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Comparison of the effects of propranolol and MJ 1999 on cardiac β-adrenoceptors in man

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Summary

1. Propranolol, a β-adrenoceptor blocking drug with local anaesthetic and a direct myocardial depressant action, and MJ 1999, a β-adrenoceptor blocking drug which has no local anaesthetic or intrinsic sympathomimetic action, were compared for β-adrenoceptor blocking activity in man.

2. Propranolol was 2·67 times more active than MJ 1999 in reducing by 50% the tachycardia produced by the intravenous infusion of isoprenaline in healthy volunteers.

3. Propranolol and MJ 1999 intravenously both reduced resting heart rate in the standing position and an exercise tachycardia, but there was no qualitative or quantitative difference between them.

4. On oral administration, both propranolol and MJ 1999 reduced resting heart rate and an exercise induced tachycardia ; propranolol was only slightly more active than MJ 1999.

5. In patients with thyrotoxicosis propranolol was about twice as active as MJ 1999 in reducing the heart rate.

Introduction

Since the introduction of pronethalol (Black & Stephenson, 1962), an increasing number of drugs which block β-adrenoceptors has been described (Shanks, 1966 ; Fitzgerald, 1969). Many of these differ from each other in the possession of a variety of additional properties (Fitzgerald, 1969). Pronethalol and propranolol are potent local anaesthetics, abolish ouabain-induced arrhythmias in animals and have a direct depressant action on the heart (Morales-Aguilera & Vaughan Williams, 1965 ; Levy & Richards, 1966 ; Barrett & Cullum, 1968 ; Levy, 1968). These actions are probably not the result of blockade of β-adrenoceptors but are manifestations of effects on membrane activity (Fitzgerald, 1969). I.C.I. 45763 (Kö 592), I.C.I. 50172 (practolol), alprenolol and oxprenolol have intrinsic sympathomimetic activity (Shanks, 1966 ; Fitzgerald, 1969). MJ 1999 (" Sotalol ") is the only compound which blocks β-adrenoceptors and is devoid of both membrane activity and intrinsic sympathomimetic activity (Lish, Weikel & Dungan, 1965 ; Shanks, 1966). The contribution of membrane activity and intrinsic sympathomimetic activity to the therapeutic effectiveness and to the production of and protection against unwanted effects in patients is still not clear. Elucidation of these problems would be advanced by studies comparing the effects of compounds possessing membrane activity or intrinsic sympathomimetic activity with MJ 1999, which has neither property.

Before the initiation of such studies the β-adrenoceptor blocking activity of MJ 1999 in man should be compared with propranolol so that clinical studies are carried out using doses with equivalent β-adrenoceptor blocking activity. In this paper we compare the effects of MJ 1999 and propranolol on the changes in heart rate produced in healthy subjects by exercise and by isoprenaline and on the tachycardia of patients with thyrotoxicosis.

Methods

Observations were made on healthy volunteers and on patients with thyrotoxicosis to whom the procedures to be used had been described. In all subjects lead II of the electrocardiogram was recorded on a direct writing electrocardiograph (Cardiomat, Siemens) at a paper speed of 25 mm/s. The heart rate was obtained by determining the time taken for five complete cardiac cycles.

Infusion of isoprenaline

Observations were made with the subjects supine. A needle was inserted into an antecubital vein and 0·9% sodium chloride solution infused at 3 ml/min using a mechanically driven syringe. When the heart rate was constant, isoprenaline sulphate, diluted in isotonic saline containing 0·003% ascorbic acid, was infused intravenously at 3 μg/min for 4 min. Heart rate was recorded at minute intervals before, during and for 3 min after the infusion of isoprenaline. In each subject isoprenaline was infused before and 5 min after each of a series of doses of propranolol or MJ 1999 given intravenously. These drugs were not given until the effects of the preceding dose of isoprenaline had worn off.

Exercise studies

The effects of the oral and intravenous administration of MJ 1999 and propranolol were studied using the same test procedure. Heart rate was recorded with the subject standing before and within 4 s of completion of a 3 min period of exercise which consisted of stepping on and off a box 38 cm high at the rate of 30 times/min. After two control exercise tests, 20 min apart, each subject was given orally a dose of MJ 1999 or propranolol. The exercise was repeated 1, 2, 3 and 4 h after administration of the drug. All subjects received all doses of each drug. The effects of the drugs on intravenous administration were studied in different subjects who exercised once before the administration of any drug. Twenty-five minutes later heart rate was recorded and 5 ml of saline injected intravenously. After a further 5 min heart rate was recorded before and after completion of a period of exercise. The same procedure was used during three further periods of exercise at 25 min intervals when the test drugs were administered. Drugs were injected intravenously over a period of 2–3 min. All subjects received both drugs.

Patients with thyrotoxicosis

Observations were made on five hospitalized patients with mild to moderate thyrotoxicosis confirmed by standard clinical and biochemical investigations. All patients were in sinus rhythm and none were in cardiac failure or had any other cardiac disorder. The investigations were made with the patients in a basal state and after at least 1 h resting in the supine position. A needle was inserted into a

forearm vein and left in position throughout the period of observation. Heart rate was recorded at minute intervals during each experiment and when it became constant 5 ml of normal saline was injected intravenously. Five minutes later increasing doses of MJ 1999 or propranolol were given at 5 min intervals by intravenous injection taking 1 min for each injection. All patients received both drugs.

The following drugs were used: (±)-4-(2-isopropylamino-1-hydroxyethyl)methanesulphonanilide (MJ 1999, "Sotalol", British Drug Houses), (±)-propranolol ("Inderal", Imperial Chemical Industries) both as the hydrochloride; (±)-isoprenaline sulphate (Boots). All drugs were administered as the salt and doses are expressed in terms of the salt with the exception of isoprenaline, which is expressed in terms of the base.

Results

Responses to isoprenaline

The intravenous infusion of isoprenaline at 3 μg/min for 4 min increased heart rate in all eight experiments in six subjects. The effect of isoprenaline was maximal during the third and fourth minute of the infusion and the mean of these two values has been taken as the response to isoprenaline. The mean increase in heart rate produced by isoprenaline in the eight experiments was 28·4 ± 3·74 beats/min. In four subjects, isoprenaline was infused before and after 0·2, 1·0 and 5·0 mg of MJ 1999 and in four experiments before and after 0·2 and 1·0 mg of propranolol; both drugs were injected slowly intravenously. The increase in heart rate produced by isoprenaline after each dose of MJ 1999 or propranolol has been expressed as a percentage of the increase during the control period. The averaged results are given in Fig. 1. Increasing doses of MJ 1999 produced a progressive reduction in

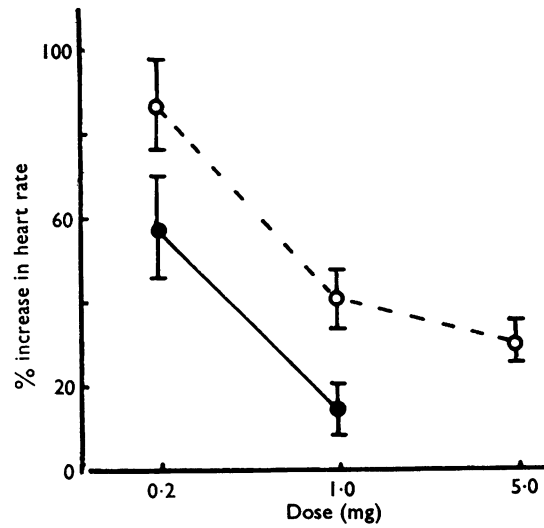

FIG. 1. Effect of the intravenous injection of propranolol (●——●) and MJ 1999 (○- - -○) on the increase in heart rate produced by the intravenous infusion of isoprenaline at 3 μg/min. The response to isoprenaline after each dose of propranolol and MJ 1999 has been expressed as a percentage of the increase during the control period. Each point is the mean (±S.E.M.) of observations in four subjects.

the isoprenaline tachycardia ; the effects of 1·0 and 5·0 but not 0·2 mg were significant ($P<0·05$). Both doses of propranolol produced a significant ($P<0·05$) reduction in the isoprenaline tachycardia. There was no significant difference between the effects of 0·2 mg of the two drugs, but 1·0 mg of propranolol produced a significantly greater reduction ($P<0·0025$) than the same dose of MJ 1999. Comparison of the doses of the two drugs to reduce the isoprenaline tachycardia by 50% showed that propranolol was 2·67 times more active than MJ 1999.

Heart rate response to exercise

MJ 1999 and propranolol by intravenous administration

The effect of the intravenous injection of three doses of MJ 1999 (8, 16 and 32 mg) and of propranolol (4, 8 and 16 mg) on heart rate at rest and at the end of exercise were compared in five subjects who received both drugs in random order on different days. The averaged results are given in Fig. 2 and in Table 1. The values for resting heart rate, the exercise tachycardia and the increase in heart rate on exercise after the injection of saline (control) were similar in both treatment groups. Each dose of MJ 1999 produced a significant ($P<0·05$) reduction in resting heart rate when the rates before and after each dose of drug were compared (Fig. 2). There was no significant difference between the heart rate after 8 mg and that after 16 and 32 mg of MJ 1999. Resting heart rate was significantly ($P<0·025$) reduced by propranolol 4 mg ; further but not significant reductions occurred after

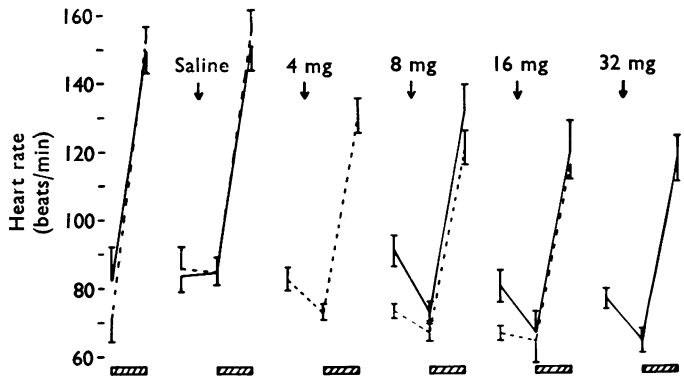

FIG. 2. Values for resting heart rate and the heart rate at the end of a 3-min period of exercise (////) before and after the intravenous administration of saline and increasing doses of propranolol (- - - -) and MJ 1999 (——). Mean of observations (±S.E.M.) in five subjects who received each drug on separate occasions. The left-hand set of responses were obtained during a control run.

TABLE 1. *Effect of the intravenous injection of a series of doses of propranolol and MJ* 1999 *on heart rate at rest and at the end of exercise*

	Propranolol				MJ 1999			
	Control	4 mg	8 mg	16 mg	Control	8 mg	16 mg	32 mg
Rest	84·4±4·5	73·0±2·2	67·0±2·4	64·6±6·8	84·2±3·5	72·6±3·3	66·8± 5·8	64·2±3·3
Exercise	154·2±6·6	130·0±4·8	120·8±4·8	115·6±4·3	150·4±7·0	131·6±7·1	119·2± 8·7	117·2±6·5
Increase	69·8±9·2	57·0±5·5	53·8±7·3	51·0±4·9	66·2±5·0	59·0±8·5	52·4±10·8	53·0±4·6

Mean of observations (with S.E.M.) from five subjects who received both drugs. The differences between the sets of observations have also been calculated.

8 and 16 mg. There was no significant difference between the resting heart rates after equal doses of the two drugs.

The heart rate at the end of exercise was significantly reduced by 4 mg of propranolol; further significant reductions occurred after 8 and 16 mg ($P<0.01$). MJ 1999 (8 mg) reduced the exercise tachycardia significantly ($P<0.01$); there was a further significant ($P<0.01$) reduction after 16 mg but little change after 32 mg. Comparison of the increases in heart rate on exercise showed that 8 mg of MJ 1999 and 4 mg of propranolol significantly reduced it; progressively greater reductions occurred with the larger doses, but these were not significant. There was no significant difference between the effects of equal doses of MJ 1999 and propranolol on the exercise tachycardia or on the increase in heart rate on exercise. These studies indicate that on intravenous administration there is no qualitative or quantitative difference between the effects of MJ 1999 and propranolol on resting heart rate in the standing position or on an exercise induced tachycardia.

MJ 1999 and propranolol by oral administration

Observations were made in five subjects who received in random order a placebo, propranolol (20 and 60 mg) and MJ 1999 (20, 60 and 180 mg) orally on different days. Figure 3 gives the average results from the five subjects for the resting heart rate and the heart rate at the end of exercise. The resting heart rate and exercise tachycardia before the administration of any drug were similar in all treatment groups (Fig. 3).

As the changes in resting heart rate and the exercise tachycardia were in most cases maximal 3 h after administration of the different doses of both drugs; statistical analysis of the results has been carried out using the values obtained at this time. Resting heart rate was reduced significantly ($P<0.05$) by the placebo, MJ 1999 (60 and 180 mg) and by both doses of propranolol. The effects of these doses of MJ 1999 and propranolol were significantly greater than that of the placebo. There was no significant difference in the reductions produced by the largest dose of both drugs.

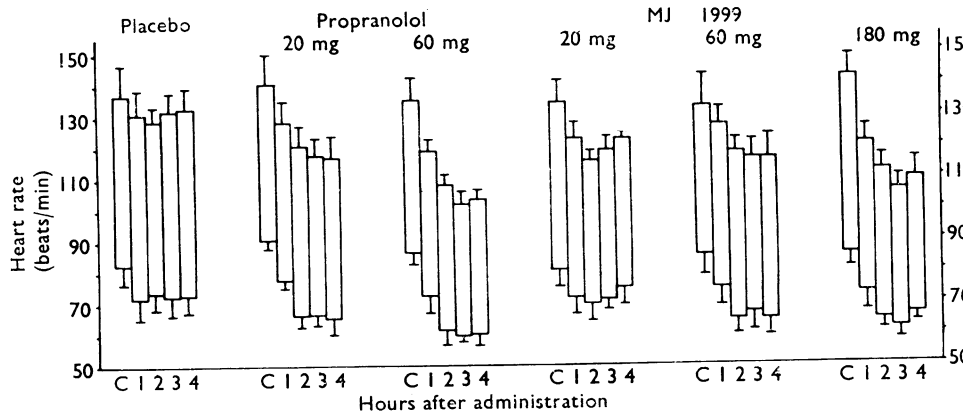

FIG. 3. Mean changes (±S.E.M.) in heart rate following the oral administration of a placebo and different doses of propranolol and MJ 1999 in five subjects. The bottom of each rectangle represents the resting heart rate and the top the heart rate at the end of a 3 min period of exercise. Observations were made before (C) and 1, 2, 3 and 4 h after the administration of each drug.

The drugs have been compared for their effect on the heart rate recorded at the end of the period of exercise performed 3 h after their administration. The placebo had little effect on the exercise heart rate, which was reduced by all doses of both drugs, but the effect of 20 mg of MJ 1999 was not significant. Although the effect of propranolol (60 mg) was significantly greater ($P<0.001$) than MJ 1999 (180 mg) there was no significant difference between the effects of 20 mg of propranolol and 20 and 60 mg of MJ 1999. These results indicate that propranolol was slightly more active than MJ 1999 in reducing an exercise tachycardia.

Heart rate changes in patients with thyrotoxicosis

The effect of the intravenous injection of a series of doses of MJ 1999 (2, 4, 8 and 16 mg) and of propranolol (2, 4 and 8 mg) on resting heart rate were compared in five patients with thyrotoxicosis. All patients received both drugs. The averaged results are given in Table 2. The administration of both drugs reduced heart rate. A significant effect occurred after 4 mg of MJ 1999 and after 2 mg of propranolol. As the dose of each drug was increased there was a progressive and usually significant fall in heart rate. The heart rate was less after each dose of propranolol than after the same dose of MJ 1999; this difference was significant for the 2 mg ($P<0.01$) and 8 mg ($P<0.025$) doses. These results indicate that propranolol is about twice as active as MJ 1999 in reducing heart rate in these patients.

Discussion

These results show that MJ 1999 blocks β-adrenoceptors in the heart in man, for it antagonized an isoprenaline tachycardia, reduced resting heart rate, exercise tachycardia and the heart rate of patients with thyrotoxicosis. These effects of MJ 1999 were similar to those obtained with propranolol in the present experiments and to those described in previously published studies with propranolol (Harris, Schoenfeld, Brooks & Weissler, 1966; Brick, Hutchison, McDevitt, Roddie & Shanks, 1968; McDevitt, Shanks, Hadden, Montgomery & Weaver, 1968). These results confirm those of Lish, Shelanski, La Budde & Williams (1967) and Frankl & Soloff (1968), who showed that the intravenous and oral administration of MJ 1999 inhibited the increase in heart rate produced in man by the intravenous infusion or subcutaneous injection of isoprenaline.

In animals propranolol has been shown to be 5 to 10 times more active than MJ 1999 in blocking the cardiac actions of isoprenaline (Shanks, 1966). A similar ratio of activity was not found in the present studies. Propranolol was twice as active in inhibiting the isoprenaline tachycardia and reducing the thyrotoxic tachy-

TABLE 2. *Effect of the intravenous injection of MJ 1999 and propranolol on resting heart rate in five patients with thyrotoxicosis*

			2 mg		4 mg			8 mg			16 mg		
				P less than		*P* less than			*P* less than			*P* less than	
	Control	Saline		*a*		*a*	*b*		*a*	*b*		*a*	*b*
MJ 1999	98·0 ±6·6	94·2 ±6·1	92·2 ±4·2	N.S.	87·4 ±3·9	0·05	0·01	83·0 ±2·5	0·025	N.S.	76·2 ±2·2	0·01	0·01
Propranolol	98·8 ±4·4	97·0 ±5·3	86·8 ±3·8	0·01	82·2 ±3·4	0·01	0·025	77·4 ±3·5	0·01	0·025			

a, Comparison with heart rate after saline.
b, Comparison with heart rate after preceding dose of drug.
The mean value (±S.E.M.) from the five patients obtained 5 min after each injection is given.

cardia. It was not possible to compare accurately the effects of the two drugs either on the exercise tachycardia or on the increase in heart rate on exercise, but the results indicate that both for intravenous and oral administration propranolol has not more than twice the activity of MJ 1999. The reason for the difference in potency ratio for the two drugs between man and animals is not clear.

Propranolol, unlike MJ 1999, is a potent local anaesthetic and has a quinidine-like action on the heart. It has been suggested that these actions may contribute to its therapeutic effectiveness in angina and cardiac arrhythmias (*British Medical Journal*, 1969a, b). The present study indicates that this property of propranolol does not appear to contribute to its effect on resting heart rate, on exercise tachycardia or the raised heart rate in patients with thyrotoxicosis, as its effect was similar to that of MJ 1999. A similar conclusion was reached as a result of earlier observations which showed that the dextro isomer of propranolol, which has only one-fiftieth the β-adrenoceptor blocking activity of racemic propranolol but the same local anaesthetic activity, had no significant effect on an exercise tachycardia and much less effect on the tachycardia of thyrotoxicosis than racemic propranolol (Brick *et al.*, 1968; McDevitt *et al.*, 1968).

The absence of intrinsic sympathomimetic activity with MJ 1999 in animals (Shanks, 1966) has been confirmed in the present experiments as it reduced resting heart rate in normal subjects and in patients with thyrotoxicosis. Propranolol had a similar effect. β-adrenoceptor blocking drugs with intrinsic sympathomimetic activity—for example, alprenolol, oxprenolol and LB 46—produce little change in resting heart rate in normal subjects and in patients with thyrotoxicosis (Ablad, Johnsson, Norby & Sölvell, 1967; Turner & Hill, 1968; Hill & Turner, 1969).

In man MJ 1999 is a potent β-adrenoceptor blocking compound which has about half the activity of propranolol. It has no local anaesthetic action or intrinsic sympathomimetic activity, and so it would appear to be important to initiate clinical studies with MJ 1999 to determine the role of these properties, which are present in some β-adrenoceptor blocking drugs, in contributing to the therapeutic and unwanted effects of β-adrenoceptor blocking drugs. The present studies indicate that in investigations designed to compare the effects of MJ 1999 and propranolol, the same degree of blockade of β-adrenoceptors in the heart will probably be produced by doses of MJ 1999 double those of propranolol.

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