Br. J. Pharmac. (1968), **34**, 116–126.

A comparison of some cardiovascular properties of propranolol, MJ 1999 and quinidine in relation to their effects in hypertensive animals

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1. A comparison of some cardiovascular effects of propranolol, MJ 1999 and quinidine has been made in rats and dogs.

2. After intravenous, subcutaneous or oral administration to rats and dogs, propranolol was found to be 2–4 times more potent than MJ 1999 in blocking the chronotropic and vasodepressor responses to intravenously administered isoprenaline.

3. Propranolol and quinidine affected the e.c.g. of rats and dogs in a similar manner.

4. At dose-levels causing effective blockade of β-receptors propranolol and MJ 1999 had no hypotensive effect after short- or long-term administration to conscious hypertensive rats and dogs.

5. At very high dose-levels propranolol and quinidine, but not MJ 1999, lowered blood pressure in the hypertensive rat. This effect of propranolol is probably related to one or more of the properties that propranolol and quinidine have in common rather than to a blockade of β-receptors.

6. The possible relevance of these results to the use of propranolol as a hypotensive agent in man is discussed.

Propranolol is the first β-receptor antagonist to enjoy wide clinical use. While its principal applications have been in the relief of anginal pain and control of arrhythmias, the drug has also been reported to lower blood pressure in hypertensive subjects, although estimates of its efficacy in this respect vary (Prichard & Gillam, 1964, 1966a ; Richards, 1966 ; Waal, 1966 ; Paterson & Dollery, 1966). It has been postulated that propranolol exerts its antihypertensive effect through either a specific blockade of β-receptors (Prichard & Gillam, 1964) or a non-specific (local anaesthetic, quinidine-like) action (Waal, 1966). In this paper an attempt has been made to reproduce the antihypertensive action of propranolol in hypertensive animals and to offer some explanation of its mode of action. Accordingly, the cardiovascular effects of propranolol in normotensive and hypertensive rats and dogs have been determined and compared with those obtained with quinidine and MJ 1999 [4-(2-isopropylamino-1-hydroxyethyl) methanesulphonanilide hydrochloride], a β-receptor

antagonist devoid of non-specific activity (Lish, Weikel & Dungan, 1965). A preliminary account of this work has been given to the British Pharmacological Society (Farmer & Levy, 1968). The chemical structures of the three drugs are given in Fig. 1.

Methods

Anaesthetized normotensive animals

Rats. Rats of either sex weighing 350–450 g were anaesthetized with urethane (1.5–2.5 g/kg) given intraperitoneally. Arterial blood pressure was recorded from a cannula in a carotid artery by a Devices blood pressure transducer coupled to a Devices polygraph recorder. Heart rate was measured by a Neilson instantaneous ratemeter triggered from the pulse pressure. Drugs were injected through a cannula in a jugular vein.

In some experiments rats were anaesthetized with ether and records of the e.c.g. and heart rate were taken each day at noon. The e.c.g. (lead II) was recorded using fine needle electrodes implanted subcutaneously and the *QRS* complex was used to trigger a Neilson instantaneous ratemeter. Changes in e.c.g. records were analysed using the method of Thompson & Letley (1967).

Dogs. Beagle dogs of either sex weighing 7–12 kg were anaesthetized with pentobarbitone sodium (30 mg/kg) given intravenously. Arterial blood pressure was recorded from a cannula in the right femoral artery by a blood pressure transducer. Heart rate was recorded by a Neilson instantaneous ratemeter triggered by the pulse pressure. Respiration was recorded via a Magill cuffed endotracheal tube by a Statham low-pressure transducer. In some experiments e.c.g. (lead II) was recorded using fine needle electrodes implanted subcutaneously. Drugs were injected or infused through a cannula in the left femoral vein.

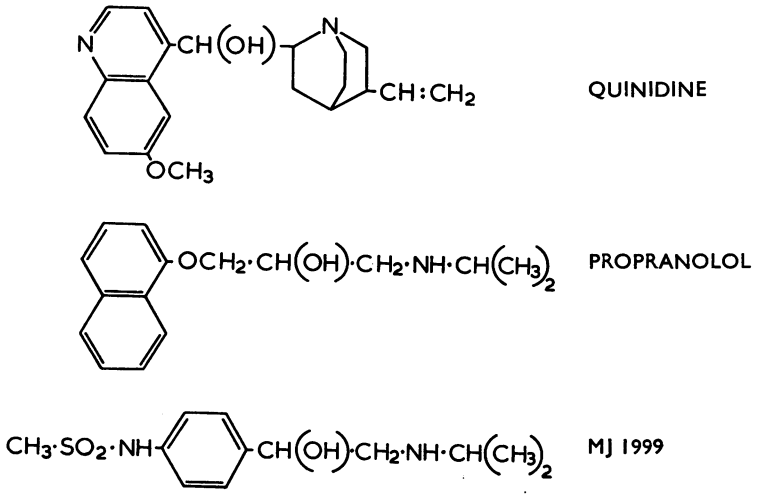

FIG. 1. Chemical structures of quinidine, propranolol and MJ 1999.

Conscious normotensive and hypertensive animals

Normotensive dogs. Beagle dogs were trained to lie quietly on their right side. The e.c.g. was recorded from plate electrodes attached to the limbs on a shaved area of skin. The *QRS* complex of the e.c.g. was used to trigger a Neilson instantaneous ratemeter to give a continuous record of heart rate. Control responses to isoprenaline (0.3 μg/kg) given intravenously were obtained. Propranolol and MJ 1999 were given by mouth in hard gelatine capsules and responses to isoprenaline obtained at intervals over a period of 6 hr after dosing.

Hypertensive rats. Male Wistar rats of a weight range 100–150 g were made hypertensive by unilateral nephrectomy and subcutaneous implantation of 50 mg deoxycorticosterone acetate (DOCA). The rats were given drinking water containing 0.9% w/v NaCl. Further injections of DOCA 2 mg/rat were given subcutaneously twice weekly in the second, third and fourth post-operative weeks. In the fifth post-operative week routine blood pressure and heart rate measurements were made. Only rats with a systolic blood pressure consistently greater than 150 mm Hg were used. Systolic blood pressure was measured from the tail by an indirect method using a sphygmomanometer and strain gauge to detect the pulse, which was amplified and monitored on an oscilloscope (A. W. Lessin, personal communication). The output of the amplifier was also used to trigger a Neilson instantaneous ratemeter to give a record of heart rate.

Hypertensive dogs. Hypertension was induced in male beagle dogs as described by Cullum, Farmer & Handley (1967). Anaesthesia was induced with thiopentone and maintained with nitrous oxide and oxygen (3:1 v/v) containing 3% halothane. The left carotid sinus was denervated and the left common carotid artery exteriorized in a tube of skin. At a second operation 3 weeks later both kidneys were mobilized and close fitting rubber capsules placed around each one in such a way that the renal vessels were not constricted. Three weeks later the capsules were removed, leaving the kidney permanently encased in a layer of fibrous tissue. Dogs maintaining a systolic blood pressure of about 150 mm Hg or greater were considered hypertensive. Systolic blood pressure was measured from the exteriorized carotid artery using a sphygmomanometer. Measurements were taken each day at 10.00, 12.00, 14.00 and 16.00 hr.

Drugs

The doses of drugs given refer to the base except where the salt is specifically named. Drugs used were: isoprenaline sulphate (Burroughs Wellcome), MJ 1999 (Mead Johnson), propranolol hydrochloride (I.C.I.), and quinidine sulphate (B.D.H.).

Results

Determination of β-receptor antagonist potencies of propranolol and MJ 1999

Intravenous administration to anaesthetized normotensive dogs

Propranolol (0.4 mg/kg) and MJ 1999 (1.6 mg/kg) given intravenously to anaesthetized dogs produced immediate falls in blood pressure (30–40 mm Hg) and heart rate (20–40 beats/min). The effects on respiration, heart rate and blood pressure of isoprenaline (2 μg/kg given intravenously) were almost abolished for up to 30 min after administration. After 2 hr responses to isoprenaline were still reduced, but to a greater extent with propranolol than with MJ 1999 (Fig. 2). The pressor response to occlusion (30 sec) of the common carotid arteries was markedly reduced

by propranolol and MJ 1999 and did not return to control levels throughout the experiment. The effects of propranolol and MJ 1999 on blood pressure, heart rate and responses induced by isoprenaline were found to be dose dependent. In the dose range investigated propranolol (0.05–0.4 mg/kg) was found to be 3–4 times more potent than MJ 1999 (0.2–1.6 mg/kg) and possessed a longer duration of action.

Subcutaneous administration to anaesthetized normotensive rats

In the anaesthetized rat the comparative abilities of propranolol and MJ 1999 given subcutaneously to block responses of the blood pressure and heart rate to isoprenaline (0.6 μg/kg given intravenously) were determined. Propranolol, in doses of 0.6 mg/kg and above, and MJ 1999, 2 mg/kg and above, abolished the fall in blood pressure and increase in heart rate produced by isoprenaline.

Oral administration to conscious normotensive dogs

The β-receptor antagonist potencies of propranolol and MJ 1999 were compared after oral administration to the conscious dog. In these experiments the increase in heart rate produced by an intravenous injection of isoprenaline sulphate (0.3 μg/kg)

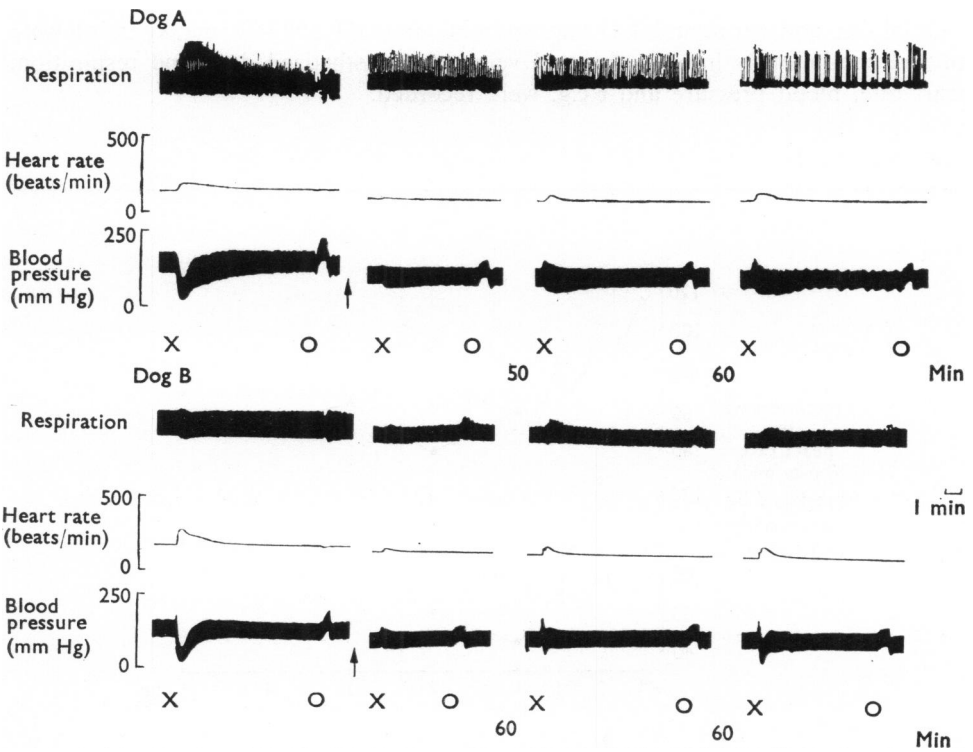

FIG. 2. Effects of propranolol and MJ 1999, given intravenously, on blood pressure, heart rate, respiration, carotid occlusion reflex and response to isoprenaline in the anaesthetized dog. ×, Isoprenaline sulphate, 2 μg/kg, i.v.; ○, bilateral occlusion of the carotid arteries for 30 sec. At ↑ propranolol (0.4 mg/kg, i.v.) administered to dog A (weight 8.75 kg) and MJ 1999 (1.6 mg/kg, i.v.) to dog B (weight 9.0 kg).

was recorded before and at intervals after the oral administration of placebo, propranolol or MJ 1999. The changes in isoprenaline-induced tachycardia after placebo administration were not greater than $\pm 10\%$ over a 5 hr period. Propranolol was given at 0.25, 0.5 and 1 mg/kg and MJ 1999 at 0.5, 1 and 2 mg/kg, orally. Two dogs were used at each dose level. Propranolol, at 0.25 mg/kg, and MJ 1999, at 0.5 mg/kg, caused only small decreases in the response to isoprenaline. Propranolol, 0.5 mg/kg, and MJ 1999, 1 mg/kg, reduced isoprenaline-induced tachycardia to a similar degree as shown in Fig. 3.

After MJ 1999 the responses to isoprenaline returned to near control levels within 4 hr but after propranolol the responses remained below those of the control for greater than 5 hr. At the highest dose levels investigated, both propranolol, 1 mg/kg, and MJ 1999, 2 mg/kg, almost abolished the isoprenaline tachycardia within the first hour after administration. Thereafter responses returned only slowly towards control levels over a 6 hr period. Propranolol, administered orally, was about twice as potent as MJ 1999 in antagonizing the effects of isoprenaline at β-receptors.

Comparison of the effects of quinidine, propranolol and MJ 1999 on e.c.g. in normotensive animals

Intravenous infusions in anaesthetized dogs

Quinidine and propranolol (1 mg/kg/min) and MJ 1999 (4 mg/kg/min) were infused continuously into the femoral veins of anaesthetized dogs and respiration, heart rate, blood pressure and e.c.g. were recorded.

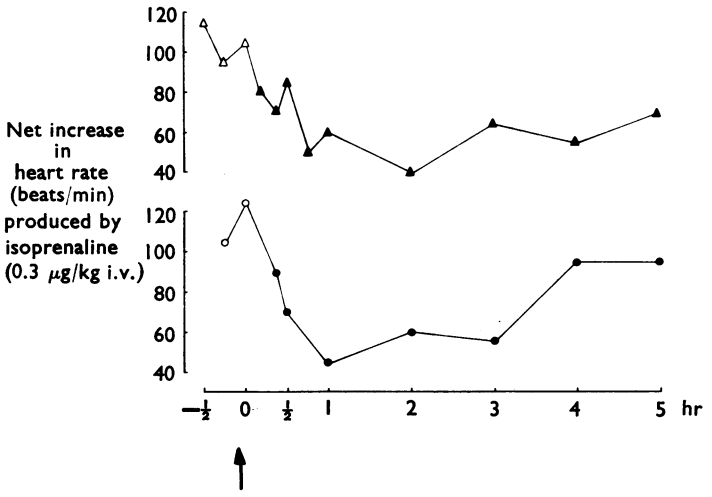

FIG. 3. Effects of propranolol and MJ 1999, given orally, on isoprenaline-induced tachycardia in the conscious dog. Propranolol (△▲, 0.5 mg/kg) and MJ 1999 (○●, 1 mg/kg) administered orally at ↑. The two experiments were carried out in the same dog on different days. Open symbols refer to control values.

Quinidine (1 mg/kg/min) caused an immediate sharp fall in blood pressure of 50 mm Hg followed by a further slow fall in blood pressure together with a narrowing of pulse pressure (Fig. 4a). Both heart rate and respiration rate slowly decreased. The pattern of the e.c.g. was such that the *P–R* and *Q–T* intervals were increased and there was marked right axis deviation of the *QRS* complex. Cardiovascular collapse and death occurred after 50 min.

Continuous infusion of propranolol (1 mg/kg/min) caused a gradual fall in blood pressure accompanied by marked narrowing of pulse pressure and decrease in heart rate. The results of one experiment are shown in Fig. 4b. Both the rate and depth of respiration were decreased. The e.c.g. pattern was altered in a similar manner to that seen with quinidine. *P–R* and *Q–T* intervals were both increased and some right axis deviation of the *QRS* complex occurred. In this experiment respiration ceased after only 10 min and death occurred shortly after. In another experiment in which propranolol was infused at the same rate, death resulting from cardiovascular collapse occurred after 30 min.

MJ 1999 (4 mg/kg/min) had similar effects on respiration, blood pressure and heart rate to propranolol (Fig. 4c), except that the e.c.g. pattern showed less change, the most marked effect being an alteration in the shape and amplitude of the *T* wave. The *P–R* interval was increased to a lesser degree than with quinidine or propranolol and the mean electric axis of the *QRS* complex was unaltered. Death due to respiratory failure occurred after 28 min.

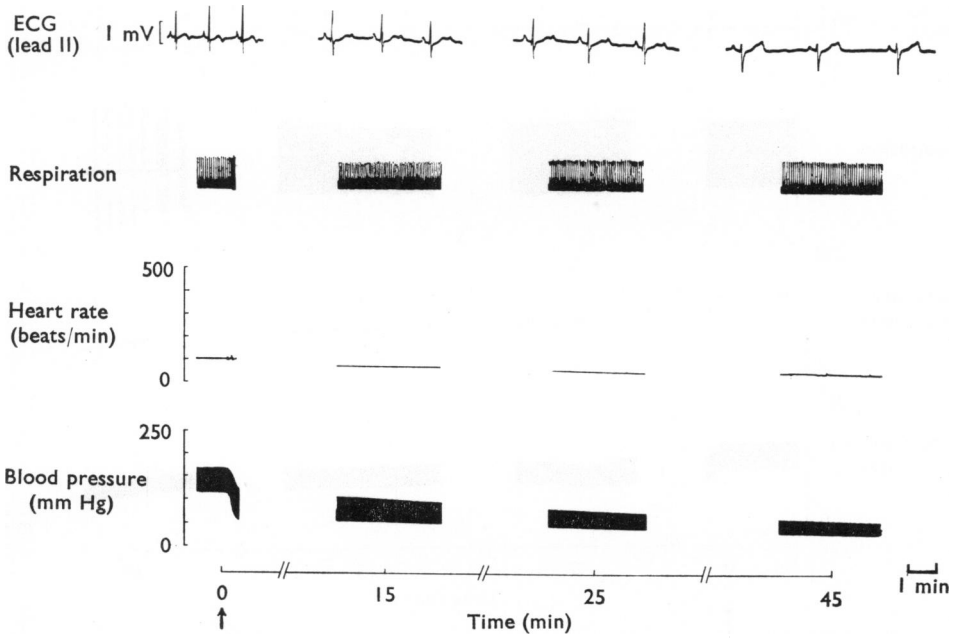

FIG. 4a. Effects of quinidine given by intravenous infusion on respiration, blood pressure, heart rate and e.c.g. in the anaesthetized dog. At ↑ infusion of quinidine (1 mg/kg/min) commenced.

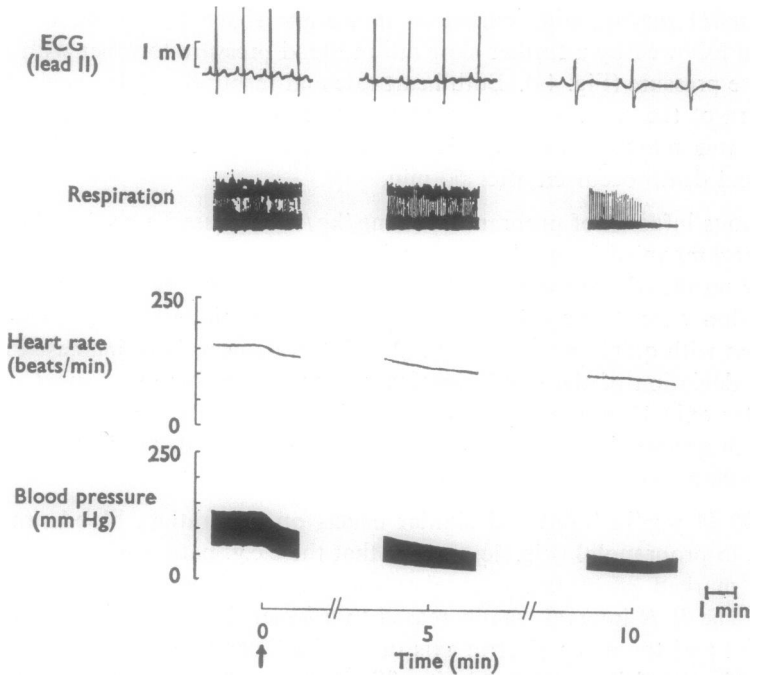

FIG. 4b. Effects of propranolol given by intravenous infusion on respiration, blood pressure, heart rate and e.c.g. in the anaesthetized dog. At ↑ infusion of propranolol (1 mg/kg/min) commenced.

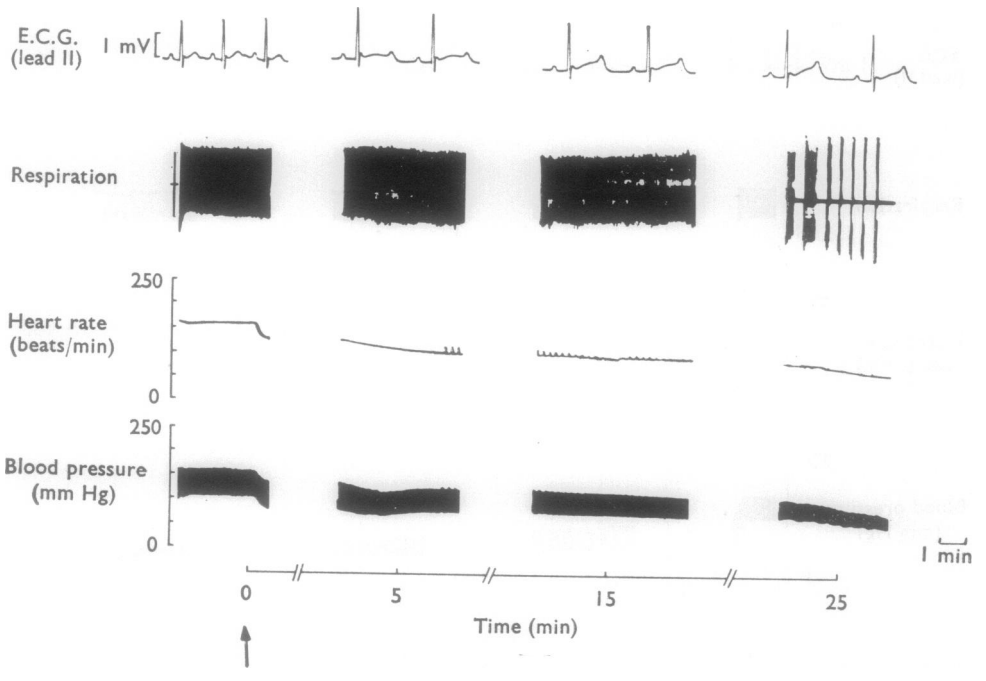

FIG. 4c. Effects of MJ 1999 given by intravenous infusion on respiration, blood pressure, heart rate and e.c.g. in the anaesthetized dog. At ↑ infusion of MJ 1999 (1 mg/kg/min) commenced.

Subcutaneous administration to anaesthetized rats

The effects of repeated doses of quinidine and propranolol (50 mg/kg) and MJ 1999 (150 mg/kg) were investigated on heart rate and e.c.g. in anaesthetized rats. During a treatment period of 3 days, drugs were administered to groups of three rats at 10.00 hr and 16.00 hr on the first 2 days and at 10.00 hr on the third day. A control group of three animals received subcutaneous injections of saline. Heart rate and e.c.g. recordings were obtained daily at 12 noon from animals anaesthetized with ether.

Administration of saline had no effect on heart rate or e.c.g. With successive doses quinidine produced slight bradycardia and increased the *P–R* interval from 0.055 sec to nearly 0.07 sec (Fig. 5). Propranolol caused marked bradycardia and increased the *P–R* interval to a slightly greater degree than quinidine. Both drugs also increased the *Q–T* interval and produced similar degrees of axis deviation. MJ 1999 produced less bradycardia than propranolol and, in contrast to quinidine and propranolol, caused no increase in the *P–R* interval.

Effects of quinidine, propranolol and MJ 1999 in hypertensive animals

Hypertensive rats

The effects of repeated subcutaneous doses of quinidine, propranolol and MJ 1999 on systolic blood pressure and heart rate were determined in conscious hypertensive rats. Quinidine was given at 50 mg/kg, propranolol in doses ranging from 5 to 50 mg/kg and MJ 1999 in doses ranging from 5 to 150 mg/kg. Throughout a treatment period of 3 days groups of four rats received the drugs at 10.00 hr and 16.00 hr on the first 2 days and at 10.00 hr on the third day. The systolic blood pressure and heart rate were measured daily at 12 noon. Fig. 6 illustrates the effects of quinidine (50 mg/kg) and propranolol (10, 20 and 50 mg/kg).

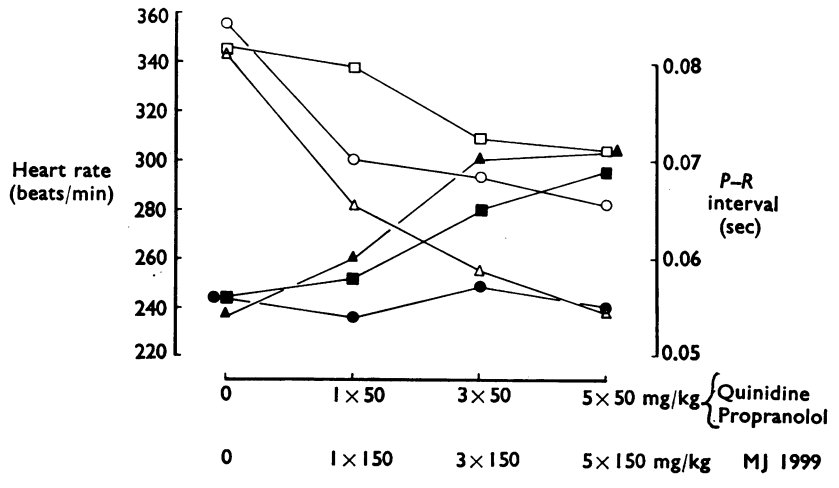

FIG. 5. Effects of quinidine, propranolol and MJ 1999 given subcutaneously on heart rate and *P–R* interval in the rat. E.c.g. and heart rate recordings obtained 2 hr after dose recorded on abscissa from rats anaesthetized with ether. Each point is the mean of readings obtained from three animals. Heart rate: □——□, quinidine; △——△, propranolol; ○——○, MJ 1999. P-R interval: ■——■, quinidine; ▲——▲, propranolol; ●——●, MJ 1999.

Quinidine (50 mg/kg) exerted a marked antihypertensive effect with an associated tachycardia. After three doses the systolic blood pressure was reduced by about 45 mm Hg. The pulse pressure measured from the tail was progressively reduced in amplitude, but still detectable after five doses.

Propranolol (2–20 mg/kg) caused substantial falls in heart rate but did not lower the blood pressure. At 20 mg/kg propranolol reduced the pulse pressure in a similar manner to quinidine. With a single dose of 50 mg/kg the blood pressure was reduced by 30 mm Hg and the pulse pressure and heart rate were markedly reduced. After a further two doses no pulse could be detected and dosing was stopped. The blood pressure returned to normal and heart rate and the pulse pressure to near normal levels within 24 hr (Fig. 6).

MJ 1999 (5 to 150 mg/kg) caused substantial falls in heart rate but did not lower blood pressure. The pulse pressure was only slightly reduced.

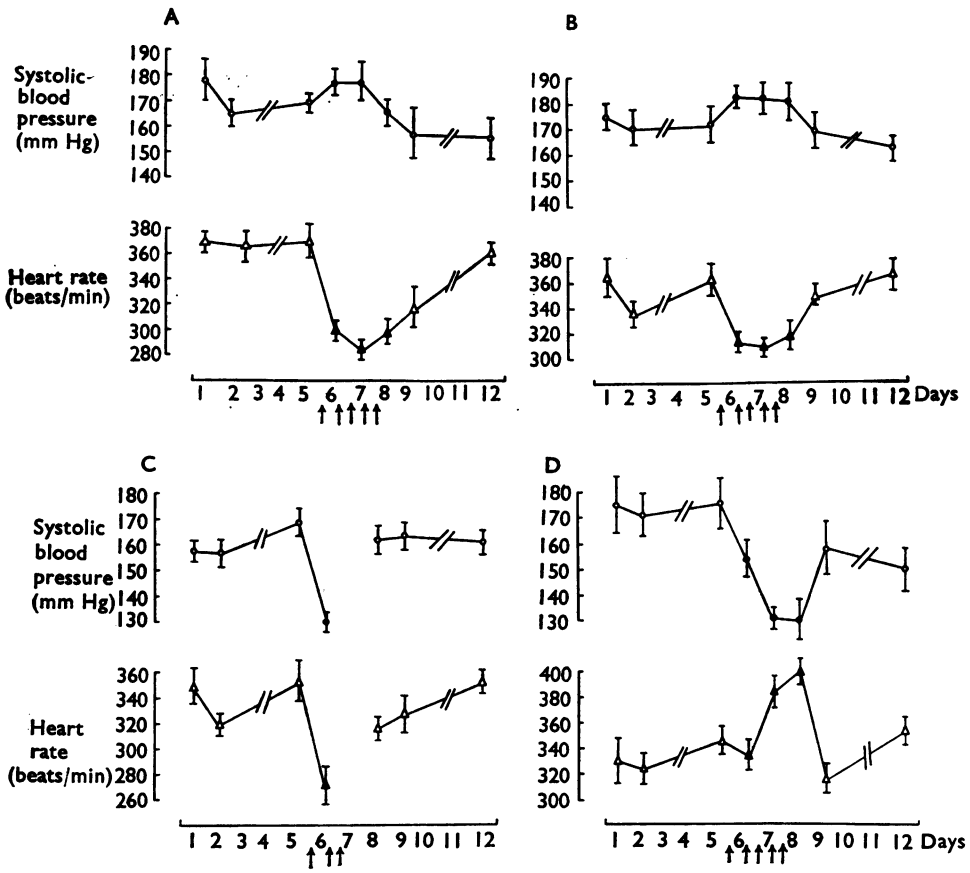

FIG. 6. Effects of quinidine and propranolol given subcutaneously, on blood pressure and heart rate of hypertensive rats. Groups of four rats dosed at 10.00 and 16.00 hr on the first 2 days and at 10.00 hr on the third day. Open symbols: readings during pre- and post-dosing periods. Closed symbols: readings during dosing period. Readings taken at 12 noon daily. A, Propranolol (20 mg/kg, s.c.) at arrows; B, propranolol (10 mg/kg, s.c.) at arrows; C, propranolol (50 mg/kg, s.c.) at arrows; D, quinidine (50 mg/kg, s.c.) at arrows.

Hypertensive dogs

Propranolol was given orally to three conscious hypertensive dogs in single daily doses ranging from 1 to 20 mg/kg. Heart rate was reduced by 10–30 beats/min at 2 mg/kg and no further decrease occurred at higher dose-levels. The systolic blood pressure was unaffected at all dose-levels.

In an experiment extending over 2 months, propranolol was given orally to three conscious hypertensive dogs in single daily doses of 5 mg/kg for the first 4 weeks and then in two daily doses of 5 mg/kg, given morning and evening, for the second 4 weeks. The readings in each successive week were averaged to give a single figure for blood pressure and heart rate. Table 1 summarizes the results from 2 control weeks and from the first, fourth, fifth and eighth weeks of dosing. The heart rate was significantly decreased during the first 4 weeks, but there was no further decrease when the dose was doubled during the second period of 4 weeks. The systolic blood pressure was not reduced throughout the period of treatment.

Discussion

β-receptor antagonists are equally effective in blocking responses to nerve stimulation and to circulating amines (Moran, 1967). These experiments, in which propranolol and MJ 1999 were shown to block the effects of large doses of isoprenaline, demonstrate that effective β-receptor blockade does not result in a lowering of blood pressure in hypertensive rats and dogs despite large reductions in heart rate. Propranolol and quinidine do lower blood pressure in hypertensive rats when given in high doses which reduce pulse pressure and cause significant changes in the e.c.g. pattern. It seems therefore probable that the hypotensive action of these drugs in rats is caused by a direct action on the heart other than β-receptor blockade, which results in a depression of myocardial contractility and reduced cardiac output. The observation that high doses of MJ 1999 did not lower blood pressure is consistent with this conclusion because this drug did not affect pulse amplitude or cause any marked changes in the e.c.g. pattern. The blocking action at α-receptors and direct peripheral vasolidator action (Lyon & DeGraff, 1965) that quinidine exerts at high doses will also contribute to its hypotensive effect.

How relevant are these results, obtained in hypertensive animals, to the use of propranolol in the treatment of human hypertension? It should be emphasized that the doses of propranolol shown to lower blood pressure in hypertensive rats bear no relation to those used in man. This may reflect a basic difference in the etiology of the hypertension in man and in hypertensive animals. It is interesting to note in this respect that propranolol blocks the action of many hypotensive drugs such as guanethidine and methyldopa in hypertensive rats (Bein & Brunner, 1966)

TABLE 1. *Effects of propranolol, administered daily for 2 months, on systolic blood pressure and heart rate in the conscious hypertensive dog*

Week no.	Control 1	Control 2	1	4	5	8
Propranolol (mg/kg/day P.O.)	—	—	5	5	10	10
Weekly mean systolic blood pressure ± S.E. (mm Hg)	155±4	148±2	146±4	148±7	146±5	152±7
Weekly mean heart rate ± S.E. (beats/min)	85±6	89±4	77±2	72±1	73±2	77±2

Mean of readings obtained from three dogs.

but is sometimes used in conjunction with them in the treatment of human hypertension (Prichard, 1968). In comparing the hypotensive effect of propranolol in animals and in man it should be noted that its effectiveness in man is in question. Prichard & Gillam (1966b) found propranolol to be a hypotensive agent of potency comparable to bethanidine, guanethidine and methyldopa, while other workers found it to be only a mild hypotensive agent (Paterson & Dollery, 1966; Richards, 1966; Waal, 1966). From the results in hypertensive animals, propranolol would not be expected to be a potent hypotensive agent in man.

The mechanism by which propranolol lowers blood pressure in man is not certain. Prichard & Gillam (1966a) have postulated that blockade of the sympathetic supply to the heart is the primary cause of its hypotensive action. Waal (1966), however, noted that the hypotension was related neither to the fall in the heart rate nor to the dose-level of drug required to produce an antiarrhythmic effect. She also drew attention to the "striking similarity" between the hypotensive action of quinidine and propranolol. It would be interesting to see whether a β-receptor antagonist like MJ 1999, which has little non-specific activity, would lower blood pressure in those subjects who respond to propranolol. Further clarification of the mode of action of propranolol in man would be obtained by testing its optical isomers, because the β-receptor blocking activity resides almost exclusively in the (−)-isomer (Howe & Shanks, 1966) while the non-specific activity resides equally in the (+)- and (−)-isomers (Shanks, 1967; Lucchesi, Whitsitt & Stickney, 1967).

We thank Miss A. Wilson for technical assistance.

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(*Received April* 23, 1968)