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β-Adrenoceptor blocking properties and cardioselectivity of M & B 17,803A

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Summary

1. The β-adrenoceptor blocking properties of (±)-1-(2-acetyl-4-*n*-butyramidophenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride (M&B 17,803A) have been compared with those of practolol and propranolol in the guinea-pig, cat and dog.

2. Following either intravenous or oral administration in the cat or dog, M&B 17,803A and practolol had similar potency in antagonizing isoprenaline-induced tachycardia and both showed cardioselectivity, but both were less potent than propranolol.

3. M&B 17,803A and practolol had approximately one hundredth the intravenous potency of propranolol in increasing the severity of anaphylactic bronchospasm in the conscious sensitized guinea-pig.

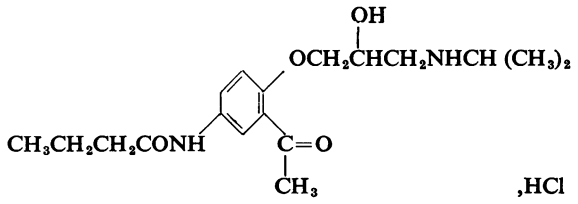
4. M&B 17,803A possessed less marked intrinsic sympathomimetic activity than practolol but, like propranolol, it had significant local anaesthetic properties and increased the refractory period of rabbit isolated atria.

Introduction

β-Adrenoceptor blocking agents are widely used in the management of angina, of cardiac arrhythmias and to some extent of hypertension (Lewis, 1971). Some of these drugs, notably propranolol, have the disadvantage of increasing airways resistance in asthmatic subjects, an effect thought to be due to inhibition of β-adrenoceptors in the bronchial tree (McNeill, 1971 ; McCulloch, Proctor & Rand, 1967). This disadvantage has led to the development of cardioselective β-adrenoceptor blocking agents, such as practolol (Dunlop & Shanks, 1968), which have a less marked inhibitory effect on bronchial as compared to cardiac β-adrenoceptors and have less tendency to increase airways resistance in asthmatic subjects.

In addition to its blocking activity on cardiac and bronchial β-receptors, propranolol also possesses membrane stabilizing or quinidine-like properties (Black, Duncan & Shanks, 1965). Practolol differs from propranolol in a number of respects in addition to its cardioselectivity ; thus practolol is devoid of membrane stabilizing and local anaesthetic activity and, in addition, possesses significant sympathomimetic properties (Barrett & Carter, 1970).

M&B 17,803A, (±)-1-(2-acetyl-4-*n*-butyramidophenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride, is intermediate between practolol and propranolol in possessing the cardioselective properties of the former and the local anaesthetic and membrane stabilizing properties of the latter.



M & B 17,803A

This paper outlines the pharmacological properties of M&B 17,803A, with particular reference to its β-adrenoceptor blocking activity in comparison with propranolol and practolol and describes the methods which have been used to compare the cardioselectivity of M&B 17,803A with that of other drugs.

A preliminary account of this work has been given (Basil, Jordan, Loveless & Maxwell, 1971).

Methods

Cardiac and peripheral vascular β-adrenoceptor blocking activity

Cats, deprived of food overnight, were anaesthetized with 80 mg/kg chloralose and 6 mg/kg pentobarbitone sodium intraperitoneally. Dogs were anaesthetized with 36 mg/kg pentobarbitone sodium intravenously supplemented at intervals as necessary. Guinea-pigs were anaesthetized with 1·5 g/kg urethane intraperitoneally and 6 mg/kg pentobarbitone sodium intraperitoneally. Systemic blood pressure was recorded from a carotid artery with a pressure transducer; the heart rate was obtained from a rate meter triggered by the lead II E.C.G. and continuously recorded. Drugs were administered either into a jugular vein or via a tube into the stomach.

Isoprenaline was administered intravenously at 7 min intervals, more than one dose being used in order to establish a dose-response relationship. Separate log dose-response lines were established for heart-rate increase and for fall in diastolic blood pressure. With intravenous doses of antagonist the compound was given 3·5 min in advance of the isoprenaline. With oral doses the extent of β-blockade was determined at intervals until partial recovery. In this case the extent of β-blockade was calculated at the time of maximal inhibition.

The extent of isoprenaline antagonism was determined from the magnitude of the isoprenaline response after the β-receptor antagonist had been given. A parallel displacement of the isoprenaline dose-response line was assumed. From this a dose-ratio (DR) was determined i.e. the increase in the dose of isoprenaline required to maintain the size of the response after the antagonist.

A computer programme based on the method of Fieller (1944) was written which calculated a regression with fiducial limits for log (DR-1) against log dose of β-antagonist.

Bronchial β-adrenoceptor blocking activity

Anaesthetized cats and guinea-pigs were prepared for recording respiratory compliance by the Konzett & Rössler (1940) method. Since the normal anaesthetized cat (but not the anaesthetized guinea-pig) has little bronchoconstrictor tone, constric-

tions were induced by the intravenous administration of 0·4 μg acetylcholine and these responses were subsequently reduced by the synchronous administration of isoprenaline at doses of 0·2–0·4 μg.

A dose-response line was established for the bronchodilator action of isoprenaline. After dosage with the β-blocker the procedure was repeated and displacement (assumed parallel) of the isoprenaline dose-response line measured and expressed as a dose-ratio (DR).

Cardiovascular changes in the anaesthetized dog

In some anaesthetized dogs, the lead II E.C.G. was recorded at a chart speed of 100 mm/s for several seconds in each minute. The β-adrenoceptor blocking compound was infused at 1 (mg/kg)/min (in some experiments with practolol, 10 (mg/kg)/minute). The P–R interval, carotid dP/dt, heart rate and mean blood pressure were determined at intervals.

Experiments in the conscious dog

Experiments were carried out in conscious trained dogs in which the blood pressure was recorded by the insertion of a needle into an exteriorized carotid artery by the method described by Maxwell & McLusky (1964). The pressure was transmitted to a transducer by a fine polythene tube and the recording made at a paper speed sufficiently fast for the identification of individual heart beats. The experiments were similar to those described for anaesthetized cats but the intervals between doses of isoprenaline were reduced to four minutes.

Potentiation of anaphylactic bronchospasm

Female guinea-pigs weighing 150–250 g were sensitized by the subcutaneous injection of 1 mg of crude egg albumin (antigen). Three weeks after sensitization a dose-response line to intravenous antigen was established in some of the animals by the use of a subjective scale of 0–12 to rate the severity of the anaphylactic shock. This scale was a follows: (12) death within 3 min ; (11) death between 3 and 4 min ; (10) death between 4 and 5 min ; (9 and 8) death between 5 and 7 min ; (7 and 6) death between 7 and 10 min ; (5) death after 10 min ; (4) convulsions in 2 min ; (3) convulsions after 2 min ; (2) laboured breathing ; (1) respiratory distress. A dose of antigen expected to induce an average anaphylactic score of 2–3 was selected for the remaining guinea-pigs. These animals were separated into groups. The β-adrenoceptor blocking compounds were injected intravenously. Ten minutes later the chosen dose of antigen was administered intravenously with six animals receiving each dose. The severity of anaphylactic shock produced was recorded and the mean score determined.

Sympathomimetic activity

The method of Barrett & Carter (1970) was used. Rats were treated with syrosingopine 5 mg/kg intraperitoneally. Twenty-four hours later, the animals were anaesthetized with pentobarbitone sodium 36 mg/kg intraperitoneally and the heart rate was determined from the E.C.G. The β-adrenoceptor blocking compounds were injected by an indwelling needle in a tail vein. Some normal animals and

some which also received 1 mg/kg propranolol intravenously 3·5 min before the test dose were also used.

Local anaesthesia

Local anaesthesia was determined by the method of Bülbring & Wajda (1945) modified only by the use of 0·05 ml of solution for the intradermal injections.

Local anaesthesia was also determined by the method of Bianchi (1956). An artery clip applied to the base of the tail evokes a vigorous reaction in the mouse. After local anaesthesia the mouse becomes indifferent to the stimulus. By injecting low concentrations of the test compound subcutaneously at the base of the tail, threshold local anaesthesia can be obtained. In these conditions some mice react and others do not. Concentrations were found which prevented the nociceptive reaction in 50% of the mice.

Studies on isolated atria

The Dawes (1946) method was used, modified by the use of a square wave stimulator. Rabbit isolated atria were suspended in Locke solution and electrically stimulated at an increasing frequency until they could no longer follow the driving frequency (maximum driving frequency). The compound under test was added to the Locke solution at various concentrations and left in contact with the atria for 10 minutes. At the end of this time the maximum driving frequency was again determined. The concentration of drug which reduced the maximum driving frequency by 25% of the control value was found by plotting log concentration against maximum driving frequency.

Drugs

Isoprenaline was used as the sulphate and propranolol as the hydrochloride. Practolol was used as the free base dissolved in an equivalent of dilute hydrochloric acid. Doses of isoprenaline, propranolol and M&B 17,803A refer to the salt. Doses of practolol refer to the base. Solutions of isoprenaline were stabilized by the addition of ascorbic acid.

Results

β-Adrenoceptor blocking activity and selectivity

Anaesthetized cat

In the anaesthetized cat the intravenous administration of low (0·1–1·0 mg/kg) doses of M&B 17,803A led to a decrease in the tachycardia induced by intravenous isoprenaline. Substantially higher (1·0–10 mg/kg) doses were required to antagonize the diastolic hypotensive response to isoprenaline.

As mentioned above the DR was calculated assuming a parallel shift of the isoprenaline dose-response line. Such a parallel displacement was observed following the oral administration of the antagonists. However, in some experiments, following the intravenous administration of the antagonist, parallel displacement was not observed. This was probably due to change in plasma levels of the

antagonist in the time involved in establishing the isoprenaline responses. From a series of experiments, the regression lines and fiducial limits of isoprenaline dose-ratio−1 (DR−1) on the dose of the β-adrenoceptor blocker for antagonism of both isoprenaline tachycardia and diastolic hypotension were computed for M&B 17,803A, practolol and propranolol (Figure 1).

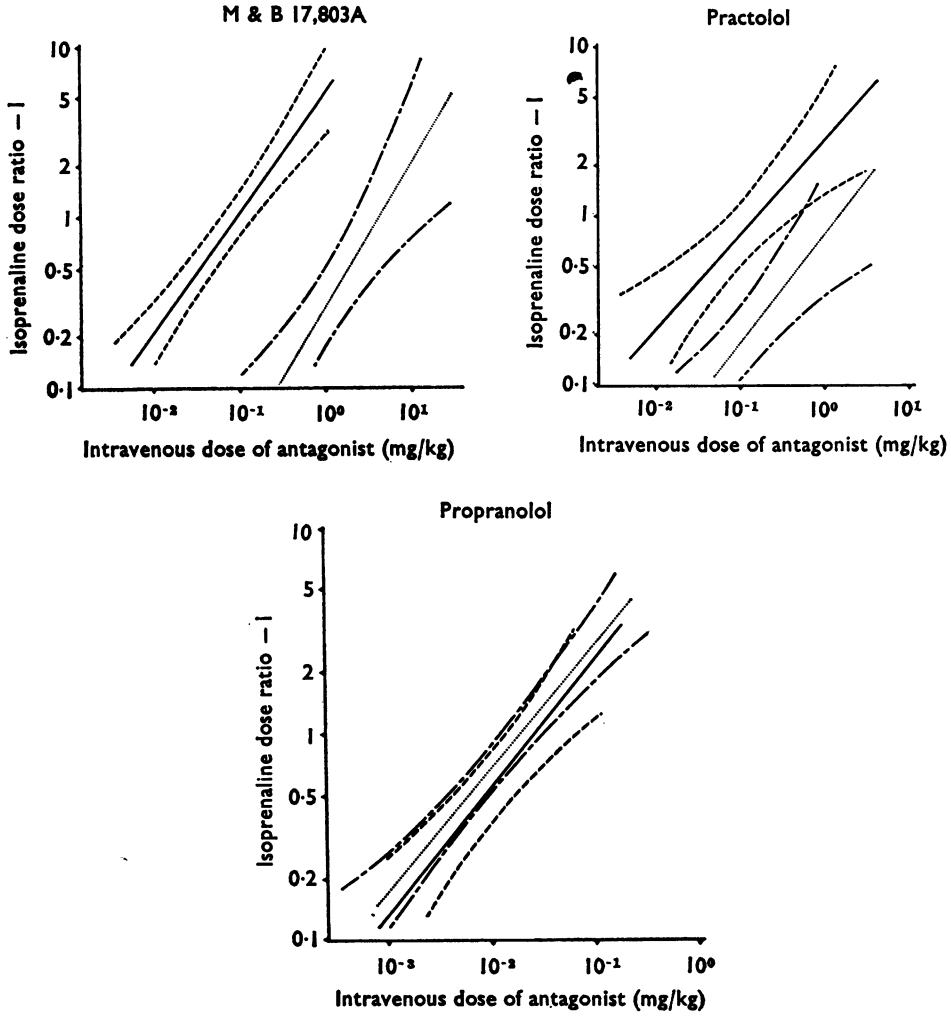


FIG 1. Regression lines computed for M&B 17,803A, practolol and propranolol in antagonizing isoprenaline-induced tachycardia (——) and diastolic hypotension (- - - -) in the anaesthetized cat. The ordinates are the isoprenaline dose ratio −1 on a logarithmic scale and abscissae the intravenous dose of β-blocking agent on a logarithmic scale. The envelopes (= = =) enclose the 95% confidence limits of the regression line.

The two dose-response lines (tachycardia and diastolic hypotension) for M&B 17,803A were clearly separated and the envelopes indicating the 95% probability regions did not overlap. The lines obtained with practolol were similar to those for M&B 17,803A although the separation was not so marked. In the case of propranolol the two dose-response lines were superimposed.

TABLE 1. *The activity of M&B 17,803A, practolol and propranolol in antagonizing isoprenaline-induced tachycardia and diastolic hypotension in various preparations.*

Effective doses (mg/kg)

Preparation	Route	M&B 17,803A Response measured (A) Tachycardia	M&B 17,803A Response measured (B) Diastolic Hypotension	M&B 17,803A Ratio B/A	Practolol Response measured (A) Tachycardia	Practolol Response measured (B) Diastolic Hypotension	Practolol Ratio B/A	Propranolol Response measured (A) Tachycardia	Propranolol Response measured (B) Diastolic Hypotension	Propranolol Ratio B/A
Anaesthetized cat	i.v.	0·09 (0·061–0·14)	4·3 (2·1–18)	48 (29–156)	0·158 (0·073–0.46)	1·6 (0·54–18)	10 (4–52·5)	0·026 (0·014–0·070)	0·020 (0·013–0·032)	0·77 (0·42–1·5)
Anaesthetized cat	oral	2·1 (1·1–4·0)	24 (9·4-Large)	11 (3·7–37·5)	2·0 (small–4·2)	45 (10-Large)	23 (3·9-Large)	0·082 (0·017–0·36)	0·042 (0·024–0·063)	0·51 (0·17–1·13)
Anaesthetized dog	i.v.	0·029 (0·011–0·058)	0·87 (0·44–2·8)	30 (11·3–100)	0·053 (0·015–0·120)	1·1 (0·226-Large)	21 (6·4-Large)	0·0087 (0·0054–0·012)	0·0071 (0·0039–0·01)	0·82 (0·47–1·2)
Conscious dog	i.v.	0·13 (0·05–0·26)	8·7 (2·07–375)	67 (19-Large)	0·61 (0·30–1·5)	5·3 (1·4–203)	8·8 (2·2–35·9)	0·010 (0·0032–0·24)	0·020 (0·0057–0·63)	2·0 (0·52–5·8)
Conscious dog	oral	2·9 (1·3–5·5)	18 (11–36)	6·2 (2·9–16·7)	6·4 (2·1–13)	14 (6·7–26)	2·2 (1·0–48)	0·62 (0·4–1·4)	0·42 (0·12–5·4)	0·68 (0·2–1·22)

The entries in the Table are the doses in mg/kg required to halve the potency of isoprenaline. Figures in brackets are the fiducial range quoted at a probability of 0·95.

TABLE 2. *The intravenous activity of M&B 17,803A, practolol and propranolol in antagonizing isoprenaline-induced tachycardia and diastolic hypotension in cats and dogs.*

Isoprenaline dose-ratio —1

Preparation	M&B 17,803A Response measured (A) Tachycardia	M&B 17,803A Response measured (B) Diastolic Hypotension	M&B 17,803A Ratio A/B	Practolol Response measured (A) Tachycardia	Practolol Response measured (B) Diastolic Hypotension	Practolol Ratio A/B	Propranolol Response measured (A) Tachycardia	Propranolol Response measured (B) Diastolic Hypotension	Propranolol Ratio A/B
	Dose 0·3 mg/kg			Dose 0·3 mg/kg			Dose 0·03 mg/kg		
Anaesthetized cat	2 (1·4–2·8)	0·1 (0·02–0·5)	20 (3·9–103)	1·4 (1·0–2·3)	0·33 (0·17–0·77)	4·2 (1·8–9·6)	1·1 (0·7–1·8)	1·3 (1·0–1·8)	0·85 (0·51–1·43)
	Dose 0·3 mg/kg			Dose 0·3 mg/kg			Dose 0·03 mg/kg		
Anaesthetized dog	7·7 (2·9–18)	0·5 (0·3–1·0)	15 (5·4–42)	2·5 (1·4–5·0)	0·3 (0·1-1·4)	8·4 (1·9–36·8)	3·3 (1·8–7·6)	4·7 (2·9–8·9)	0·7 (0·31–1·58)

Entries refer to the degree of β-blockade (isoprenaline dose-ratio —1) at the dose of β-adrenoceptor antagonist indicated. Values in brackets are the probable range at a probability of 0·95.

There are two important properties of these drugs which need quantification; first potency as β-adrenoceptor antagonists and, second, the degree of cardioselectivity. In order to measure potency, the doses of each antagonist required to produce an isoprenaline dose-ratio of 2 was determined from the dose-response curves (Figure 1). M&B 17,803A and practolol had comparable potency in antagonizing isoprenaline tachycardia and both were approximately one fifth as potent as propranolol (Table 1).

In order to measure cardioselectivity, two methods were used. The first was to compare the doses of a β-blocker required to produce a given isoprenaline dose-ratio on tachycardia and diastolic hypotension (horizontal transection of Figure 1). Thus the doses of M&B 17,803A required for an isoprenaline dose-ratio of 2 for tachycardia and diastolic hypotension were 0·09 and 4·3 mg/kg respectively. The ratio of these two doses, which gives an indication of the degree of cardioselectivity, was 48 (Table 1). According to this criterion, practolol was rather less cardioselective than M&B 17,803A in that the ratio of the doses of practolol required to produce an isoprenaline dose-ratio of 2 for tachycardia and diastolic hypotension was 10. Propranolol showed a slight, but not significant, degree of vascular selectivity.

The second method used to quantify selectivity was to compare the degree of β-blockade (isoprenaline dose-ratio − 1), for tachycardia and diastolic hypotension at a given dose of β-adrenoceptor antagonist (this corresponds to vertical transection of the lines in Figure 1). Thus following an intravenous dose of 0·3 mg/kg M&B 17,803A (Table 2), the degree of β-blockade on heart rate was 20 times larger than that on diastolic hypotension. In the case of practolol following an intravenous dose of 0·3 mg/kg the degree of β-blockade for tachycardia was 4·2 times that on diastolic hypotension, again indicative of cardioselectivity. Following the dose of 0·03 mg/kg propranolol, the degree of antagonism of isoprenaline tachycardia was similar to that seen with the ten times higher doses of M&B 17,803A or practolol. There was no indication of cardioselectivity with propranolol.

The oral potency of these drugs was also assessed in anaesthetized cats. Because of the slow absorption of drugs following oral administration, the challenge dose of isoprenaline was repeated at intervals until recovery was evident, and the isoprenaline dose-ratio was calculated from the maximal degree of inhibition recorded. This was found to be one and a half hours after an oral dose of M&B 17,803A or practolol and one hour after propranolol. M&B 17,803A and practolol showed similar potency following oral administration to the anaesthetized cat (Table 1) and both compounds showed cardioselectivity. Propranolol was some 30 times as potent as M&B 17,803A or practolol in inhibiting isoprenaline tachycardia and showed some vascular selectivity.

M&B 17,803A was studied for its activity in inhibiting isoprenaline bronchodilatation with the Konzett & Rössler (1940) preparation. Since the anaesthetized cat rarely shows any constrictor tone, bronchoconstriction was induced by the administration of acetylcholine and this increase in tone was reversed with isoprenaline.

The intravenous dose of M&B 17,803A required for a dose-ratio of 2 on bronchodilatation was 10·2 mg/kg whilst that required for a dose-ratio of 2 on tachycardia was 0·09 mg/kg. This much higher dose of M&B 17,803A required to antagonize

isoprenaline bronchodilatation and tachycardia again illustrates the cardioselectivity of the compound. Practolol and propranolol were not studied in this manner.

Anaesthetized dog

The results found in the anaesthetized dog (Table 1) were similar to those found in the cat. All three compounds were 2–3 times more potent in the anaesthetized dog than in the anaesthetized cat, but their relative potency was similar.

M&B 17,803A and practolol showed similar cardioselectivity and propranolol again showed a small degree of vascular selectivity.

Conscious dog

In the conscious trained dog (Table 1) larger intravenous doses of both M&B 17,803A and practolol were required to antagonize isoprenaline-induced tachycardia and diastolic hypotension than were required to produce the same effects in the anaesthetized dog. Propranolol was roughly equipotent in the conscious and anaesthetized dog.

Following oral administration to the conscious dog, M&B 17803A was approximately twice as potent as practolol and one fifth as potent as propranolol. M&B 17,803A showed a slightly higher degree of cardioselectivity than practolol, but the difference is not significant.

Guinea-pig

The relative potencies of M&B 17,803A and propranolol in antagonizing the tachycardia and bronchodilatation produced by intravenous isoprenaline were assessed in the anaesthetized guinea-pig.

The effective intravenous doses (mg/kg) of propranolol for antagonizing (DR=2) isoprenaline tachycardia and bronchodilatation were 0·01 and 0·009 respectively. The corresponding figures for M&B 17,803A were 0·03 and 0·16 indicating a higher potency on cardiac as compared to bronchial β-receptors.

It was found that in some guinea-pigs, propranolol, in doses of 0·02–0·2 mg/kg, produced a marked bradycardia which rendered the assay of β-adrenoceptor blocking activity difficult. In these experiments, the potency of propranolol in inhibiting isoprenaline-induced tachycardia was less than in animals where marked bradycardia was not seen. Only the experiments in which the bradycardia was not seen have been included.

In the conscious guinea-pig, inhibition of bronchial β-receptors is known to exacerbate anaphylactic bronchospasm. Intravenous doses of 0·01–0·1 mg/kg propranolol produced an increase in the severity of anaphylactic bronchospasm (Figure 2). Similar effects were produced by doses (5–50 mg/kg, i.v.) of either M&B 17,803A or practolol. The low potency of M&B 17,803A in potentiating anaphylactic bronchospasm when compared with its potency in inhibiting isoprenaline tachycardia in the anaesthetized guinea-pig is evidence of the less marked inhibitory actions of M&B 17,803A on bronchial β-receptors in comparison with propranolol.

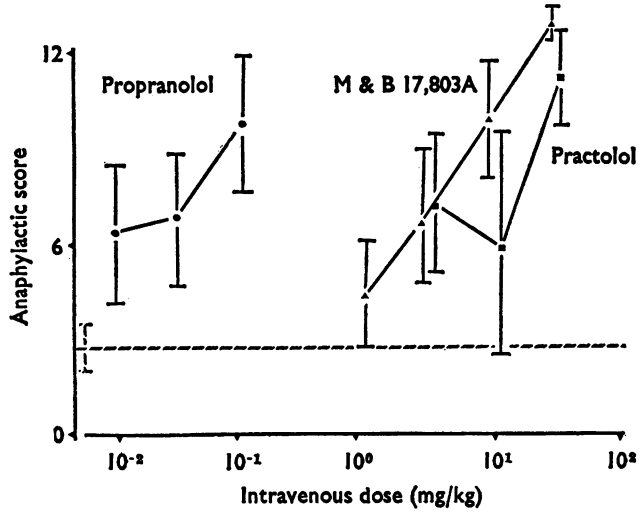


FIG. 2. Exacerbation of anaphylactic bronchospasm by intravenous M&B 17,803A (▲), propranolol (●) or practolol (■) in the conscious sensitized guinea-pig challenged intravenously with antigen. The ordinates show the severity of anaphylactic bronchospasm on a subjective 0–12 rating scale, and the abscissae the intravenous dose of β-blocking agent. Points refer to mean values from a minimum of six animals and vertical lines to the S.E.M. The horizontal line (– – –) indicates the mean anaphylactic bronchospasm score in control animals.

Duration of action of M&B 17,803A

The duration of the β-adrenoceptor blocking action was estimated in the conscious dog following the intravenous administration of 10 mg/kg M&B 17,803A using antagonism of isoprenaline-induced tachycardia and diastolic hypotension as criteria. In these experiments, the isoprenaline dose-ratio was determined at 0·25, 1, 2 and 24 h after the dose of M&B 17,803A. A plot of the logarithm of the isoprenaline dose-ratio against time approximated to a straight line with a half life of 1·9 h for tachycardia and 2·1 h for the diastolic hypotensive response. In respect to both responses, the animals responded normally to isoprenaline 24 h after dose. There was no evidence of change in cardioselectivity as a function of time.

Other actions on the cardiovascular system

Slow intravenous infusion of 1 (mg/kg)/min of propranolol to anaesthetized dogs (Fig. 3) produced a decrease in the value of dP/dt which became evident after 2 mg/kg had been infused (over 2 minutes). When 4 mg/kg (4 min) had been infused, the P–R interval of the E.C.G. began to increase and was accompanied by a fall in mean blood pressure and a bradycardia. By the time that 20 mg/kg had been infused, one dog died of cardiac arrest, and this was imminent in the remaining two dogs studied.

Practolol produced little or no cardiovascular changes. The decrease in dP/dt seen after 40 and 60 mg/kg infusion was not significant and was reversed by the time that 100 mg/kg had been infused.

M&B 17,803A was intermediate between propranolol and practolol. There was no evidence of a decrease in dP/dt until 6–10 mg/kg had been infused and only small increases in P–R interval occurred up to 20 mg/kg. After this time, the

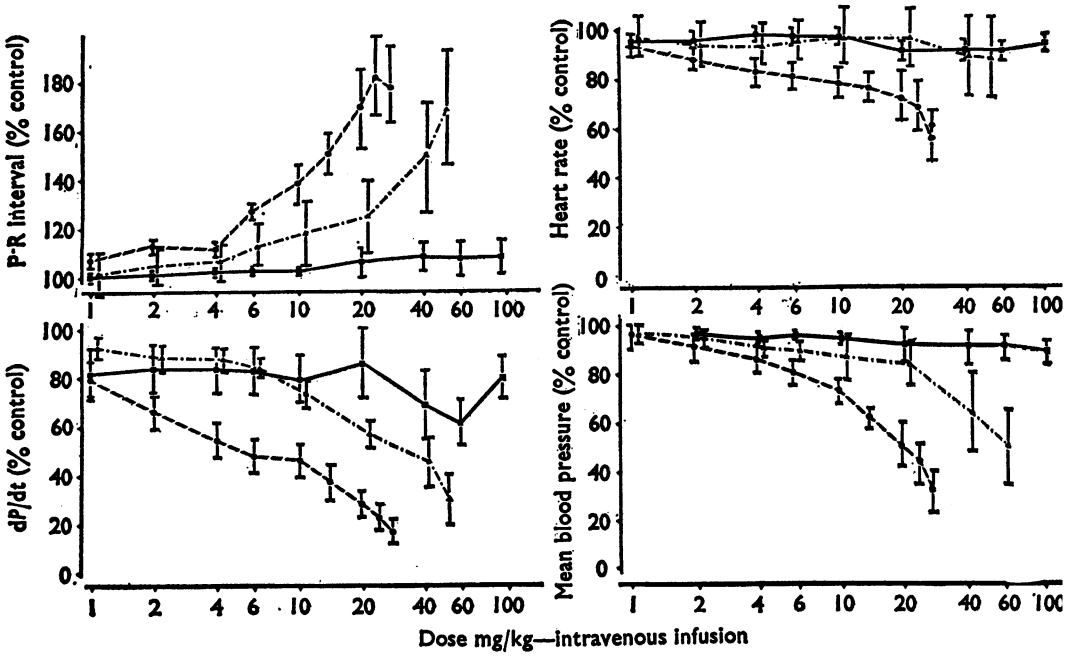


FIG. 3. Effect of the intravenous infusion of M&B 17,803A (▲), practolol (■) or propranolol (●) on (i) P-R interval of the ECG, (ii) dP/dt, (iii) the heart rate, and (iv) mean arterial pressure of the anaesthetized dog. The ordinates refer to the mean percentage of the control response and abscissae to the cumulative intravenous dose of β-blocking agent. Points are the mean values from three animals for each drug and vertical lines are the S.E.M.

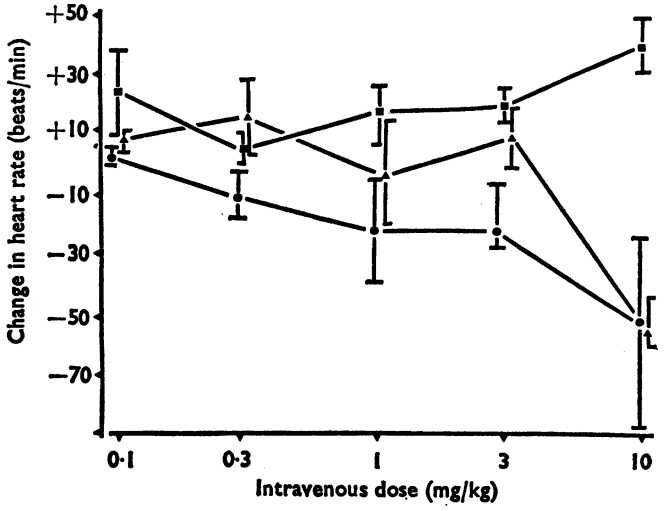


FIG. 4. Effect of intravenous M&B 17,803A (▲), practolol (■) and propranolol (●) on the heart rate of anaesthetized syrosingopine-pretreated rats. Ordinates refer to the change in heart rate (beats/min) and abscissae to the intravenous dose of β-blocking agent. Points refer to mean from at least six rats per group and vertical lines to the S.E.M.

P–R interval increases had become marked and a fall in blood pressure had begun but was not accompanied by a bradycardia.

Intrinsic sympathomimetic activity

Sympathomimetic activity was assessed by the ability of these drugs to produce increases in the heart rate of anaesthetized rats premedicated with syrosingopine (Barrett & Carter, 1970). We confirmed (Fig. 4) that propranolol had no significant intrinsic sympathomimetic activity and that practolol appeared to show a dose-related increase in heart rate, indicative of some sympathomimetic activity. M&B 17,803A produced increases in heart rate which did not appear to be dose-related and in general were smaller than those produced by the same doses of practolol. The increases in heart rate produced by practolol in the syrosingopine-treated rats were prevented by the prior administration of propranolol. At high doses, both M&B 17,803A and propranolol caused bradycardia in the syrosingopine-treated rat. In normal rats all three compounds caused bradycardia which was dose-dependent in the case of M&B 17,803A and propranolol.

Effect on refractory period and local anaesthetic activity

M&B 17,803A had approximately one fifth the potency of propranolol in increasing the refractory period of rabbit isolated atria *in vitro* (Table 3). In contrast, practolol was only effective at a very high concentration.

M&B 17,803A also possessed significant local anaesthetic properties when applied intradermally to the conscious guinea-pig (Table 3); it was considerably less effective than propranolol in this test but had an activity comparable with that of pro-

TABLE 3. *Comparison of the local anaesthetic activity of M&B 17,803A, practolol, propranolol in the guinea-pig and mouse,* in vivo, *and their action in increasing the refractory period of isolated rabbit atria* in vitro.

Species	Test	Effective concentration (mg/ml) M&B 17,803A	Practolol	Propranolol	Procaine	Quinidine
Mouse	Tail-clip	9·8 (6·07–14·66)	64 (38·0–Large)	3·6 (2·56–5·03)	3·7 (2·90–5·36)	—
Guinea-pig	Intradermal wheal	2·5 (1·27–3·43)	8·8 (4·40–12·10)	0·42 (0·37–0·46)	3·6 (1·04–5·57)	
Rabbit	Increase in refractory period of isolated atria	0·0077 (0·0019–0·012)	0·15 (0·09–0·51)	0·0015 (0·00075–0·0025)		0·0031 (0·00009–0·0071)

Figures in brackets are fiducial range at a probability of 0·95.

caine. Practolol had approximately one quarter the potency of M&B 17,803A in the guinea-pig intradermal wheal test.

When judged by their ability to prevent a nociceptive response in mice following the application of a clip to the tail, the three β-blockers had a similar rank order of potency to that found in the guinea-pig intradermal wheal test. In both tests, M&B 17,803A was less potent than propranolol but more active than practolol. The concentrations of these drugs required to produce local anaesthetic actions were much higher than those which produced an increase in the refractory period of isolated rabbit atria.

Discussion

The results presented here indicate that M&B 17,803A is a β-adrenoceptor blocking agent with potency comparable with that of practolol in various species and test situations. The measurement of the degree of selectivity for β_1-adrenoceptors (cardioselectivity) produced by M&B 17,803A and practolol presents certain problems. In general terms, the degree of cardioselectivity has been analysed in two contrasting ways. In the first, it is expressed in terms of the ratio of the doses of the antagonist required to produce a given degree of isoprenaline antagonism on various parameters in various tissues in the intact animal (heart rate, diastolic hypotension, bronchodilatation). In the second, cardioselectivity is expressed in terms of the degree of inhibition of β-receptors (measured in terms of isoprenaline dose-ratio) produced by a given dose of inhibitor.

The data obtained by the two methods are qualitatively similar, although quantitatively the degree of cardioselectivity is different. In the cat following intravenous injection, the cardioselectivity in terms of the ratio: (effective dose against isoprenaline diastolic hypotension)/(effective dose against isoprenaline tachycardia) is 48 for M&B 17,803A and 10 for practolol (Table 1). However, when the cardioselectivity is assessed in terms of the degree of β-blockade produced by 0·3 mg/kg intravenously (equivalent to about 20 mg in man), figures of 20 and 4·2 are obtained (Table 2). It is obviously important when reporting on the cardioselectivity of a drug that the method of assessment by clearly described.

The results obtained with practolol appear to be in general agreement with those described by Dunlop & Shanks (1968) although they did not attempt to quantify the degree of cardioselectivity of this drug.

Following intravenous administration to the anaesthetized dog, the degree of cardioselectivity shown by M&B 17,803A appeared to be similar to that found in the anaesthetized cat. The data obtained in the conscious dog are important since these may predict more closely than data obtained from anaesthetized preparations what might be expected in conscious man. Both M&B 17,803A and practolol were apparently less effective in the conscious dog in blocking β-adrenoceptors than in the anaesthetized dog, although the degree of cardioselectivity was not greatly altered. Propranolol had similar potency in the two preparations. M&B 17,803A and to a lesser extent practolol showed a lower degree of cardioselectivity (ratios B/A, Table 1) following oral administration to the conscious dog than following intravenous administration to this preparation.

Burden & Parkes (1972) have quantified the degree of selectivity of practolol in the anaesthetized guinea-pig using a statistical treatment similar to the one that we have used here. They found that practolol was more potent in inhibiting the tachycardia produced by either isoprenaline or cord stimulation than in inhibiting the corresponding changes in air overflow. We found that M&B 17,803A showed cardioselectivity in the guinea-pig both when assessed by antagonism of isoprenaline responses and when assessed by the enhancement of anaphylactic bronchospasm in conscious animals. Assem & Feigenbaum (1972) have found that propranolol can increase the histamine forming capacity of human leucocytes. This suggests that data on the enhancement of anaphylactic bronchospasm by β-blockers may have more relevance to the aggravation of bronchial asthma in man than do experiments on the antagonism of isoprenaline bronchodilation.

It is important to consider to what extent the data obtained with M&B 17,803A in experimental animals, particularly in respect to cardioselectivity, may be applicable to man. Cuthbert & Owusu-Ankomah (1971) found that propranolol was 7·5 to 10 times as potent as M&B 17,803A in inhibiting tilt-induced tachycardia. These authors found no consistent differences in the pattern of β-receptor blockade produced by M&B 17,803A, practolol or propranolol. Briant, Dollery, Fenyvesi & George (1971) concluded that there was no evidence of significant cardioselectivity with M&B 17,803A in man but they found a high degree of cardioselectivity in the degree of β-blockade in the anaesthetized dog.

The clinical interest in cardioselective β-blocking agents is due to their lower tendency to aggravate bronchospasm in patients with airways obstructive disease. Roetscher (1971) found that M&B 17,803A and practolol had similar properties in asthmatic subjects whereas propranolol under similar conditions (Langer, 1967) provokes bronchospasm. Furthermore propranolol, in doses of 5 to 10 mg intravenously, markedly increases airways resistance in asthmatic subjects (McNeill, 1971). This suggests that M&B 17,803A has at least some cardioselectivity in man.

Neither M&B 17,803A nor practolol produced a significant decrease in the resting heart rate of anaesthetized dogs at doses up to 60 and 100 mg/kg respectively by slow intravenous infusion whereas, with propranolol, a progressive bradycardia leading to cardiac arrest at 30 mg/kg was seen. There are two possible explanations for this difference. Firstly, that the lack of effect of M&B 17,803A and practolol on the resting heart rate is due to the presence of some sympathomimetic activity. This would appear to be unlikely since in animals depleted of catecholamines by syrosingopine, M&B 17,803A has a weaker intrinsic sympathomimetic activity than practolol and indeed high intravenous doses produce bradycardia. An alternative explanation is that the decrease in the resting heart rate produced by propranolol under these conditions is indicative of some non-specific myocardial depressant action. That M&B 17,803A in equipotent cardiac β-adrenoceptor blocking doses to propranolol may have a less marked myocardial depressant action than the latter is also indicated from the data on dP/dt. Propranolol, at 1 mg/kg, produced a significant decrease in dP/dt whereas M&B 17,803A, even at doses of 5–6 mg/kg had less effect on dP/dt. M&B 17,803A has approximately one third the cardiac β-adrenoceptor potency of propranolol in this preparation.

In addition to its selective action on myocardial β-receptors, practolol differs from propranolol in having very weak local anaesthetic properties and possessing low potency in increasing the refractory period of isolated atria. M&B 17,803A differs from practolol and resembles propranolol in possessing these properties to a significant degree. It appears likely that the activity of propranolol in angina pectoris (Wilson, Brook, Lloyd & Robinson, 1969) and in cardiac arrhythmias (Coltart, Gibson & Shand, 1971) results from the β-adrenoceptor blocking action of propranolol rather than its local anaesthetic or other actions on the myocardium. Whether this is true of M&B 17,803A remains to be seen.

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