promoting calcium retention in patients with bone-losing states such as osteoporosis.

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Beta-blockers: once or three times a day?

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Summary and conclusions

In a double-blind, crossover trial 16 hypertensive patients were treated, in random order, with placebo, metoprolol 300 mg in a single daily dose, or metoprolol 300 mg/day in three doses. Both therapeutic regimens produced detectable plasma metoprolol concentrations and appreciable beta-blockade, estimated from exercise tachycardia, throughout the day. Fluctuations throughout the day in plasma drug concentrations and degree of beta-blockade were insignificant on the thrice-daily regimen, but they varied considerably on the single-dose regimen. Both therapeutic regimens also significantly lowered blood pressure throughout the day. Although the thrice-daily regimen again tended to produce a stronger and less fluctuating hypotensive action, the differences in hypotensive effect between the two regimens were not statistically significant.

A single-dose of 300 mg of metoprolol can therefore be recommended if the only aim is to reduce blood pressure but not if a steady degree of beta-blockade is needed.

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Introduction

Ensuring that patients comply with their therapeutic regimen is a major problem in the long-term treatment of hypertension, especially if they are free of symptoms. The simpler the regimen the easier it should be for patients to comply. We describe a study performed to investigate whether the same degree of β-blockade and blood pressure control could be obtained throughout the day with a once-daily dose of the β-blocking agent metoprolol as with a thrice-daily regimen.

Patients and methods

Sixteen patients (see table I) with essential or renal hypertension (stages I-III on the criteria of the World Health Organisation) were studied. No patient had had a cerebrovascular or coronary accident. All completed the study.

TABLE I—*Details of patients. Mean values are shown ± SE of mean*

	No of patients and mean values
No of patients:	16
Male	9
Female	7
Mean age (years)	43·8 ± 1·9
Mean recumbent blood pressure (mm Hg) on placebo around 11 am	117·6 ± 8·0/113·8 ± 4·3
Cause of hypertension:	
Essential	14
Renovascular	1
Nephritis	1
Stage according to WHO:	
I	6
II	9
III	1
Hypertensive retinopathy according to Keith-Wagener:	
I	7
II	9
Mean creatinine clearance (ml/min/1·73 m²)	86·9 ± 7·8
ECG:	
Normal	11
Left ventricular hypertrophy	5

All antihypertensive drugs were stopped for at least four weeks before the study. During the run-in period the patients received placebo tablets—one with breakfast (around 8 am), three after lunch (around 1 pm), and one before bedtime (around 10 pm). During this period the patients learnt to measure their blood pressure in the morning and evening and underwent a preliminary exercise test.

During the next three consecutive four-week periods each patient was subjected to three different regimens assigned randomly in a double-blind trial. The patients continued to measure their blood pressure at home and to take five tablets daily. During one period all the tablets were placebo; during another the morning and evening tablets contained inert material and the three noon tablets each contained 100 mg of metoprolol (the once-daily regimen); and during the third period the morning tablet, one of the noon tablets, and the evening tablet each contained 100 mg of metoprolol, while the remaining two noon tablets contained inert material (thrice-daily regimen). All tablets were identical in taste, shape, and colour.

At the end of each four-week period the patients were investigated for one day in hospital. After 30 minutes' rest five recumbent blood pressure readings were made at about 11 am and blood was drawn for determining plasma metoprolol concentrations[1]; an uninterrupted multistage graded exercise test with a 30-watt increment every four minutes was then performed on the bicycle ergometer.[2] Within one minute after the exercise, a new blood sample was drawn. Patients then had a light lunch at the hospital, took their three noon tablets around 1 pm, and were restudied in the afternoon using the same protocol as in the morning; the first afternoon blood sample was withdrawn at 2.30 pm, just before the exercise test.

STATISTICAL METHODS

The results were subjected to standard analysis of variance (ANOVA) techniques.[3] Four variables were taken into account: treatment (T), moment of observation (M), sequence of treatment (S), and variation between individuals (P). The first three factors are fixed (conclusions are drawn only for the particular treatments, moments, and sequences studied), but individual variation is random (the patients studied constituted a sample from a larger population). The first three factors are "crossed" (each possible combination of their values or categories is studied), but individual variation is nested within sequence, that is, each patient is assigned to only one sequence of treatment.

Because of the small number of patients sequence was reduced to two categories: (*a*) placebo before and (*b*) placebo after the thrice-daily treatment. Patients with missing data were excluded to keep the ANOVA model balanced and computations manageable. In the case of plasma metoprolol concentration, only four patients in the first sequence category had complete data as against six in the second category.

Differences between averages were tested by means of orthogonal contrasts; these tests are independent.

Results

Statistical remarks—The following general conclusions may be drawn from the ANOVA tables. Firstly, the order of treatment, S, and its interactions were not significant; secondly, P (S) × T interaction was present in the case of heart rate at rest and both P (S) × T and P (S) × M interactions were present for systolic and diastolic blood pressure; thirdly, the T effect was always significant, except in the case of metoprolol concentration and maximum exercise capacity.

Because of the P (S) × T interaction no conclusion about the T effects was possible for heart rate at rest and systolic and diastolic blood pressure without further close scrutiny of the data.

Plasma metoprolol concentration—Plasma metoprolol concentrations were not significantly different before and after exercise either in the morning or the afternoon and the mean of both was therefore considered as the value for the late morning or early afternoon. During the placebo period metoprolol was undetectable (less than 20 nmol/l) in all samples. During the thrice-daily regimen the plasma values before noon were not significantly different from those in the early afternoon (table II). During the once-daily regimen plasma metoprolol was detectable in all samples before noon, when the concentration averaged 295 ± (SE of mean) 144 nmol/l (15·8 ± 7·7 μg/100 ml).

TABLE II—*Plasma metoprolol concentrations (in nmol/l), according to treatment and time of day (mean of values for 10 patients)*

	Thrice-daily regimen	Once-daily regimen	P: thrice *v* once-daily
Late morning	692·6	295·0	>0·05
Early afternoon	1103·7	1571·2	>0·05
P: morning *v* afternoon	>0·05	<0·001	

S^2 = 207 608 (from ANOVA).
Conversion: SI to traditional units—Metoprolol: 1 nmol/l ≈ 0·0535 μg/100 ml.

This sample was drawn about 22 hours after the previous drug intake. In the samples withdrawn in the early afternoon—that is, about two hours after the single daily dose—plasma metoprolol concentrations were significantly higher than the late morning values ($P < 0·001$).

Exercise capacity—During the placebo period maximal exercise capacity averaged 136 ± 2·9 watts in the morning and 136 ± 2·9 watts in the afternoon; the values during the three treatment periods did not differ ($P > 0·1$). A decrease in exercise heart rate was therefore not related to a decreased exercise capacity.

Heart rate—In the late morning the resting and exercise heart rates were significantly reduced during the active treatment periods ($P < 0·001$) compared with the placebo period (table III). The reduction in the exercise heart rate during the single-dose period was, however, significantly smaller than that during the thrice-daily period ($P < 0·001$). In the afternoon the heart rates at rest and exercise were significantly ($P < 0·01$) decreased during the active treatment periods compared with the placebo period, but the differences in heart rates between the thrice-daily and the once-daily regimens were not significant ($P > 0·05$).

Blood pressure—Both active regimens produced significant falls in systolic and diastolic blood pressure at all times of day compared with

TABLE III—*Heart rates (beats/min) at rest and at maximum exercise, according to treatment and time of day (mean of values for 14 patients)*

	Placebo period	Thrice-daily regimen	Once-daily regimen	P:thrice *v* once daily
Late morning				
At rest	83	58	66	<0·05
At exercise	168	126	140	<0·001
Afternoon				
At rest	92	60	62	>0·05
At exercise	172	117	112	>0·05

S^2 at rest: 21; S^2 at maximum exercise: 128 (from ANOVA).

the values on placebo ($P < 0.001$) (table IV). But there were no significant differences in blood pressure at any time of day between the once-daily and the thrice-daily regimens.

TABLE IV—*Systolic and diastolic blood pressures (mm Hg) according to treatment and time of day (mean of values for 12 patients)*

	Placebo period	Thrice-daily regimen	Once-daily regimen
8 am standing	157·0/107·8	145·2/97·8	145·7/96·8
8 am recumbent ..	151·7/99·5	140·4/90·0	143·0/90·3
11 am recumbent ..	180·0/115·6	155·5/99·8	159·3/99·3
3 pm recumbent ..	173·5/112·9	149·6/95·6	147·7/96·8
9.30 pm standing ..	169·7/109·1	150·6/95·2	150·3/95·8
9.30 pm recumbent ..	160·8/102·1	142·8/88·5	143·7/89·9
Day's average	165·4/107·8	147·3/94·5	148·3/94·8

S^2 for systolic blood pressure: 49·3; S^2 for diastolic blood pressure: 26·2 (from ANOVA).

Discussion

Our study aimed at comparing the degree of β-blockade and the hypotensive effects produced by a single daily dose of 300 mg metoprolol with those produced by three daily doses of 100 mg of metoprolol. The single daily dose was not given in the morning or evening, which are the usual times, but at noon, since this enabled us to study the patients within a few hours before and after the single daily dose. A single daily dose of 300 mg was chosen since this can reduce the exercise heart rate by 35% (table III), which is close to the maximum β-blockade that can be achieved in man.[2] Our findings confirm the β-blocking activity of metoprolol.[4,5]

Douglas-Jones *et al*[6] have shown that atenolol, which has a plasma half life of nine hours, decreases the blood pressure and is still effective 24 hours after it has been taken. They did not, however, compare a once-daily with a thrice-daily regimen and they measured the blood pressure only at one time of the day. Bühler *et al*[7] gave a single daily dose of a slow-release form of oxprenolol (3·5 mg/kg/day) and found the hypotensive action as effective as that of a thrice-daily regimen with propranolol (3·3 mg/kg/day). The two treatment periods were, however, not randomised and blood pressure measurements were not made throughout the day.

We found that the β-blocker metoprolol, which has a shorter plasma half life (2·9 hours[3]), produced a hypotensive effect throughout the day with a single daily dose of 300 mg or with a thrice-daily regimen of the same amount. The hypotensive effect tended to be more pronounced and less fluctuating at different times of the day during the thrice-daily regimen, but these differences were not significant.

In conclusion, although a single daily dose of 300 mg of metoprolol can maintain detectable plasma metoprolol concentrations throughout the day, the peak concentration is five times the lowest concentration, even during long-term treatment (table II). Consequently, a single daily dose of 300 mg of metoprolol can produce a significant degree of β-blockade throughout the day but its degree varies on average from 17% two hours before the single dose to 35% two hours after it (table III). A single patient showed variations in β-blockade from 7% in the late morning to 36% in the early afternoon. If a steady degree of β-blockade is the therapeutic goal a single daily dose of 300 mg metoprolol cannot therefore be recommended.

Both the once-daily and the thrice-daily regimens significantly reduce blood pressure throughout the day, but the thrice-daily regimen tends to have a more potent and less fluctuating hypotensive action. The differences in the hypotensive effects of the two regimens are not statistically significant, however, so that a single daily dose of metoprolol may be used if the hypotensive effect is the only therapeutic goal.

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Simplified oesophageal transection for bleeding varices

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Summary and conclusions

Thirty patients with bleeding oesophageal varices were treated by oesophageal transection using the SPTU gun. Any form of shunt was contraindicated in all the patients. Twelve operations were done as urgent procedures within 36 hours of haemorrhage. The overall operative mortality rate was 10%, and there were two late deaths during follow-up, which has so far extended from two months to two years. Three of the patients had recurrent bleeding, and residual varices were probably the source in two. There were no cases of portal systemic encephalopathy.

Although the follow-up is too short to allow any definite conclusions, these early results suggest that oesophageal transection with the SPTU gun may be useful in the large proportion of patients in whom injection sclerotherapy, shunt surgery, or conservative treatment is inappropriate.

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Introduction

Since Whipple[1] introduced the Eck fistula into clinical medicine more than 30 years ago, portacaval shunt has been the most popular operation for portal hypertension. About one-third of