Br. J. Pharmac. (1974), **50**, 323-333

A COMPARISON OF THE EXPERIMENTAL ANTI-ARRHYTHMIC PROPERTIES OF ACEBUTOLOL (M & B 17,803), PROPRANOLOL AND PRACTOLOL

B. BASIL, R. JORDAN, A.H. LOVELESS & D.R. MAXWELL

Pharmacological Research Laboratories, May & Baker Ltd, Dagenham, Essex

1 The β-adrenoceptor blocking agent, acebutolol (M & B 17,803), has been compared with propranolol, practolol, lignocaine and quinidine for its ability to revert or prevent various types of experimental arrhythmias.

2 By intravenous infusion, acebutolol had one half the potency of propranolol in reverting an established ouabain-induced ventricular arrhythmia in the anaesthetized dog. Practolol was ineffective in the conditions used.

3 High oral doses of acebutolol or propranolol significantly increased the arrhythmic dose of ouabain in the conscious rabbit. Similar doses of practolol produced a significant decrease (i.e. potentiation) in the dose of ouabain required to produce arrhythmia. Lignocaine and quinidine showed no or little activity in this test.

4 Propranolol, acebutolol and practolol were all effective in decreasing the frequency of ectopic beats induced by adrenaline and methylchloroform in the anaesthetized cat. Lignocaine and quinidine were only weakly effective.

5 Acebutolol and propranolol were equally effective either intravenously or orally in reducing the incidence of ventricular fibrillation produced by chloroform in mice.

6 It is suggested that the wide spectrum of experimental anti-arrhythmic activity of acebutolol coupled with its cardioselectivity may make it an interesting compound in the treatment of cardiac arrhythmias in man.

Introduction

The sympathetic β-adrenoceptor blocking agents, propranolol, practolol and alprenolol are used in the treatment of some types of cardiac arrhythmias of ventricular or supraventricular origin (Gibson & Sowton, 1969; Gent, Davis & McDonald, 1970).

These drugs differ from each other in a number of respects. Thus propranolol possesses local anaesthetic properties, reduces the rate of increase in the intracellularly recorded action potential in isolated atrial muscle and reduces the maximum driving frequency. Practolol has a selective action on cardiac β-adrenoceptors and has little local anaesthetic activity. It has 1/20th to 1/90th the potency of propranolol in reducing the maximum rate of rise of the intracellular action potential in isolated atria (Dohadwalla, Freedberg & Vaughan Williams, 1969) although it is useful in the treatment of supraventricular tachycardia (Jewitt, Mercer & Shillingford, 1969a; Gent, Davis & McDonald, 1970).

In experimental animals acebutolol hydrochloride (M & B 17,803A; (±)-1-(2-acetyl-4-*n*-butyramidophenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride) has some of the pharmacological properties of both propranolol and practolol. It possesses cardioselective β-adrenoceptor blocking activity whilst it also has local anaesthetic activity and reduces the maximal driving frequency of isolated rabbit atria (Basil, Jordan, Loveless & Maxwell, 1973b; Levy, 1973). It is not clear to what extent properties other than β-blockade are relevant to the clinical anti-arrhythmic action of β-adrenoceptor blocking agents, but it is of interest to compare the experimental anti-arrhythmic properties of acebutolol with those of propranolol and practolol. This paper describes the results of this comparison.

Methods

Ouabain-induced arrhythmias

Two methods have been used to study the effects of acebutolol, practolol and propranolol on ouabain-induced arrhythmias. In the anaesthetized dog, the drugs were tested for their ability to revert an established ouabain-induced arrhythmia. In the conscious rabbit the test drug was given in advance to protect the animal from the effect of a subsequent dose of ouabain.

Reversion of ouabain arrhythmia in the anaesthetized dog. Beagle dogs of body weight 6 to 12 kg and of either sex were anaesthetized with 30 mg/kg pentobarbitone sodium. Lead II ECG was recorded from needle electrodes. Ouabain was administered intravenously in divided doses commencing with an initial dose of 40 μg/kg. Thirty minutes later, 20 μg/kg was injected followed by additional 10 μg/kg doses at 15 min intervals until a persistent ventricular arrhythmia was obtained. In some experiments, stimulation of the distal end of the sectioned right vagus was used to demonstrate ventricular dominance. The arrythmia was allowed to stabilize for 10 min before the test compound was infused at approximately 1 mg kg^{-1} min^{-1} either until a sinus rhythm was restored or untoward symptoms were seen. When a sinus rhythm was restored, the infusion was stopped and the duration of the restored sinus rhythm noted. If sinus rhythm was not restored before untoward symptoms were produced (marked bradycardia or cardiac arrest) that animal was excluded from the calculation of the mean reverting dose.

Prevention of ouabain arrhythmias in the conscious rabbit. New Zealand White rabbits weighing 2 to 4 kg were restrained in stocks and the lead II ECG recorded from needle electrodes. A hypodermic needle was placed in a marginal ear vein for the infusion of ouabain, 5 to 10 μg kg^{-1} min^{-1}. The infusion was terminated when a ventricular tachycardia had been established for 30 s and the total dose of ouabain was determined in each rabbit.

Control responses were determined at three or four day intervals until reproducible results (ouabain dose range $\pm$ 7 μg/kg) were obtained (usually three to five responses). The initial responses were ignored and the mean of the three final control values taken as the mean control dose of ouabain required to produce arrhythmias in an animal. Three or four days later, the test compound was administered orally either 1 or 2 h before the ouabain challenge. The minimum intravenous dose of ouabain required to produce an arrhythmia was again determined.

The mean increase ($\bar{d}$) in the dose of ouabain required to produce an arrhythmia after the test drug was determined for each group. The significance of this increase was calculated by Student's t test using the expression:

$$d = (\text{test value}) - (\text{average control value})$$
$$t = \bar{d}/\text{s.e.}(\bar{d})$$

Sympathetically-induced arrhythmias

Two methods were used in which arrhythmias were precipitated by the administration of adrenaline and methylchloroform or chloroform alone.

Adrenaline/methylchloroform-induced arrhythmias in the cat. Cats weighing approximately 2 kg were anaesthetized by intraperitoneal injection of 80 mg/kg chloralose suspension and 6 mg/kg pentobarbitone sodium. The lead II ECG was recorded and ventricular arrhythmias, usually multifocal ectopic beats, were induced by an intratracheal spray of methylchloroform, 0.05 to 0.1 ml, followed in 10 s by adrenaline, 2 to 8 μg/kg, intravenously. The doses of methylchloroform and adrenaline were adjusted to give 60-90% arrhythmic beats in the 2 min period after the dose. When the doses required to produce arrhythmia had been established they were kept constant and repeated every 15 minutes. A series of control responses was thus obtained. The test drug was then administered intravenously and the methylchloroform/adrenaline challenge repeated at intervals. The reduction in the proportion of ectopic beats was determined.

Chloroform-induced fibrillation in the mouse. The method was a modification of that described by Lawson (1968). Albino mice of body weight 20-25 g were injected in groups of 10 per dose level; another group was injected with saline to serve as control. In experiments in which the test compound was given intravenously the mice were examined 2 min later. When the compound was administered orally they were examined 1 h later. The examination consisted of exposing each mouse to chloroform until respiratory arrest occurred. The mouse was then removed and lead II ECG recorded. From the record, the proportion of animals in ventricular fibrillation was determined, and the dose of compound which reduced the occurrence of ventricular fibrillation to 50% of the controls was calculated. Ventricular fibrillation occurred in 70-90% of the saline-treated controls.

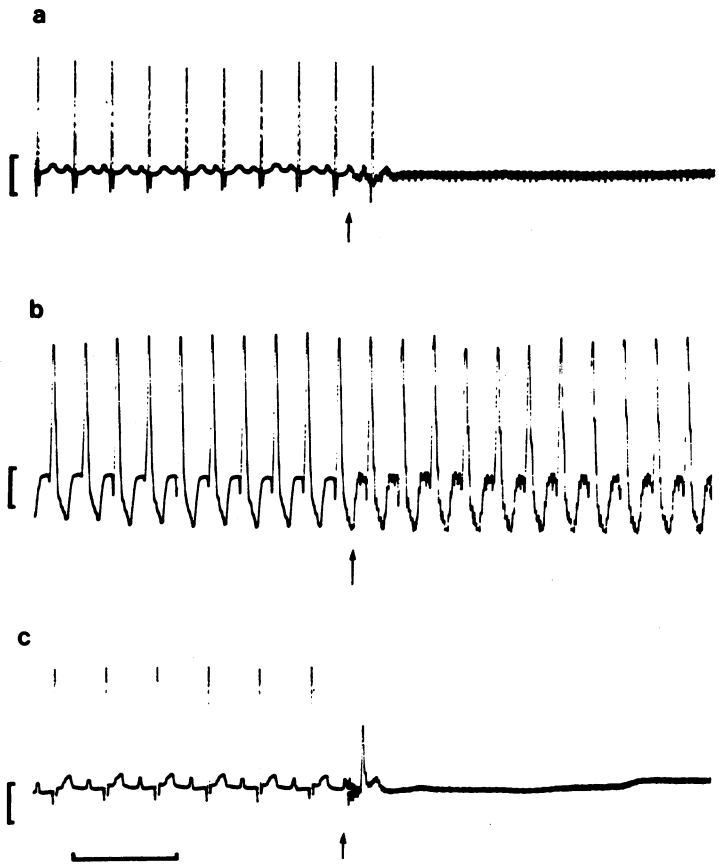

Fig. 1 Effect of intravenous acebutolol on ventricular arrhythmia induced by ouabain in the anaesthetized dog. Arrows indicate stimulation of peripheral end of cut right vagus (10 v, 30 Hz, 0.5 ms pulse width for 5 seconds). (a) Sinus rhythm prior to any drug administration (heart rate 170 beats/min)—vagal stimulation leads to asystole; (b) ventricular arrhythmia after a cumulative intravenous dose of 85 μg/kg of ouabain (rate 200 beats/min)—vagal stimulation has no effect on ventricular automaticity; (c) sinus rhythm restored after an intravenous infusion of acebutolol, 8.2 mg/kg (heart rate 123 beats/min)—vagal stimulation leads to asystole. Vertical scale, 1 mV; time mark, 1 second.

Drugs

Drugs used were: acebutolol, propranolol, lignocaine, procainamide, ouabain and (−)-adrenaline as hydrochlorides, quinidine sulphate and practolol base. Practolol was prepared for injection by dissolving the free base in an equivalent of dilute hydrochloric acid. Adrenaline was prepared for injection by dilution of adrenaline solution, 1 in 1000 w/v (M & B) and addition of ascorbic acid (1 mg/ml) to prevent oxidation. Doses of acebutolol, propranolol, lignocaine, quinidine and procainamide refer to the salt. Doses of practolol and adrenaline refer to the base.

Results

Ouabain-induced arrhythmia

Reversion of ouabain arrhythmia in the anaesthetized dog. The intravenous administration of ouabain produces a ventricular arrhythmia, characterized by ventricular dominance. Although vagal stimulation suppresses sinus rhythm, the ventricular wave persists (Figure 1c). This arrhythmia is persistent but is reverted by an appropriate intravenous dose of some anti-arrhythmic agents (Figure 1).

The intravenous infusion of acebutolol resulted

in restoration of a sinus rhythm from the ouabain ventricular arrhythmia in all five dogs tested at a mean dose of 8 mg/kg (Table 1). Two dogs maintained a sinus rhythm until the experiment ended 30 min after cessation of the infusion. In the other three animals the sinus rhythm was maintained for a mean of 16 min after the infusion of acebutolol was terminated.

Propranolol restored a sinus rhythm in four of the six animals in which it was studied; the mean intravenous dose was 3.8 mg/kg in these four dogs. The mean duration of sinus rhythm after cessation of the infusion in three of the dogs was 18 min, and in the fourth dog the ECG was normal 30 min after the infusion was stopped. In the remaining two dogs in which a sinus rhythm was not restored, the infusion of propranolol was continued until cardiac arrest occurred after 7.3 mg/kg in one dog and 12 mg/kg in the other.

In none of the four experiments carried out with practolol was a sinus rhythm restored. The total doses given were 35 mg/kg in two dogs and 70 mg/kg in the other two dogs without untoward symptoms. Lignocaine restored a normal rhythm in three of four dogs at a mean dose of 0.95 mg/kg. The duration of action of lignocaine under these conditions was short, ventricular arrhythmia returning after 2.5 minutes. In the fourth dog a sinus rhythm was not restored and cardiac arrest occurred at 7.0 mg/kg. Quinidine had a potency comparable with that of propranolol with a long duration of action. Procainamide was effective in three of the four dogs at an average dose of 10.5 mg/kg. In the fourth dog it was not effective up to 23 mg/kg.

Prevention of ouabain arrhythmia in the conscious rabbit. The intravenous infusion of ouabain to conscious rabbits produces ventricular arrhythmias of short duration.

An increase in the minimal dose of ouabain required to produce an arrhythmia may be taken as a measure of the anti-arrhythmic action of a drug. After the oral administration of acebutolol a dose-related increase in the arrhythmic dose of ouabain was recorded (Table 2). The increase was greater at 1 h than at 2 h after acebutolol. After oral practolol there was a *decrease* in the minimal arrhythmic dose of ouabain in all groups, although this decrease was only significant 1 h after the

Table 1 Comparison of the effect of acebutolol and standard drugs in reverting ouabain-induced arrhythmias in the anaesthetized dog

Drugs	*Mean arrhythmic dose of ouabain ±s.e. mean (μg/kg)*	*Mean dose of drug to restore sinus rhythm ±s.e. mean (mg/kg i.v.)*	*Proportion of dogs in which sinus rhythm restored*	*Duration of restored sinus rhythm (min)*	*Effect in non-reverted animals*
Acebutolol	83 ± 2.0	8.0 ± 1.2	5/5	16 (3) >30 (2)	–
Propranolol	83 ± 6.5	3.8 ± 0.6	4/6	18 (3) >30 (1)	Cardiac arrest following a mean dose of 9.6 mg/kg
Practolol	85 ± 6.3	–	0/4	–	No effect on arrhythmias up to 35 mg/kg (2) or 70 mg/kg (2)
Lignocaine	86 ± 3.6	0.95 ± 0.03	3/4	2.5 (3)	Cardiac arrest following 7.0 mg/kg
Quinidine	99 ± 6.6	3.7 ± 1.1	3/4	>30 (3)	15 mg/kg produced partial reversion only. (67% of sinus origin.)
Procainamide	99 ± 3.1	10.5 ± 1.3	3/4	>30 (3)	No effect on arrhythmias up to 23 mg/kg

Ventricular arrhythmias were produced by intravenous administration of ouabain. After arrhythmias had persisted for 10 min, the compound under test was infused at 1 mg kg^{-1} min^{-1}.

Table 2 Effect of acebutolol on ouabain-induced arrhythmias in the rabbit in comparison with standard anti-arrhythmic compounds

		1 h after test compound				*2 h after test compound*			
		Dose (μg/kg i.v.) of ouabain inducing arrhythmia		*Mean increase in ouabain dose*		*Dose (μg/kg i.v.) of ouabain inducing arrhythmia*		*Mean increase in ouabain dose*	
Compound	*Oral dose (mg/kg)*	*Mean control*	*Test value*	*(μg/kg) ± s.e. mean*	P	*Mean control*	*Test value*	*(μg/kg) ± s.e. mean*	P
Acebutolol	12.5	78.7	95.0	7.5 ± 3.1	0.07	88.0	91.0	−7.3 ± 5.4	0.25
		55.7	68.5			49.9	52.0		
		87.4	92.5			88.7	88.2		
		70.0	74.4			101	80.0		
		70.7	69.5			88.4	68.2		
	25	66.5	122.5	47.9 ± 10.3	0.005	79.8	105	11.1 ± 5.6	0.1
		41.1	87.0			98.7	122		
		55.0	92.5			76.9	83.5		
		61.7	117			104	109		
		46.8	131.5			37.0	33.0		
		62.7	70.5						
	50	42.9	193	72.9 ± 22.5	0.03	86.3	148	26.6 ± 11	0.07
		49.7	104			91.2	122		
		72.3	147			65.3	90.5		
		58.9	133			60.4	83.5		
		67.4	78.5			75.6	68.0		
Practolol	50	89.9	90.0	−9.4 ± 3.8	0.06	56.7	81	−1.0 ± 8.8	0.9
		102	99.0			100	107		
		81.0	70.0			95.7	99.5		
		91.7	79.2			95.1	81.5		
		154	133			114	86.9		
	100	74.0	66.1	−17.6 ± 4.9	0.02	72.5	68.7	−13.9 ± 5.1	0.052
		76.7	69.2			77.6	72.0		
		99.0	82.0			77.7	70.0		
		77.3	55.4			69.5	40.8		
		106	72.0			81.9	58.2		
Propranolol	25	100	142	−3.9 ± 13	0.8	61.7	68.5	−2.8 ± 3.6	0.5
		105	103			97.2	97.5		
		86.2	75.6			64.0	62.5		
		50.2	37.5			94.2	89.5		
		125	88.0			111.5	96.5		
	50	62.0	81.9	−0.9 ± 6.0	0.9	118	200	31.6 ± 18	0.2
		60.0	56.5			76.8	140		
		72.8	71.5			104	122		
		68.5	66.5			78.8	90.5		
		103	85.0			78.7	61.5		

Table 2—*continued*

		1 h after test compound				*2 h after test compound*			
Compound	*Oral dose (mg/kg)*	*Dose (μg/kg i.v.) of ouabain inducing arrhythmia* *Mean control*	*Test value*	*Mean increase in ouabain dose (μg/kg) ± s.e. mean*	P	*Dose (μg/kg i.v.) of ouabain inducing arrhythmia* *Mean control*	*Test value*	*Mean increase in ouabain dose (μg/kg) ± s.e. mean*	P
Lignocaine	25	135	118	−2.5 ± 5.1	0.7	98.3	141	4.8 ± 9.7	0.7
		126	131			32.5	31.6		
		94.2	97.5			108	106		
		82.5	81.0			88.4	84.7		
						46.9	34.4		
	50	67.7	59.5	0.9 ± 3.4	0.8	90.8	129	7.1 ± 11	0.6
		54.0	61.0			110	129		
		68.8	74.0			92.1	98.0		
		47.8	47.5			105	104		
						99.8	73.0		
	100	50.0	53.5	0.2 ± 3.4	0.96	97.7	121	9.5 ± 4.7	0.1
		84.3	86.0			104	121		
		66.6	72.0			111	119		
		70.3	60.5			116	115		
						109	110		
Quinidine	25	58.3	71.5	1.7 ± 3.6	0.7	85.7	80.0	−15.4 ± 7.4	0.1
		89.3	94.0			103	106		
		61.4	63.5			85.3	76.5		
		55.3	52.0			88.2	57.5		
		80.6	72.5			128	93		
	50	68.1	95.5	11.0 ± 6.8	0.2	92.8	143	13.2 ± 16	0.5
		99.8	119			81.5	130		
		65.9	81.7			61.4	61.5		
		90.5	94.5			112	108		
		77.8	66.0			121	92.8		

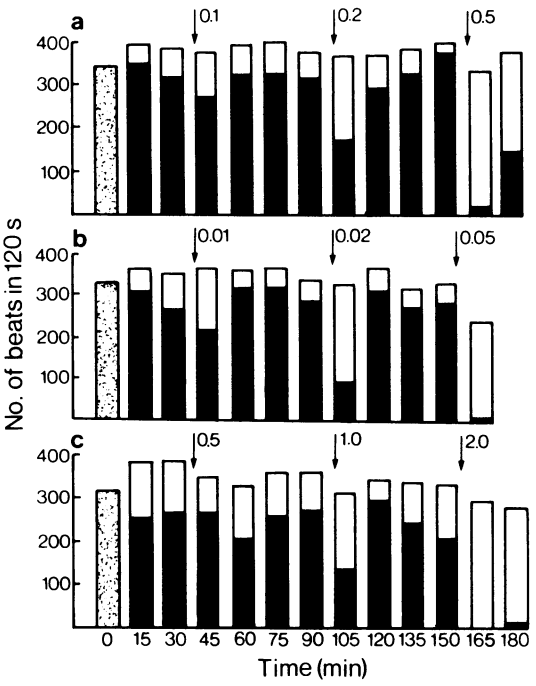

Fig. 2 Effect of (a) acebutolol, (b) propranolol or (c) practolol on adrenaline/methylchloroform-induced arrhythmias in the anaesthetized cat. Total column indicates the number of heart beats in a 2 min period following methylchloroform and adrenaline administration. The solid portion represents the number of ectopic beats. The stippled column in each panel indicates the heart rate before adrenaline and methylchloroform administration. At the arrows the doses (mg/kg) indicated were administered intravenously.

highest (100 mg/kg) dose of practolol. With propranolol (25 and 50 mg/kg orally) there was no consistent or significant change in the arrhythmic dose of ouabain.

Lignocaine produced no significant change in the arrhythmic dose of ouabain. Quinidine showed some protective effect, but did not reach the level of significance.

In view of the somewhat surprising difference between acebutolol and propranolol in these experiments, the β-blocking activities of the two compounds were compared following oral administration to the conscious rabbit (Basil *et al.*, 1973b). The oral doses of propranolol and acebutolol required to halve the potency of intravenous isoprenaline in producing tachycardia were 0.15 and 0.9 mg/kg respectively at 40-80 min, confirming that with the conditions of this experiment the two compounds have β-adrenoceptor blocking potency comparable with that seen in other species (Basil *et al.*, 1973b).

Sympathetically-induced arrhythmias

Adrenaline/methylchloroform-induced arrhythmias in the cat. After the administration of methylchloroform by inhalation and adrenaline intravenously, anaesthetized cats show arrhythmias in the form of multi-focal ventricular ectopic beats. When the frequency is high, occasional normal atrial beats fail to induce contraction of the ventricles, possibly because they are still refractory.

Intravenous injections of acebutolol in the range of 0.1-0.5 mg/kg produced graded reductions in the number of ectopic beats (Figure 2).

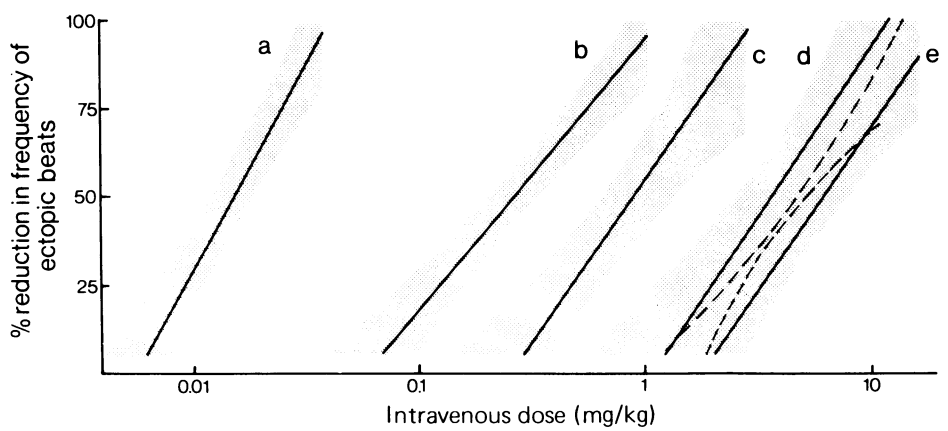

Fig. 3 Regression lines computed for (a) propranolol, (b) acebutolol, (c) practolol, (d) lignocaine and (e) quinidine in reducing adrenaline/methylchloroform-induced arrhythmias in the anaesthetized cat. The envelopes enclose the 95% confidence limits of the regression lines.

After the high doses of acebutolol there was some reduction in the total number of beats. This was also seen after high doses of propranolol and practolol.

The dose-response lines for the three β-blocking drugs were approximately parallel (Figure 3). The intravenous doses of acebutolol, propranolol and practolol producing a 50% reduction in the frequency of ectopic beats were 0.27, 0.015 and 0.92 mg/kg respectively. These three drugs had a similar duration of action (15-30 min) following intravenous administration in the cat (Figure 2).

The anti-arrhythmic agents lignocaine and quinidine which are devoid of β-adrenoceptor blocking activity were less potent than the β-adrenoceptor blocking agents although they showed significant activity. Thus the effective doses for lignocaine and quinidine were 3.7 mg/kg and 6.2 mg/kg respectively. Four of the nine cats in which it was studied showed no response to 10 mg/kg intravenously of lignocaine. These four cats were not included in the calculation of Figure 3.

Chloroform-induced fibrillation in the mouse. Mice to which chloroform is administered until respiratory arrest occurs rapidly develop ventricular fibrillation. Protection from the ventricular fibrillation can be effected by prior treatment either orally or intravenously. Acebutolol and propranolol (Table 3) were equally active both orally and intravenously. Practolol had half the potency of these and lignocaine had only low activity intravenously. There was some indication that lignocaine afforded protection when given orally at high doses despite its known poor oral absorption. Quinidine was the least effective of the drugs tested, both intravenously and orally.

Table 3 Activity of acebutolol and standard compounds in protecting mice from chloroform-induced ventricular fibrillation

	Protection from chloroform-induced fibrillation ED_{50} (mg/kg)	
Compound	*Intravenous*	*Oral*
Acebutolol	0.067 (0.017-0.11)	1.8 (1.1-2.8)
Propranolol	0.097 (0.053-0.14)	1.5 (0.61-3.4)
Practolol	0.19 (0.13-0.28)	2.6 (1.5-4.8)
Lignocaine	2.8 (1.9-4.8)	26 (19-41)
Quinidine	9.7 (7.0-14)	49 (42-57)

Fiducial range $P = 0.95$ are in parentheses.
Mice were tested 2 min after the intravenous dose and 1 h after the oral dose. The effective dose (ED_{50}) refers to the dose of compound reducing the incidence of ventricular fibrillation to 50% of the control value.

Discussion

The experiments described in this paper had two objectives, firstly to compare the experimental anti-arrhythmic properties of acebutolol with those of various clinically used anti-arrhythmic agents, including two β-adrenoceptor blocking agents, propranolol and practolol. Secondly, by comparison of the experimental anti-arrhythmic properties of acebutolol with its other pharmacological actions, to attempt to obtain some insight into the possible importance of the membrane-stabilizing action of this compound in relation to its anti-arrhythmic activity.

The varying aetiology of clinical arrhythmias makes the choice of a single experimental model difficult and possibly unwise. In the present study we have used four tests for anti-arrhythmic activity; two of these involved arrhythmias induced by ouabain and the other two involved the action of chloroform or methylchloroform in sensitizing the myocardium to catecholamines.

In many respects the test involving the reversion of an established ouabain arrhythmia in anaesthetized dogs is one of the most reliable. Data are reproducible, and furthermore the effective dose of lignocaine in this test (c. 1 mg/kg) is comparable with the dose in man required to revert some types of arrhythmias (Jewitt, Kishon & Thomas, 1968). On the other hand, practolol, a drug known to be effective in the treatment of some types of cardiac arrhythmias (Jewitt *et al.*, 1969a; Allen, Pantridge & Shanks, 1971), was ineffective in this test even at the high doses ultimately infused. The lack of activity of practolol in reverting an established ouabain arrhythmia is in agreement with the data of Dunlop & Shanks (1968). It is important to note that the doses of acebutolol and propranolol required to revert an established ouabain-induced arrhythmia in the dog (8.0 and 3.8 mg/kg i.v. respectively) are 200-400 times higher than the doses of the same compounds required to halve the potency of isoprenaline in producing tachycardia in the anaesthetized dog (effective doses 0.029 and 0.0087 mg/kg respectively; Basil *et al.*, 1973b).

The experiments carried out in the conscious rabbit differed from those in the anaesthetized dog

in that the test drugs were administered orally and prophylactically, i.e. prior to the administration of ouabain. Somewhat surprisingly, acebutolol was the only compound tested which showed a clear-cut dose-related action in increasing the dose of ouabain required to produce ventricular arrhythmias. The difference observed between acebutolol and propranolol in this test is not due to lack of absorption of propranolol since the oral β-adrenoceptor blocking activities of these two compounds in the conscious rabbit, under the conditions used for the ouabain arrhythmia tests, were found to be in agreement with those obtained in other species. The slight, although not significant, *decrease* in the dose of ouabain required to produce arrhythmias in animals premedicated with practolol was also surprising.

Papp & Vaughan-Williams (1969) have compared the effects of practolol and (−)-propranolol on the toxicity to the heart of intravenous ouabain in guinea-pigs premedicated intravenously with β-adrenoceptor blockers. These workers found that practolol in intravenous doses up to 12 mg/kg did not significantly increase the dose of ouabain required to produce ventricular arrhythmias. A significant increase was seen however in the dose of ouabain required to produce ectopic extrasystoles and in the dose of ouabain required to produce ventricular fibrillo-flutter. With propranolol a statistically significant reduction in the incidence of ventricular fibrillation induced by ouabain was produced by as little as 0.375 mg/kg. A significant effect on ventricular arrhythmias was only produced by higher intravenous doses of 3 mg/kg. The dose of ouabain required to produce ventricular fibrillation could not be determined in our experiments since we wished to use the same animals on successive occasions.

Kelliher & Roberts (1972) have also studied the effects of premedicating animals with practolol on the intravenous dose of ouabain required to produce ventricular tachycardia. In these experiments, carried out on the cat, 4 mg/kg intravenously of (−)-practolol produced a significant increase in the dose of ouabain required to produce ventricular arrhythmias. We have no explanation for the differences observed in our experiments and those referred to above; it is possible however that after the intravenous administration of these compounds the blood levels were substantially higher than those occurring following the high oral doses used in our studies.

Tests involving catecholamine-induced arrhythmias may have better predictive value for the action of drugs in man in preventing or reverting arrhythmias following a myocardial infarction than tests involving ouabain, since Jewitt, Mercer, Reid, Valori, Thomas & Shillingford (1969b) have reported high levels of catecholamines in such patients. Propranolol was the most potent of the drugs tested in reducing the frequency of ectopic beats following methylchloroform and adrenaline administration in the anaesthetized cat and the order of potency (propranolol, acebutolol, practolol) of the β-adrenoreceptor blocking agents in this test follows their order of potency in inhibiting cardiac β-receptors (Basil *et al.*, 1973b). Furthermore the doses used, 0.01-2 mg/kg, are low compared to the doses required to revert an established ouabain-induced arrhythmia. It seems likely therefore that the activity of the β-receptor blocking agents in this test is related to their action on cardiac β-receptors. The fact that both lignocaine and quinidine were to some extent effective in this test situation indicates that properties other than β-adrenoceptor-blockade can be implicated.

The β-adrenoceptor blocking agents were again highly effective in preventing ventricular fibrillation in mice exposed to chloroform. Somewhat surprisingly acebutolol had similar potency to propranolol both intravenously and orally. The fact that both lignocaine and quinidine showed some activity in this test again indicates that properties other than β-adrenoceptor blockade can be of prophylactic value.

The possible importance of the membrane stabilizing action of some β-adrenoceptor blocking agents in their therapeutic activity in the treatment of arrhythmias has been discussed by various workers. From a pharmacological study of the two optical isomers of propranolol, Barrett & Cullum (1968) found that (−)-propranolol was considerably more effective than the (+)-isomer in preventing adrenaline-induced arrhythmias in cats anaesthetized with halothane. (−)-Propranolol was also more effective than (+)-propranolol in reverting established ouabain-induced arrhythmias in cats or dogs. These authors concluded that the local anaesthetic or membrane stabilizing action was essential for anti-ouabain activity and since practolol was ineffective in this context they considered that β-adrenoceptor blockade may not be involved.

The maximum plasma levels of acebutolol in the rabbit following infusion of doses of 2 or 10 mg/kg at the rate of 1.5 mg kg^{-1} min^{-1} were 6 and 19 μg/ml respectively (R.F. Collins, personal communication). Doses of 8 mg/kg in the dog might be expected to produce plasma levels which are comparable with the *in vitro* concentration of acebutolol required to produce a 25% increase in the refractory period of isolated rabbit atria (7.7 μg/ml; Basil *et al.*, 1973b) and to reduce the rate of rise of the intracellularly recorded action

potential from isolated rabbit atria (Vaughan Williams, personal communication). These latter considerations suggest that the abilities of acebutolol and propranolol to revert an established ouabain-induced arrhythmia in the anaesthetized dog are reflections primarily of their membrane stabilizing actions rather than of β-adrenoceptor blockade.

On the other hand, Coltart, Gibson & Shand (1971), argued that the plasma levels of propranolol required to produce a direct effect on the myocardium are considerably higher than those likely to be produced by the usual therapeutic doses of the drug. These authors measured the plasma levels of propranolol associated with abolition of chronic stable ventricular ectopic beats in patients. They found that racemic propranolol suppressed ectopic foci and produced blood levels of 40-85 ng/ml in eight patients, but was ineffective in four others with blood levels of 70-200 ng/ml. In contrast, (+)-propranolol levels of 180-310 ng/ml were ineffective in four patients who had previously responded at levels of 60-75 ng/ml racemic propranolol. The concentrations of propranolol required to produce changes in the human and canine trans-membrane action potential (Coltart & Meldrum, 1970) are about 9 μg/ml, which is considerably higher than those found in the plasma of patients receiving the drug.

The plasma levels of acebutolol in healthy volunteers receiving 300 mg of the compound orally are of the order of 1 μg/ml (Basil, Collins & Cuthbert, 1973a) which is from one-fifth to one-tenth of the concentration required to produce effects on isolated rabbit atria (Basil *et al.*, 1973b; Vaughan Williams, personal communication). This difference in concentration is not very large and we have no information on the degree of effect on the myocardial muscle that is required to produce a therapeutic action in arrhythmias.

It is relevant to compare the degree of cardiovascular disturbance produced by the doses of β-adrenoceptor blocking agents used to revert ouabain-induced arrhythmias in the dog. In previous experiments (Basil *et al.*, 1973b) the effects of propranolol, practolol and acebutolol on various cardiovascular parameters in the anaesthetized dog have been measured. The rates at which the drugs were infused in those experiments were the same as those used in the experiments involving reversion of an established ouabain arrhythmia. The dose of acebutolol which reverted ouabain-induced arrhythmia (c. 8 mg/kg intravenously) increased the P-R interval of the ECG by about 15% and had little effect on the resting heart rate. In contrast propranolol at 3.8 mg/kg (the dose needed to revert ouabain-induced ventricular arrhythmia) produced a similar increase in the P-R interval but a greater depression of the carotid dP/dt *max.* and heart rate than produced by 8 mg/kg acebutolol.

The general impression obtained from the results of the experiments described in this paper is that in the conscious rabbit and anaesthetized cat and dog acebutolol is a potent anti-arrhythmic agent and that in the anaesthetized dog it produces possibly less cardiac depression (Basil *et al.*, 1973b) than an equi-antiarrhythmic dose of propranolol.

Although data on such anti-arrhythmic tests in experimental animals do not necessarily indicate useful therapeutic activity in patients with cardiac arrhythmias, the data presented suggest that acebutolol may have interesting clinical anti-arrhythmic properties.

References

ALLEN, J.D., PANTRIDGE, J.P. & SHANKS, R.G. (1971). Practolol in the treatment of ventricular dysrhythmias in acute myocardial infarction. *Postgraduate Medical Journal* (Supplement Advances in adrenergic β-receptor therapy), **47**, 29-35.

BARRETT, A.M. & CULLUM, V.A. (1968). The biological properties of the optical isomers of propranolol and their effects on cardiac arrhythmias. *Br. J. Pharmac.*, **34**, 43-55.

BASIL, B., COLLINS, R.F. & CUTHBERT, M.F. (1973a). Pharmacokinetics of M&B 17,803A in animals and man. *Br. J. Pharmac.*, **47**, 620P.

BASIL, B., JORDAN, R., LOVELESS, A.H. & MAXWELL, D.R. (1973b). β-Adrenoceptor blocking properties and cardioselectivity of M&B 17,803A. *Br. J. Pharmac.*, **48**, 198-211.

COLTART, D.J., GIBSON, D.G. & SHAND, D.G. (1971). Plasma propranolol levels associated with suppression of ventricular ectopic beats. *Br. med. J.*, **1**, 490-491.

COLTART, D.J. & MELDRUM, S.J. (1970). The effect of propranolol on the human and canine transmembrane action potential. *Br. J. Pharmac.*, **40**, 148-149P.

DOHADWALLA, A.N., FREEDBERG, A.S. & VAUGHAN WILLIAMS, E.M. (1969). The relevance of beta-receptor blockade to ouabain-induced cardiac arrhythmias. *Br. J. Pharmac.*, **36**, 257-267.

DUNLOP, D. & SHANKS, R.G. (1968). Selective blockade of adrenoceptive β-receptors in the heart. *Br. J. Pharmac. Chemother.*, **32**, 201-218.

GENT, G., DAVIS, T.C. & McDONALD, A. (1970). Practolol in the treatment of supraventricular cardiac dysrhythmias. *Br. med. J.*, **1**, 533-535.

GIBSON, D. & SOWTON, E. (1969). The use of beta-adrenergic receptor blocking drugs in dysrhythmias. *Progr. Cardiovasc. Dis.*, **12**, 16-39.

JEWITT, D.E., KISHON, Y. & THOMAS, M. (1968). Lignocaine in the management of arrhythmias after acute myocardial infarction. *Lancet*, i, 266-270.

JEWITT, D.E., MERCER, C.J., REID, D., VALORI, C., THOMAS, M. & SHILLINGFORD, J.P. (1969b). Free noradrenaline and adrenaline excretion in relation to the development of cardiac arrhythmias and heart-failure in patients with acute myocardial infarction. *Lancet*, i, 635-641.

JEWITT, D.E., MERCER, C.J. & SHILLINGFORD, J.P. (1969a). Practolol in the treatment of cardiac dysrhythmias due to acute myocardial infarction. *Lancet*, ii, 227-230.

KELLIHER, G.J. & ROBERTS, J. (1972). The effects of d(+)- and l(−)-practolol on ouabain-induced arrhythmias. *European J. Pharmacol.*, **20**, 243-247.

LAWSON, J.W. (1968). Anti-arrhythmic activity of some isoquinolone derivatives determined by a rapid screening procedure in the mouse. *J. Pharmac. exp. Ther.*, **160**, 22-31.

LEVY, B. (1973). The selective beta-receptor blocking properties of DL-1-(2-acetyl-4-*n*-butyramidophenoxy) -2-hydroxy-3-isopropylaminopropane hydrochloride (M&B 17,803-A) in the anaesthetised dog. *J. Pharmac. exp. Ther.*, **186**, 134-144.

PAPP, J.G. & VAUGHAN WILLIAMS, E.M. (1969). A comparison of the anti-arrhythmic actions of ICI 50172 and (−)-propranolol and their effects on intracellular cardiac action potentials and other features of cardiac function. *Br. J. Pharmac.*, **37**, 391-399.

(Received May 29, 1973)