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Effects of the cardioselective beta-adrenergic receptor blocking agent metoprolol in angina pectoris *Subacute study with exercise tests*

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The effect of a cardioselective beta-adrenergic blocking agent, metoprolol[1], on symptoms and exercise tolerance was studied in 16 patients with angina pectoris.

Metoprolol was compared with placebo at two dose levels (20 mg t.d.s. and 50 mg t.d.s.) in a double-blind trial in 14 patients. Compared with placebo, metoprolol caused a significant reduction of heart rate and systolic blood pressure during exercise, and consequently a reduction of the rate-pressure product. The reduction was greater with 50 mg t.d.s. than with 20 mg t.d.s. The exercise tolerance measured as total work increased significantly by 21 per cent during treatment with metoprolol 20 mg t.d.s., and by 17 per cent during treatment with 50 mg t.d.s. There was a reduction in the number of anginal attacks and in nitroglycerin consumption, and subjective improvement of angina pectoris at both dose levels of metoprolol. No signs of cardiac failure appeared during any of the four treatment periods. Heart volume showed no significant change. Unwanted effects were of the same frequency and severity during treatment with metoprolol at both dose levels as with placebo.

The sixteen patients were included in a long-term tolerance study with unchanged doses of metoprolol and have now been followed for 24 months without any unwanted effects.

In animal studies, metoprolol has been found to inhibit the heart rate and contractile force responses to isoprenaline in considerably lower doses than were required to block the vasodilator and bronchodilator effects of isoprenaline (Åblad, Carlsson, and Ek, 1973). By the criteria of Lands, Luduena, and Buzzo (1967), metoprolol selectively blocks $beta_1$-adrenergic receptors. Metoprolol has been found to be devoid of beta-receptor stimulating properties (Åblad *et al.*, 1973). Compared with placebo metoprolol significantly increased the exercise tolerance in patients with angina pectoris, in an acute study reported by Adolfsson *et al.* (1974). In view of these findings the present study was undertaken to evaluate the effects of metoprolol in patients with angina pectoris in a subacute study.

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[1] Metoprolol is also known as H 93/26 (AB Hässle, Sweden) and CGP 2175 (Ciba-Geigy AG, Switzerland), and is marketed in the U.K. as Betaloc (Astra) and Lopresor (Geigy).

Subjects

Sixteen patients, previously treated with a beta-adrenergic blocking drug for angina pectoris for at least three months, entered the study. All had a typical history of angina pectoris by the criteria of Rose (1962). The mean age was 59 years (range 51 to 66 years), and the mean duration of angina pectoris was 6 years (range 6 months to 14 years). Nine patients had previously suffered myocardial infarction and four were treated with digoxin because of previous signs of heart failure. All patients but one had cardiac volumes within normal limits and one was at the upper limit of the normal range. Pertinent clinical information is given in Table 1.

Methods

During a run-in period of 3 weeks, the patients were treated with alprenolol 100 mg t.d.s. This was followed by a 3-week period of treatment with placebo and a 3-week period of treatment with metoprolol 20 mg t.d.s., and subsequently by 3-week periods of treatment with placebo and metoprolol 50 mg t.d.s. The sequence of treatment with metoprolol and placebo was randomized

TABLE 1 *Clinical findings*

Case No.	*Sex*	*Age (yr)*	*Duration of angina pectoris (yr)*	*Supine heart volume (ml per m² BSA)*	*Previous myocardial infarction*	*Current treatment daily*
1	M	54	1	580	+	Digoxin 0·25 mg, antilipaemic drug
2	M	60	3	330	+	Clofibrate 2 g, nicotinic acid 3 g
3	M	66	11	450	+	Digoxin 0·25 mg, clofibrate 2 g
4	M	62	10	480	-	—
5	F	61	11	400	+	Clofibrate 2 g
6	F	64	7	420	+	Prednisolone 5 mg, mepacrine 5 mg, chlorthalidone 50 mg +KCl
7	M	59	4	440	+	Clofibrate 2 g
8	M	60	8	440	+	Digoxin 0·25 mg, anticoagulant
9	M	56	12	480	-	Chlorthalidone 50 mg+KCl, clofibrate 2 g
10	M	63	14	460	+	Dicoumarol
11	M	56	0·5	460	-	—
12	M	59	10	380	+	Chlorthalidone 100 mg+KCl, nicotinic acid 3 g
13	M	63	10	460	-	Nicotinic acid 3 g
14	M	51	2	No measurement	-	Nicotinic acid 3 g, dicoumarol
15	M	61	2	440	-	—
16	M	51	0·5	420	-	Digoxin 0·13 mg

at each dose level independently (Fig. 1). The metoprolol and placebo tablets used in this study were identical in size, shape, colour, and taste.

Patients were examined and had exercise tests at the end of each period. Laboratory tests were performed at the same times, as follows: haemoglobin, leucocyte count, platelets, ESR; serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, cholesterol, triglycerides, and uric acid; plasma sodium, potassium, and bicarbonate.

A. Clinical assessment

A simple diary card, to which the patients had become accustomed during the run-in period, was completed by the patient and returned to the physician at each visit. The diary card showed the number of nitroglycerin tablets taken each day, the number of anginal attacks, and a daily subjective assessment of angina pectoris according to a four-point scale. In addition, the patients were asked to express a general preference for each treatment period.

For statistical evaluation of the attack rate, the mean values for the 14 patients for each three-week period have been used.

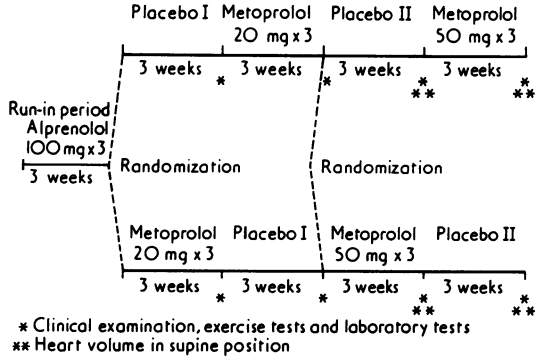

FIG. 1 *Design of the study.*

B. Exercise test

Exercise tests were performed in the sitting position on an electrically braked bicycle ergometer (Siemens-Elema EM 380) by a standardized procedure, with stepwise increasing work loads. The exercise tests were performed with six minutes at each work load; the increments of work load were so adjusted that the patients could complete at least two six-minute exercise periods before being stopped by chest pain during the third period. Electrocardiograms were monitored continuously and recorded intermittently during exercise using six praecordial leads (chest-head).

'Perceived exertion' was estimated on a 16-point scale (Borg, 1970). Corresponding scales were constructed for grading angina pectoris, dyspnoea, and the sensation of fatigue in the legs. Blood pressure was measured using the cuff method. Before exercise, systolic and diastolic pressures were recorded with the patient in the supine position and after 8 minutes standing. During exercise, systolic blood pressure was measured during the fifth minute at each work level. Cardiac volume was measured twice in the supine position (Kjellberg, Lönroth, and Rudhe, 1951).

Statistical significance was analysed by Student's t-test or Wilcoxon's matched pairs signed ranks test for comparison of paired data (Siegel, 1956; Snedecor and Cochran, 1967). The χ^2 test was used for evaluation of subjectively reported changes. All P values refer to two-tailed tests.

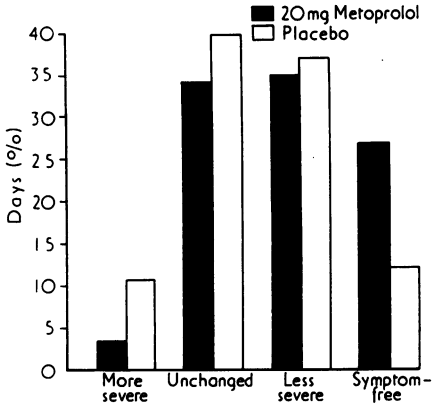

FIG. 2 *Daily subjective assessment of angina pectoris (metroprolol 20 mg t.d.s.). Statistical significance:* $\chi^2=9{\cdot}84$, $P=0{\cdot}02$.

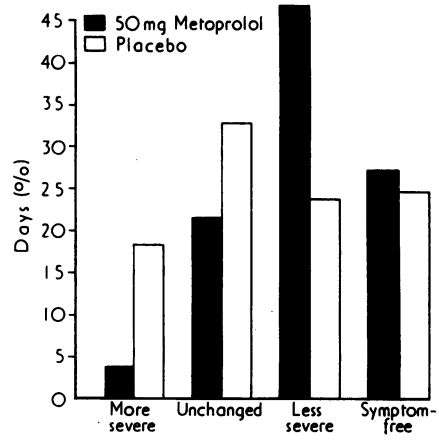

FIG. 3 *Daily subjective assessment of angina pectoris (metoprolol 50 mg t.d.s.). Statistical significance:* $\chi^2=19{\cdot}09$, $P<0{\cdot}001$.

Results

Of 16 patients entering the study, 14 completed it. Cases 15 and 16 were excluded from the evaluation as they had less than five anginal attacks a week during placebo treatment. These two patients were on treatment with metoprolol for 12 months without any unwanted effects or abnormal results of laboratory tests.

A. Clinical assessment

The results are given in Table 2 and Fig. 2 and 3.

Attacks per week A significant reduction in the number of attacks compared with the corresponding placebo period was achieved with metoprolol 20 mg t.d.s. ($P<0{\cdot}001$) but not with 50 mg t.d.s. However, it must be stressed that the two corresponding placebo periods were not identical. Cases 5, 8, and 12 had fewer anginal attacks during the second

TABLE 2 *Frequency of anginal attacks and nitroglycerin consumption*

Case No.	*Attacks per week*				*Nitroglycerin consumption (tablets/week)*			
	Placebo 20 mg	*Metoprolol* 20 mg	*Placebo* 50 mg	*Metoprolol* 50 mg	*Placebo* 20 mg	*Metoprolol* 20 mg	*Placebo* 50 mg	*Metoprolol* 50 mg
1	12	9	17	15	7	6	14	11
2	65[1]	23	–[2]	16	39[1]	15	–[1]	11
3	4	1	7	4	8	7	6	4
4	21	12	16	12	18	13	18	15
5	8	4	3	4	1	4	1	2
6	10	9	13	3	10	9	10	3
7	9	8	7	11	3	3	2	3
8	54	45	39	46	75	66	72	75
9	20	16	26	29	67	57	80	76
10	6	4	7	1	5	3	6	1
11	20	15	17	7	18	14	7	6
12	8	5	4	5	8	9	3	2
13	13	6	7[2]	3	5	2	4[2]	0
14	15	12	10	8	11	8	6	4
Median	12·5	9	10	7·5	9	8·5	6	4
Range	4–65	1–45	3–39	1–46	1–75	2–66	1–80	0–76
P	<0·001		NS		<0·05		<0·05	

[1]Angina worse, placebo discontinued after four days.
[2]Angina worse, placebo discontinued after two days.

TABLE 3 *Effect of metoprolol 20 mg and 50 mg on heart rate and blood pressure at rest and during exercise*

	Mean	*SEM*	*P*
Heart rate at rest, supine (beats/min)			
Metoprolol 20 mg (n=13)	62	2·0	<0·001
Placebo	74	2·8	
Metoprolol 50 mg (n=11)	58	2·3	<0·001
Placebo	74	2·0	
Heart rate at comparable work load (beats/min)			
Metoprolol 20 mg (n=12)	88	3·5	<0·01
Placebo	104	6·1	
Metoprolol 50 mg (n=11)	80	4·5	<0·001
Placebo	103	4·7	
Heart rate at end of work (beats/min)			
Metoprolol 20 mg (n=13)	96	4·6	<0·05
Placebo	115	6·1	
Metoprolol 50 mg (n=11)	90	4·9	<0·001
Placebo	119	6·3	
Blood pressure at rest; supine (mmHg)			
Metoprolol 20 mg (n=13)	133/81	4·9/2·6	<0·05/NS
Placebo	138/83	5·2/2·5	
Metoprolol 50 mg (n=11)	118/72	4·2/2·8	<0·001/<0·001
Placebo	137/85	5·0/2·4	
Systolic blood pressure at comparable work load (mmHg)			
Metoprolol 20 mg (n=12)	154	7·0	<0·05
Placebo	171	8·6	
Metoprolol 50 mg (n=11)	146	7·8	<0·01
Placebo	169	7·7	
Systolic blood pressure at end of work (mmHg)			
Metoprolol 20 mg (n=12)	159	7·9	<0·05
Placebo	180	8·2	
Metoprolol 50 mg (n=11)	160	7·9	<0·01
Placebo	187	10·0	
Rate-pressure product ($\times 10^{-2}$), at comparable work load			
Metoprolol 20 mg (n=12)	138	10·0	<0·01
Placebo	180	15·8	
Metoprolol 50 mg (n=11)	118	11·9	<0·001
Placebo	174	12·6	
Rate-pressure product ($\times 10^{-2}$) at end of work			
Metoprolol 20 mg (n=12)	157	13·6	<0·05
Placebo	207	18·7	
Metoprolol 50 mg (n=11)	146	13·1	<0·001
Placebo	222	20·0	

Conversion factor from Traditional Units to SI Units: 1 mmHg ≈ 0·133 kPa.

placebo period than during the period on treatment with metoprolol 50 mg t.d.s.

Nitroglycerin consumption was significantly reduced by metoprolol at both dosage levels, compared with the corresponding placebo periods ($P < 0·05$) (Table 2).

A significant improvement was also apparent from the patients' *subjective daily assessment* of their angina, both with metoprolol 20 mg t.d.s.

($P < 0{\cdot}02$) (Fig. 2) and with the dosage of 50 mg t.d.s. ($P < 0{\cdot}001$) (Fig. 3).

The *general preference* at the end of each period showed that 8 patients had a clear preference for metoprolol 20 mg t.d.s. compared with placebo, and 10 patients for metoprolol 50 mg t.d.s. compared with placebo.

B. Cardiovascular effects at rest and during exercise (Tables 3 and 4).

Case 4 was excluded from this evaluation because he was unable to exercise on the bicycle. Two patients (Cases 2 and 13) did not tolerate placebo treatment, because of worsening of their angina, and were switched over to active drug treatment after a few days. Neither of these patients was able to exercise during the second placebo period.

Mean values for heart rate, blood pressure, and rate-pressure product during exercise are given in in Table 3.

Heart rate Calculations of the mean values showed that metoprolol at both dose levels produced a significant reduction in resting heart rate, heart rate recorded at comparable work load, and heart rate at the end of exercise, compared with placebo. The effect was greater at the higher dose.

Systolic blood pressure measured resting supine, at comparable work load, and at the end of exercise, was also significantly reduced with both doses.

Rate-pressure product was significantly reduced with both doses of metoprolol at comparable work load, and at the end of exercise. The reduction was greater with the dosage of 50 mg t.d.s.

Total work was calculated as the product of work load in Watts and number of minutes of exercise. There was a statistically significant increase in total work with metoprolol at both 20 mg t.d.s. ($P < 0{\cdot}05$), and 50 mg t.d.s. ($P < 0{\cdot}05$), compared with placebo (Table 4).

Work load at break point, the highest calculated load tolerated for 6 minutes (Ekelund, Melcher, and Orö, 1974), increased significantly with metoprolol 20 mg t.d.s. ($P < 0{\cdot}05$) and 50 mg t.d.s. ($P < 0{\cdot}01$) compared with placebo.

Eight patients increased their total work by 20 per cent or more on the dosage of 20 mg t.d.s. compared with placebo. These patients are regarded as responders to the dosage of 20 mg t.d.s. Three patients increased their total work by more than 20 per cent on the dosage of 50 mg t.d.s. Two patients (Cases 2 and 13) did not perform any exercise test during the second placebo period because of worsening of angina pectoris, and were switched over to metoprolol 50 mg t.d.s. after a few days. These 5 patients are regarded as responders to the dosage of 50 mg t.d.s. Cases 6, 12, and 14 are regarded as responders to the 20 mg t.d.s. but not to 50 mg t.d.s. However, these 3 patients showed a distinct improvement in exercise tolerance when the second placebo period was compared with the first.

The *perceived exertion, angina pectoris, dyspnoea,* and sensation of *fatigue in the legs* were not significantly affected, by either dose of metoprolol.

Cardiac volume, calculated as total volume, showed no significant differences at the end of the treatment periods with metoprolol 50 mg t.d.s. or placebo.

Complications and unwanted effects

Two patients (Cases 2 and 13) did not tolerate the placebo because of worsening of angina pectoris, and were, therefore, given active drug treatment after 2 to 4 days. One patient (Case 4) complained of dizziness on metoprolol 50 mg t.d.s., but when the dose was halved, this symptom disappeared. The frequency of unwanted effects was low and about the same during treatment with metoprolol and placebo.

All 16 patients were included in a long-term tolerance study with unchanged doses of meto-

TABLE 4 *Effect of metoprolol on total work and work load at break point*

	Metoprolol (20 mg t.d.s.)	*Placebo*	*% change from placebo*	*Metoprolol (50 mg t.d.s.)*	*Placebo*	*% change from placebo*
Total work (W min) (n=13)						
Mean	596	492	21	672	581	17
SEM	87·4	84·0		79·3	89·6	
Range	110–1080	120–1080		300–1080	143–1080	
P	<0·05			<0·05		
Work load at break point (W) (n=13)						
Mean	56·4	49·4	14	60·7	55·9	9
SEM	6·49	6·66		5·77	6·43	
Range	18·3–90·0	15·4–90·0		30·90	21·3–90·0	
P	<0·05			<0·01		

prolol. Thus, one patient had 25 mg t.d.s. and the remainder had 50 mg t.d.s. Patients were examined after 6, 12, 18, and 24 months' treatment with metoprolol. The following laboratory investigations were done: haemoglobin, white blood cell count, and ESR; serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, cholesterol, triglycerides, uric acid, and antinuclear factor (ANF).

During the long-term tolerance study, one patient had a non-fatal myocardial infarction. In the whole group no severe unwanted effects were observed and there were no abnormal laboratory findings. Blood pressure and body weight remained unchanged throughout the study.

Discussion

This study was performed to evaluate the anti-anginal effect of metoprolol in 16 patients previously treated with alprenolol. As this was one of the first studies with chronic metoprolol treatment in angina pectoris, the study was designed to evaluate response to two dosage levels, with 20 mg t.d.s. always preceding 50 mg t.d.s.

The results of the exercise test show that total work was significantly increased, compared with placebo, by about 20 per cent after both dose levels of metoprolol. The increase in exercise tolerance was largest in the patients who had a decrease or only a very small increase in cardiac volume after metoprolol. Determination of the cardiac volume in combination with exercise tests might thus be of value for evaluating the effect of a beta-receptor blocking agent (Jonsson, Olsson, and Orö, 1973). The increase in exercise tolerance was of the same magnitude as reported by Adolfsson *et al.* (1974) and was accompanied by a corresponding subjective improvement. The reduction of heart rate and systolic blood pressure was of the same magnitude as in the acute study by Adolfsson *et al.* (1974).

All the patients were well known to us, having been treated for long periods, were familiar with exercise testing, and could be regarded as having stable angina pectoris. Therefore, only minor differences were expected to appear between the two placebo periods. However, many of the patients showed unexpected improvement during the second placebo period, with both reduction in frequency of angina and increased exercise capacity. This difference in exercise tolerance between placebo periods could be attributed to increased activity and physical fitness resulting from previous treatment. The effect of the exercise testing on exercise capacity could certainly be neglected. This improvement during the second placebo period probably had an unfavourable effect on the apparent results of treatment with 50 mg t.d.s. relative to treatment with 20 mg t.d.s. of metoprolol. Therefore, from the results of the present investigation it is difficult to state which of the two dosage levels used is the optimal one.

However, if only the median and mean values are taken into consideration, there was an improvement during the 50 mg t.d.s. treatment period compared with the 20 mg t.d.s. period. These results suggest that 20 mg t.d.s. is a suitable initial dose of metoprolol, and that many patients derive further benefit from 50 mg t.d.s. In this study, neither of the doses used induced any clinically significant unwanted effects nor were there any abnormal findings in the laboratory tests.

Both the increase in exercise tolerance and the subjective improvement indicate that metoprolol is effective in angina as are other beta-adrenergic blocking agents (Dagenais, Pitt, and Ross, 1971; Adolfsson, Areskog, and Rasmuson, 1971; Hetherington *et al.*, 1973). Furthermore, metoprolol should have advantages resulting from its selective effect on $beta_1$-adrenergic receptors, especially in patients with bronchial asthma, and could in special cases be combined with a $beta_2$-stimulating agent such as salbutamol or terbutalin (Thiringer and Svedmyr, 1976).

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