British Heart Journal, 1977, **39**, 834–838

Metoprolol—a new cardioselective β-adrenoceptor blocking agent for treatment of tachyarrhythmias

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The antiarrhythmic effect of the cardioselective β-adrenoceptor blocking agent metoprolol, given intravenously, was studied in 44 patients with various tachyarrhythmias, including patients with congestive heart failure and signs of digitalis intoxication. All patients with atrial tachycardia (12 cases) reverted to normal sinus rhythm. In 3 out of 18 patients with atrial fibrillation, sinus rhythm was restored, and in the others there was a significant reduction in ventricular rate. In 6 of 10 patients with ventricular ectopic beats, and 1 of 2 patients with ventricular tachycardia, the ectopic rhythm was abolished. The drug was well tolerated, without any significant changes in blood pressure, even by patients with signs of digitalis intoxication and varying degrees of pulmonary or peripheral circulatory congestion. Metoprolol is of clinical value for treatment of tachyarrhythmias, especially those of supraventricular origin.

Metoprolol is a potent cardioselective β-adrenoceptor blocking agent lacking intrinsic sympathomimetic activity and significant effects on the peripheral vascular bed (Åblad *et al.*, 1973; Johnson, 1975). We have previously studied the haemodynamic effects of metoprolol at rest and during exercise in normal subjects (Stenberg *et al.*, 1975). In the present study, we have investigated the effect of metoprolol on tachyarrhythmias of varying aetiology in patients with and without cardiac failure.

Subjects and methods

Forty-four consecutive patients, 30 men and 14 women, with various tachyarrhythmias were studied. Thirty-five had supraventricular and 9 had ventricular arrhythmias. The majority of the patients were between 20 and 40 years of age. Twenty-five patients suffered from rheumatic heart disease, 9 from ischaemic heart disease, and the remaining 10 had pericardial disease (2 cases), myocarditis (1 case), thyrotoxicosis (1 case) or idiopathic arrhythmias (6 cases). Twelve of the patients with supraventricular arrhythmias had atrial tachycardia, 5 had atrial flutter, and 18 had atrial fibrillation, in 3 combined with premature ventricular contractions. The patients with isolated ventricular arrhythmias included 7 with ventricular premature contractions and 2 with ventricular tachycardia.

Patients with systolic blood pressure less than 80 mmHg, or with gross congestive heart failure, were excluded from the study, while those with mild congestive failure, bronchospasm, or signs of digitalis intoxication were included. Of 44 patients, 30 were receiving digitalis, and 9 of these had clinical and electrocardiographic evidence of digitalis intoxication. One patient had chronic obstructive lung disease, and 2 suffered from acute myocardial infarction.

It was difficult to assess the precise duration of arrhythmia in the patients with atrial fibrillation, atrial flutter, and ventricular premature beats, but from the history this was usually several months. The duration of atrial tachycardia was less than 4 hours in 4 patients, from 4 to 8 hours in 6 patients, and more than 8 hours in the other 2. Two patients with atrial tachycardia received the drug on two occasions with an interval of several days.

After an electrocardiographic diagnosis of the arrhythmia had been made, the electrocardiograms of the patients were continuously monitored. The study was said to have started when persistent arrhythmia had been observed over a period of at least 1 hour, during which time other antiarrhythmic drugs had been tried in several patients. Metoprolol was given intravenously in a dose of 0·15 mg per kg body weight at a rate of 1 mg per minute. The

Received for publication 8 November 1976

Table 1 *Effect of intravenous metoprolol in atrial fibrillation and flutter*

Case No.	Age and sex	Weight (kg)	Diagnosis	Dose of metoprolol (mg)	Heart rhythm Before	After	Ventr. rate Before	After	Blood pressure (mmHg) Before	After	Onset of action (min)	Remarks
1	59 M	59	RHD, MS	8	AF	AF	160	90	120/80	120/80	2	NSR 7 days afterwards on oral metoprolol
2	20 M	40	RHD, MS, MR	6	AF	AF	150	115	115/80	120/80	10	—
3	55 M	55	RHD, MS, MR	8	AF	AF	140	85	110/70	115/70	10	—
4	60 F	50	RHD, MS, AS, AR, CHF	5	AF	AF	110	60	150/80	160/80	10	NSR after 12 h; unchanged CHF
5	29 F	64	RHD, MS, MR	9·5	AF	AF	126	98	120/80	110/80	10	—
6	16 F	33	RHD, MS, TR, dig. intox.	5	AF PVC	AF	110	84	110/80	90/70	2	PVC disappeared after metoprolol
7	36 F	35	RHD, MS, MR, dig. intox.	5·5	AF	AF	102	66	120/80	110/70	5	—
8	33 M	56	RHD, MS, MR	7·5	AF	AF	114	85	105/75	105/70	10	—
9	28 F	65	RHD, MS	9	AF PVC	AF	162	114	105/70	100/70	10	PVC (6–8/min) disappeared at 40 min
10	25 M	60	RHD, MS, dig. intox.	9	AF PVC	AF	165	120	130/70	110/80	5	No change in PVC (5–8/min)
11	24 M	45	RHD, MR	6·5	AF	AF	160	140	120/70	110/60	15	—
12	38 F	42	RHD, MS	6	AF	NSR	160	100	120/80	125/80	5	NSR after 5 min
13	45 F	30	RHD, MS	4·5	AF	AF	150	90	110/75	100/65	5	—
14	27 M	50	RHD, MS	7·5	AF	AF	140	110	120/80	120/75	2	—
15	22 M	47	RHD, MS, MR	7	AF	AF	147	48	150/30	130/30	15	—
16	20 M	40	RHD, MS, MR	6	AF	AF	114	87	115/80	105/80	5	—
17	20 M	55	Constrictive pericarditis	8·25	AF	AF	108	60	115/80	110/80	10	—
18	36 M	40	RHD, MS, TR, dig. intox.	6	AFL	AFL	120	78	120/75	110/70	5	No change in atrial rate (280/min)
19	35 M	50	RHD, MS	7·5	AFL	AFL	150	150	100/80	100/80	—	No response; atrial rate unchanged (300/min)
20	60 M	45	Pericardial effusion	6·75	AFL	AFL	130	120	120/70	110/70	5	No change in atrial rate (350/min); after 14 h→NSR
21	41 M	46	RHD, MS	7	AFL	AFL	90	70	110/80	105/80	5	No change in atrial rate (330/min); occasional PVC after metoprolol
22	34 M	50	Thyrotoxicosis	7·5	AF	NSR	200	75	120/80	125/80	5	After 9 h→NSR
23	40 M	70	RHD, MS, MR, TR, CHF	10	AFL	AFL	140	100	100/70	100/70	5	No change in atrial rate (280/min)

Abbreviations: Diagnosis: AR, aortic regurgitation; AS, aortic stenosis; CHF, chronic heart failure; MR, mitral regurgitation; MS, mitral stenosis; RHD, rheumatic heart disease; TR, tricuspid regurgitation. *Heart rhythm:* AF, atrial fibrillation; AFL, atrial flutter; NSR, normal sinus rhythm; PVC, premature ventricular contractions.

cardiac rhythm, heart rate, blood pressure, and clinical condition were continuously monitored. Electrocardiograms were obtained at 10-minute intervals for 1 hour after the injection, and then at hourly intervals for the next 12 hours.

Results

Pertinent clinical data and the results of treatment with metoprolol are given in Tables 1 to 3 and Fig. 1 and 2. In 17 patients the cardiac rhythm was restored to normal, while in 23 patients there was a beneficial response, i.e. either the heart rate dropped to normal or the ectopic activity was much reduced (Fig. 1). In four patients there was no response. Twenty patients responded in less than 10 minutes, 14 patients in 10 to 19 minutes, and 6 patients in over 20 minutes (Fig. 2).

ATRIAL TACHYARRHYTHMIAS

All patients with paroxysmal atrial tachycardia whatever the aetiology and duration reverted to normal sinus rhythm (Table 2); two of these patients received the drug a second time several days later with the same result. On 8 occasions

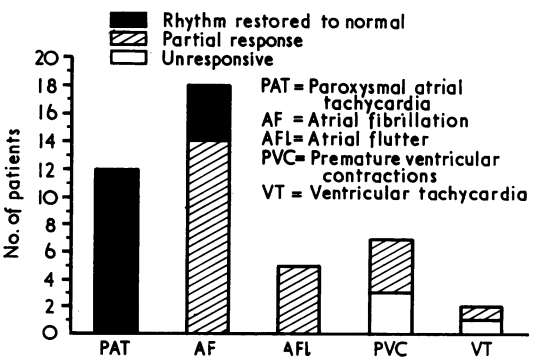

Fig. 1 *Results of treatment with intravenous metoprolol in patients with various cardiac arrhythmias.*

Table 2 *Effect of intravenous metoprolol in paroxysmal atrial tachycardia*

Case No.	Age and sex	Weight (kg)	Diagnosis	Dose of metoprolol (mg)	Heart rhythm Before	Heart rhythm After	Ventr. rate Before	Ventr. rate After	Blood pressure (mmHg) Before	Blood pressure (mmHg) After	Onset of action (min)	Remarks
1	35 M	60	Idiopathic	9	PAT	NSR	166	80	100/80	90/70	30	—
2	20 M	45	RHD, MI, AI	6·75	PAT	NSR	200	100	140/20	120/20	10	Unresponsive to mechanical stimulation of vagus, digitalis, and practolol; 2nd trial diff. day
3	22 F	60	Idiopathic	9	PAT	NSR	160	108	110/70	100/70	5	—
4	25 M	37	RHD, op. MS	5·5	PAT	NSR	190	93	95/60	85/60	20	—
5	34 M	64	Idiopathic	9	PAT	NSR	220	120	120/75	110/75	5	Unresponsive to mechanical stimulation of vagus and digitalis
6	15 F	35	RHD, MS, MI	6	PAT	NSR	190	100	100/80	110/70	10	Decrease in atrial rate to 160/min at 5 min; NSR at 10 min
7	18 F	40	Myocarditis, CHF dig. intox.	6	PAT	NSR	180	80	100/60	90/60	20	Gross CHF and cardiomegaly
8	36 F	40	Op. MS; dig. intox.	6	PAT	NSR	180	72	100/70	110/75	10	Success also at second trial later
9	51 F	60	Intracranial tumour	9	PAT	NSR	190	130	130/80	120/80	5	Persistent sinus tachycardia after PAT abolished
10	14 M	50	WPW syndrome	8	PAT	NSR	210	75	120/80	120/80	30	At 30 min sinus bradycardia (30–60/min) alternating with PAT; at 45 min stabilisation at NSR 76–80 min
11	34 M	60	Idiopathic	9	PAT	NSR	180	100	120/90	120/80	10	PAT developed while on oral practolol (100 mg b.d.)
12	38 M	46	MS, dig. intox.	7	PAT	NSR	180	90	100/70	100/70	20	—

Abbreviations: See Table 1. PAT, paroxysmal atrial tachycardia.

Table 3 *Effect of intravenous metoprolol in ventricular tachyarrhythmias*

Case No.	Age and sex	Weight (kg)	Diagnosis	Dose of metoprolol (mg)	Heart rhythm Before	Heart rhythm After	Ventr. rate Before	Ventr. rate After	Blood pressure (mmHg) Before	Blood pressure (mmHg) After	Onset of action (min)	Remarks
1	46 M	60	AMI	9	VT	NSR	180	100	80/50	80/50	5	No response to lignocaine procainamide, ajmaline, and practolol; VT for several h
2	50 M	60	CHD	8	SR PVC	NSR	72	60	110/70	100/70	2	PVC initially 30/min; disappeared at 5 min, but reappeared after 45 min
3	60 F	60	CHD, AMI	9	SR PVC	NSR	120	84	130/90	120/80	2	PVC initially 40/min; disappeared completely
4	33 M	52	Idiopathic	8	SR PVC	SR PVC	100	96	130/90	120/90	—	No effect; no response to ajmaline, practolol, lignocaine, atropine, propranolol, and phenytoin
5	62 M	70	CHD, emphysema, and chronic bronchitis	10	SR PVC	NSR	110	78	160/70	150/70	5	Junctional and PVC initially 30/min, disappeared completely
6	55 F	60	CHD, diabetes	9	VT	VT	165	165	80/?	80/?	—	No response
7	40 M	70	CHD	10	SR PVC	SR PVC	123	81	130/80	135/80	20	Partial response, PVC reduced from 30 to 6/min
8	64 M	65	CHD	10	SR PVC	SR PVC	114	75	160/50	150/50	—	No change in PVC 24/min; earlier also procainamide, lignocaine, and phenytoin without response
9	49 M	80	CHD	10	SR PVC	SR PVC	80	70	100/60	100/70	—	No change in PVC 20/min

Abbreviations: See Table 1. AMI, acute myocardial infarction; CHD, coronary heart disease; VT, ventricular tachycardia; SR, sinus rhythm.

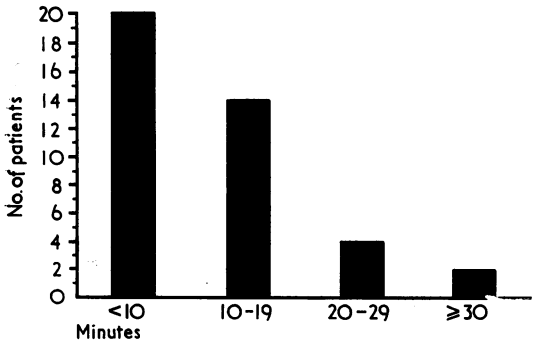

Fig. 2 *Time until response after intravenous metoprolol in patients with various cardiac arrhythmias.*

reversion to normal rhythm occurred within 10 minutes, on 4 occasions within 20 minutes, and in 2 patients 30 minutes after injection of the drug.

Of the 18 patients with atrial fibrillation, 2 reverted to sinus rhythm within 5 minutes after the injection, and 1 was in normal rhythm 12 hours afterwards (Table 1). In the remaining 15 patients the atrial fibrillation persisted, though the ventricular rate decreased from an average of 140 per minute (102 to 200 per minute) before therapy to an average of 90 per minute (48 to 140 per minute). In 2 out of 3 patients with associated ventricular ectopic beats these disappeared after metoprolol. The degree of atrioventricular block increased in 4 of 5 patients with atrial flutter, thus decreasing the ventricular rate.

VENTRICULAR TACHYARRHYTHMIAS

Of 10 patients with ventricular ectopic beats, 6 became completely free from their arrhythmia after the administration of metoprolol (Table 3), including 2 who were in atrial fibrillation (Table 1). In 1 further patient the number of ectopic beats decreased significantly from 30 to 6 per minute.

One of the two patients with ventricular tachycardia reverted to normal sinus rhythm less than 5 minutes after the injection. This patient (case 1) was suffering from an acute myocardial infarction with shock, and his arrhythmia had previously failed to respond to lignocaine, procainamide, ajmaline, and practolol; no further fall of blood pressure was observed.

SIDE EFFECTS

No side effects were observed in any patient, and there were no significant changes in blood pressure. In patients with congestive heart failure, the pulmonary congestion did not increase, and there was no deterioration in pulmonary function in the patient with chronic obstructive lung disease and junctional and ventricular ectopic beats.

Discussion

β-adrenoceptor blocking agents have become established drugs for the treatment of cardiac arrhythmias, and their use for this purpose has been extensively reviewed by Singh and Jewitt (1974) and Wit *et al.* (1975a, b, c). Of the various β-adrenoceptor blocking agents available propranolol has been most commonly used, and is of proven value in, for example, arrhythmias complicating acute myocardial infarction (Lemberg *et al.*, 1970). However, the drug has a significant negative inotropic action on the heart and may also cause bronchial constriction (Stephen, 1966), and this will limit the use of propranolol in patients with manifest or threatening bronchospasm or cardiac failure. Such risks are considerably less with practolol, which also has a proven value as an antiarrhythmic agent (Gibson *et al.*, 1968; Jewitt *et al.*, 1969; Gent *et al.*, 1970). Unfortunately, however, practolol has the well-known drawback of causing severe immune reactions when used over prolonged periods (*British Medical Journal*, 1975), and this has substantially limited its clinical usefulness.

Metoprolol, another cardioselective β-adrenoceptor blocking agent, has in earlier studies in animals and man been found to be a potent drug largely devoid of any influence on the smooth muscles of the bronchioles (Åblad *et al.*, 1975). Hence, this drug was used in the present study even in patients with pulmonary congestion, low arterial blood pressure, and airways obstruction. Metoprolol was found to be effective in all cases of paroxysmal atrial tachycardia, and produced significant decreases in heart rate in cases of atrial fibrillation and flutter. Cardiac rhythm was restored to normal in 3 out of 18 patients with atrial fibrillation. The number of patients with ventricular arrhythmias was small, but it is of interest to note that in 6 out of 10 cases the ventricular premature beats disappeared, and in one further patient a significant reduction in the frequency of ectopic beats was observed. Moreover, 1 of the 2 patients with ventricular tachycardia associated with shock secondary to acute myocardial infarction reverted to normal rhythm after previous failure to respond to administration of lignocaine, ajmaline, procainamide, and practolol.

Clinical experience with metoprolol in patients with cardiac arrhythmias has not previously been reported. In a similar study using practolol 5 out of 6 episodes of paroxysmal atrial tachycardia, and 4 out of 7 instances of ventricular ectopic beats re-

sponded to practolol (Manjuran *et al.*, 1977). Thus, the results with practolol appear to be similar to those in the present study, but the number of patients in the former study was only 27.

Clinically, the use of metoprolol has so far been reported only in hypertensive patients (Bengtsson, 1976; Sannerstedt and Wasir, 1977). In the present study, however, metoprolol was found to be a useful antiarrhythmic agent and virtually free from side effects. It may safely be given even to patients with congestive heart failure, signs of digitalis intoxication, and bronchial obstruction.

The authors are grateful to AB Hässle, Sweden, for the supply of metoprolol.

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