then four active treatments in balanced cross-over fashion. Criteria for inclusion were systolic blood pressure > 150 or diastolic blood pressure > 90 mm Hg in the placebo phase. The following were taken once daily at approximately 09.00 h.

- Placebo (one tablet identical with non-market image atenolol)
- Atenolol 100 mg (one non-market image tablet)
- Conventional metoprolol 200 mg (two tablets Geigy)
- Film-coated sustained release metoprolol 200 mg (one tablet of Lopressor SR Geigy)
- Sustained action metoprolol durules 200 mg (one tablet Betaloc SA Astra)

The diuretic was continued unchanged throughout the study. Each trial period lasted a month after which patients were seen in a clinical laboratory at 09.00 h. Resting heart rate (5 min supine), blood pressure and exercise heart rate were then measured before and 3.5 h after drug dosing. Each patient was assessed by the same observer who was blind to the regimens. Blood pressure (phase V diastolic) was measured supine (5 min) and standing (1 min) with a Dinamap semi-automated recorder (Silas *et al.*, 1980). The mean of three values was used.

Exercise test

Patients were exercised on a bicycle ergometer for 4 min with incremental work-loads at 1 min intervals. For each patient the work necessary to achieve a heart rate of > 140 beats min^{-1} on placebo had been predetermined. The load was then held constant during the study. Typically the workload used was 50 watts, 100 watts, 125 watts and 150 watts. Exercise systolic blood pressure was measured at 3.5 min using a standard mercury sphygmomanometer. Post-exercise heart rate was measured on a continuous ECG recording and was defined as the mean heart rate calculated from the first four heart beats after stopping exercise. The ECG was read by two observers in minimise errors.

Metoprolol plasma concentrations

To coincide with the 'trough' and 'peak' plasma metoprolol concentrations after the slow release formulations (Freestone *et al.*, 1982a), blood was taken at 24 h and 3.5 h after dosing on all four active phases. Plasma metoprolol concentrations were measured by h.p.l.c. (Lennard & Silas, 1983). The coefficient of variation of the assay was 4.7%.

Oxidation status

Metoprolol metabolism is subject to polymorphism of the debrisoquine type (Lennard *et al.*, 1982, 1983). Therefore oxidation phenotype was determined by measuring the ratio of debrisoquine/4-hydroxydebrisoquine (metabolic ratio) in an 8 h urine collection following a 10 mg single oral dose of debrisoquine (Mahgoub *et al.*, 1977; Lennard *et al.*, 1977).

Statistics

The placebo data did not appear to differ significantly from a normal distribution and the coefficient of skewness was acceptably low at 1.00 for systolic blood pressure and 0.46 for diastolic blood pressure. Analysis of variance was therefore used to assess differences in the effects of various regimens taking into account inter-patient variability and order effects. Significance was taken at $P < 0.05$.

Results

At 3.5 h all regimens were associated with a significant and similar reduction in resting heart rate, exercise heart rate, supine, standing and exercise blood pressure. At 24 h, however, resting and exercise heart rate were significantly lowered only by atenolol ($P < 0.001$) and metoprolol SA ($P < 0.01$) (Table 1). At this time the reduction in heart rate was significantly greater after atenolol than after conventional metoprolol ($P < 0.02$) or metoprolol SR ($P < 0.05$). In contrast to the metoprolol formulations atenolol was always associated with at least a 10% reduction in exercise heart rate 24 h after dosing (range 10–31%). All active treatments lowered blood pressure 24 h after dosing but this was significant only for atenolol.

Treatment with the 'longer-acting' formula-

Table 1 Mean (± s.d.) heart rate, blood pressure and plasma metoprolol concentration in relation to time after dosing

	3.5 h after dose				
	P	*A*	*M*	*B*	*L*
Heart rate (beats min^{-1})					
Supine	77 ± (11)	54 ± (8)***	62 ± (12)**	59 ± (11)***	61 ± (9)**
Exercise	154 ± (20)	105 ± (13)***	110 ± (14)***	112 ± (15)***	110 ± (12)***
Blood pressure (mm Hg)					
Supine	159 ± 15 / 98 10	**140 ± 13 / **85 7	*145 ± 17 / *88 12	**142 ± 13 / **85 7	**142 ± 18 / *88 9
Standing	155 ± 12 / 101 14	**136 ± 15 / ***82 10	**134 ± 17 / **88 11	**138 ± 15 / **86 10	**139 ± 19 / **88 10
Exercise systolic	238 ± (18)	***194 ± (20)	***190 ± (23)	***198 ± (20)	***195 ± (23)
Metoprolol concentration (ng ml^{-1})			249 ± (122)	††172 ± (80)	183 ± (99)

	24 h after dose				
	P	A	M	B	L
Heart rate (beats min^{-1})					
Supine	82 ± (12)	62 ± 9†***	74 ± 15	68 ± 13**	74 ± 14
Exercise	156 ± (18)	128 ± 17†***	148 ± 21	137 ± 23**	144 ± 21
Blood pressure (mmHg)					
Supine	164 ± 16 / 99 13	**147 ± 14 / *89 10	155 ± 16 / 95 14	155 ± 15 / 94 9	153 ± 15 / 91 10
Standing	158 ± 12 / 101 12	*145 ± 15 / *90 12	149 ± 15 / 97 13	150 ± 14 / 95 9	150 ± 14 / 92 12
Exercise systolic	239 ± 14	218 ± 24**	229 ± 16	225 ± 20	227 ± 18
Metoprolol concentration (ng ml^{-1})			6 ± (11)	††23 ± (24)	14 ± (19)

* $P < 0.05$ *vs* placebo ** $P < 0.01$ *vs* placebo *** $P < 0.001$ *vs* placebo
† A significantly lower than M ($P < 0.01$) and L ($P < 0.05$) †† B significantly different from M ($P < 0.05$)

P placebo; A atenolol; M conventional metoprolol; B Betaloc (metoprolol SA durules); L Lopressor (metoprolol SR).

tions of metoprolol was associated with lower 'peak' concentrations and higher 'trough' concentrations than conventional metoprolol. However, this was significant only for metoprolol SA ($P < 0.05$). All patients were extensive metabolisers of debrisoquine with metabolic ratios in the range 0.12–1.07, (median 0.30, mean 0.38). The median for the population is 0.60. There was no correlation between metabolic ratio and clinical effects or plasma metoprolol concentrations in this relatively homogeneous group.

Discussion

Reybrouck *et al.* (1978) suggested that the antihypertensive effect of conventional metoprolol was similar when it was taken once daily or three times daily! However, they used a relatively high dose (300 mg daily) and it has been shown that the antihypertensive effect of lower doses of conventional metoprolol wanes at 24 h (Karlberg *et al.*, 1979). The development of the long-acting formulations of metoprolol, film-coated SR and SA durules, was therefore logical. However, it has not been shown that these formulations prolong the antihypertensive action of metoprolol by direct comparison with the conventional formulation. Our results show that all the preparations had similar effects 3.5 h after dosing. However, after 24 h metoprolol SR had no advantage over conventional metoprolol as regards the degree of β-adrenoceptor blockade or plasma metoprolol concentration. Metoprolol SA durules were associated with a 12% average reduction of exercise heart rate and with significantly higher plasma metoprolol concentrations, at 24 h, confirming that this formulation has some merit as regards 24 h control of the exercise heart rate (Wilcox & Hampton, 1981; Harron & Shanks, 1981). Nevertheless, its effect on heart rate at 24 h was variable and in some patients there was negligible β-adrenoceptor blockade at the end of a dose interval. In agreement with previous studies (Freestone *et al.*, 1982a; Petrie *et al.*, 1980) treatment with atenolol 100 mg was associated with substantial and consistent β-adrenoceptor blockade after 24 h, with the reduction in exercise heart rate averaging approximately 18%.

Considering the antihypertensive response to the four β-adrenoceptor antagonists the important finding was that none of the three formulations of metoprolol lowered blood pressure significantly 24 h after dosing. This can be explained in part by the small sample size, as the study could only be expected to detect a 20/10 mm Hg difference between treatments with a power of 80% (Freestone *et al.*, 1982b). However, the antihypertensive response at 24 h showed no trend to be larger with the two slow-release formulations than with conventional metoprolol. In contrast the response 24 h after 100 mg atenolol was significantly different from placebo, and larger than that of any of the metoprolol formulations. The metabolism of metoprolol exhibits polymorphism of the debrisoquine type with about 9% of the population having the poor metaboliser phenotype, 91% the extensive metaboliser phenotype. Poor metabolisers have substantially higher plasma metoprolol concentrations and longer half-lives compared to extensive metabolisers (Lennard *et al.*, 1982, 1983). In the present study all the patients were extensive metabolisers who would be expected to have relatively low plasma metoprolol concentrations and relatively short half-lives. Because of this feature of the sample of patients the formulations were at a slight disadvantage in the study. A strict interpretation is that the metoprolol formulations proved unsatisfactory for once daily treatment in patients who have the extensive metaboliser phenotype. However, in the UK over 90% of patients have this phenotype.

It is axiomatic that a slow-release formulation ought to confer some advantage over the original dose-form. In agreement with other studies, film-coated metoprolol SR does not do this, with no advantage as regards 24 h plasma concentration, β-adrenoceptor blockade or blood pressure control (Scott *et al.*, 1982; Kierso *et al.*, 1983). The performance of this film-coated preparation is reminiscent of that of similar oxprenolol formulations which have also proved unsatisfactory for once-daily treatment of angina or hypertension (Wilcox & Hampton, 1981; Petrie *et al.*, 1980; Leahey *et al.*, 1980; Bobik *et al.*, 1979). Metoprolol SA durules are superior to conventional metoprolol at 24 h as regards plasma metoprolol concentration and degree of β-adrenoceptor blockade. This formulation also has an antihypertensive action after 24 h (Wilcox & Hampton, 1981). However, it has *not* been shown to be superior to conventional metoprolol as regards the duration of antihypertensive action, and our study does not suggest that it is. We suggest that these slow-release formulations of metoprolol should not be used for hypertension, and that conventional metoprolol should be preferred and prescribed twice daily. The ceiling dose of metoprolol is probably 100 mg twice daily (Jeffers *et al.*, 1978). In agreement with previous studies atenolol 100 mg daily appears to provide satisfactory β-adrenoceptor blockade and antihypertensive effects over 24 h.

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(Received 10 December 1984, accepted 17 June 1985)