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The effect of bretylium on intracellular cardiac action potentials in relation to its anti-arrhythmic and local anaesthetic activity

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1. The initial effect of bretylium tosylate on isolated rabbit atria was to increase conduction velocity, contraction heights, spontaneous frequency and maximum driven frequency, and to reduce electrical threshold. At concentrations of 200 mg/l. or less, these were the only effects, and were consistent with the known sympathomimetic actions of bretylium.

2. At extremely high concentrations, 1,200 and 2,400 mg/l., the initial actions were succeeded by weak quinidine-like effects; reduced conduction velocity, spontaneous and maximum driven frequencies, and rate of rise of action potential. The electrical threshold was raised, but contraction heights were not reduced.

3. The local anaesthetic activity of bretylium, measured by reductions in the frog nerve action potential, was 1/90 that of procaine and 1/300 that of propranolol, on a molar basis.

4. Acute pretreatment with bretylium, 20 mg/kg intravenously, significantly increased the amount of infused ouabain required before the appearance of the first signs of atrial arrhythmia in anaesthetized guinea-pigs, but did not prevent ventricular arrhythmias.

5. Pretreatment with bretylium 30 mg/kg subcutaneously 24 hr, and again 4 hr before ouabain infusion, increased the dose of ouabain inducing atrial irregularity and slightly but significantly reduced the incidence of ventricular fibrillation.

Most drugs with anti-arrhythmic actions, including β-receptor blocking agents, have been found to share with quinidine the property of reducing the rate of depolarization of cardiac muscle and slowing conduction velocity (Szekeres & Vaughan Williams, 1962; Vaughan Williams, 1966). The majority are also local anaesthetics, and although some β-receptor blocking agents have little local anaesthetic activity, their affinity for β-receptors is also low (Levy, 1968; Jackson, 1968; Brick, Hutchison, McDevitt, Roddie & Shanks, 1968), and it is difficult to be certain that in high concentrations they do not have some direct action on the cardiac muscle membrane. Indeed the relevance of β-receptor blockade to anti-arrhythmic

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action has been the subject of controversy for several years (Dohadwalla, Freedberg & Vaughan Williams, 1969). It would be useful, therefore, if a drug were available which blocked sympathetic action on cardiac muscle without directly causing any depression of electrical or mechanical activity in the heart.

Adrenergic neurone blocking drugs have recently been reported to possess anti-arrhythmic properties, including bretylium (Leveque, 1965; Bacaner, 1968a, b; Ellis, Barnes & Cozzi, 1968; Hashimoto, Chiba, Tanaka, Hirata & Suzuki, 1968; Nayler, Chan & Lowe, 1968), guanethidine (Leveque, 1964; Raines, Moros & Levitt, 1968), bethanidine (Leveque, 1966) and N-(1-phenylethyl)guanidine (Boger & Leveque, 1968). Some of these compounds have a weak but persistent local anaesthetic action (Boura & Green, 1959; Boyd, Chang & Rand, 1961), which could contribute to the anti-arrhythmic effect. The present experiments were undertaken to discover to what extent, if any, one of the above compounds with a reported weak local anaesthetic action, bretylium, possessed "quinidine-like" properties.

Methods

Intracellular records, and other measurements of atrial function

These were obtained by methods already described (Szekeres & Vaughan Williams, 1962) from isolated rabbit atria suspended horizontally in a bath, maintained at 32° C, containing modified Locke solution (NaCl, 125; $NaHCO_3$, 25; KCl, 5·6; $CaCl_2$, 2·16 and glucose, 11 mM) at pH 7·4, gassed with 95% oxygen and 5% carbon dioxide, and driven by electrical stimuli at 180/min. The reason for employing this rather high frequency was that bretylium itself increased the rate of spontaneous contractions, and the driving stimulus had to be set at a higher frequency than the spontaneous rate. An addition to the previously used equipment was a differentiator of simple design, to give a direct record of the rate of rise of the action potential. The rates of rise were always measured subsequently from photographs of the action potential, but the differentiator proved very useful during the experiment as an indicator of a successful penetration. The circuit of the differentiator is shown in Fig. 1. The 100 Ω resistor and the 50 pF condenser eliminate oscillation. A high gain high impedance amplifier, T52, holds point A as a virtual earth, so that the current through the 100 kΩ resistor at any instant equals the current through the 0·1 μF capacitance. This current is proportional to $\frac{dV\text{-input}}{dt}$, therefore the output voltage, which determines the current through the 100 kΩ resistance, must also be proportional to $\frac{dV\text{-input}}{dt}$.

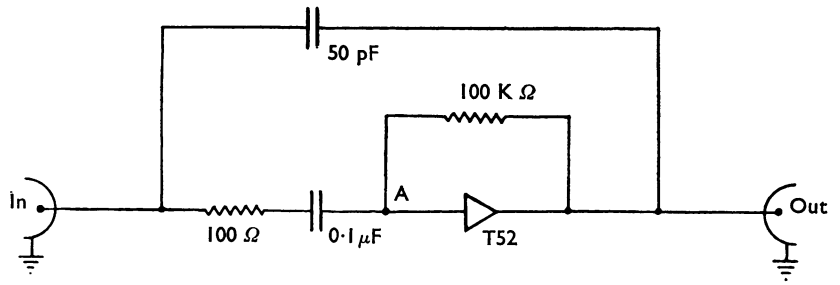

FIG. 1. Circuit of differentiator. The Philbrick Rexus T52 was employed in conjunction with a 9·0 V battery.

Local anaesthesia

Frog sciatic nerves were stimulated, and their action potentials recorded, as described previously (Dohadwalla, Freedberg & Vaughan Williams, 1969). All nerves were desheathed. The centre portion of the nerve was exposed to stepwise increases in the concentrations of either procaine or the test drug, for 30 min at each concentration, except in one experiment when 60 min exposures were used. The nerve was washed for 1 hr, and the procedure was repeated with another drug. The solution contained NaCl, 120 ; $CaCl_2$, 1·08 ; KCl, 1·88 and $NaHCO_3$, 2·38 mM, and the pH was adjusted with Tris buffer to 7·5.

Anti-arrhythmic activity

Protection against ouabain induced arrhythmias in guinea-pig, anaesthetized with 1·6 g/kg of urethane intraperitoneally, was assessed by the method of Vaughan Williams & Sekiya (1963), with the exception that the concentration of infused ouabain was 90 μg/ml. instead of 80 μg/ml., and the switching on of the infusion pump and e.c.g. was automatic (Dohadwalla, Freedberg & Vaughan Williams, 1969), so that 3·6 μg was infused during 30 sec and repeated every 2 min.

Drugs used

Bretylium tosylate (Burroughs Wellcome) ; (−)-propranolol (I.C.I. 4732), kindly supplied by Dr. Barrett ; procaine hydrochloride (B.D.H.) ; strophanthin G (ouabain) (B.D.H.) ; isoprenaline sulphate BP and adrenaline BP (Burroughs Wellcome). The doses have been expressed as weights of the salts.

Results

Concentrations of bretylium of 20 mg/l. or less had no consistent effects on the intracellularly recorded potentials of isolated rabbit atria. In some experiments there was a clear increase in the rate of rise of the action potential, and there was never any reduction. Such an increase would be consistent with the statistically significant sympathomimetic effects observed on contractions, frequency, conduction velocity and electrical threshold. There was no evidence of any quinidine-like action of bretylium at any concentration which might occur clinically.

A tenfold increase in the concentration of bretylium to 200 mg/l. still had no effect on the isolated atrium apart from the early sympathomimetic action, and a reduction in the rate of rise of the action potential, which appeared after an hour. At 1,200 mg/l., however, " quinidine-like " effects became prominent, with reduction in the rate of rise of the action potential and overshoot, and slowing of conduction velocity (Fig. 2). In contrast to the action of quinidine, however, there was no reduction in the force of contraction, even when the concentration was again doubled to 2,400 mg/l. The effects of bretylium at different concentrations between 5 and 2,400 mg/l. in eleven experiments on various parameters of the intracellular records have been summarized in Table 1. The figures represent the mean differences between measurements made during a control period and those made during exposure to the drug. The results of different experiments have been pooled, and the average number of individual fibres penetrated was fifteen for the controls, sixteen for each bretylium concentration, and twenty-one for (−)-propranolol.

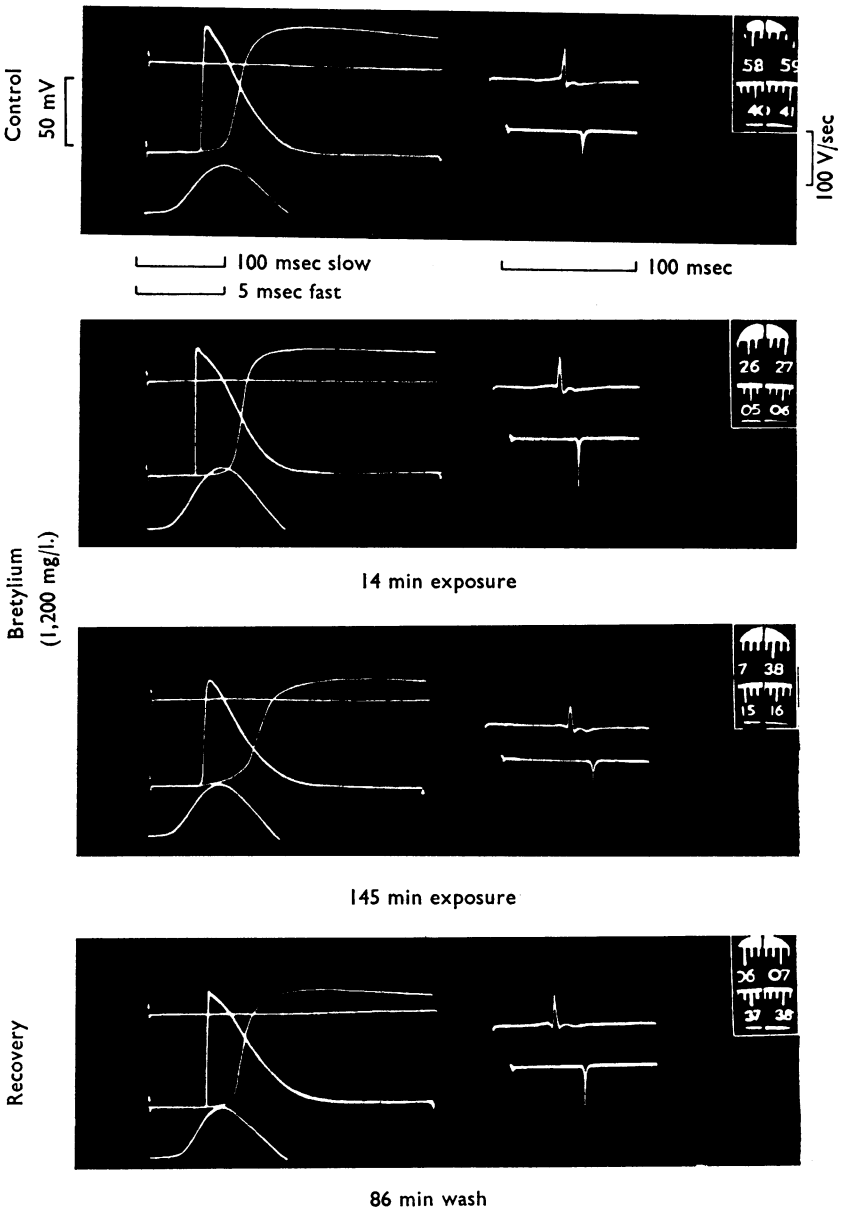

FIG. 2. Effect of bretylium, 1,200 mg/l., on isolated rabbit atrium. Left, In each figure the horizontal line indicates zero potential; the superimposed middle traces depict intracellular potentials at slow and fast sweep speeds. Bottom trace: contraction. Right, Upper trace gives interval between the stimulus artefact at the beginning and an action potential recorded by an extracellular bipolar electrode on the atrial surface at a measured distance away from the stimulating electrode. Lower trace carries the output of the differentiator; the height of the spike is proportional to dV/dt of intracellular record. Inset, Time in minutes (lower figures) and seconds (upper) at which the last of the three superimposed exposures were taken. The early sympathomimetic action of bretylium (increases in conduction velocity, rate of rise of action potential and contractions) is followed by quinidine-like effects.

When rabbit atria are allowed to beat for many hours without exposure to drugs, measurements of resting potential, action potential, rate of rise of the action potential, electrical threshold and other parameters are remarkably stable (Morales-Aguilerá & Vaughan Williams, 1965; Vaughan Williams, 1967). Exposure to quinidine-like drugs causes a reduction in rate of rise which persists so long as the drug is present. After wash-out contraction height and conduction velocity sometimes return to values higher than those obtaining during the period before exposure to the drug (Vaughan Williams, 1964). Similarly, during recovery from a very high concentration of bretylium (Fig. 2), conduction velocity was faster than during the control period.

Other actions on cardiac muscle

At low concentrations of bretylium the only effect on the spontaneous frequency of isolated atria was to increase it. At very high concentrations an initial increase was followed by a decrease. A similar dual effect was observed on other functions. At low concentrations contraction heights, conduction velocity and, to a small extent, the maximum driven frequency were increased; the electrical threshold was decreased. Very high concentrations of bretylium caused similar changes at first (usually not for longer than 30 min), but after an hour these were reversed. The maximum driven frequency and conduction velocity were reduced, and the electrical threshold was raised. All the above actions would be consistent with an initial sympathomimetic effect of bretylium, which at low concentrations was the only effect (Table 2), followed by a very weak quinidine-like action.

Local anaesthetic activity

Boura & Green reported the local anaesthetic activity of bretylium in 1959. They used the guinea-pig wheal method, and we thought it worth while to do an assay

TABLE 1. *Effects on intracellular potentials*

Bretylium concentration mg/l. ($M \times 10^{-5}$)	Duration of exposure (min)	% difference from control				Repolarization time	
		Resting potential	Action potential	Maximum rate of rise	Mean rate of rise	to 50% diastolic potential	to 90% diastolic potential
5·0 (1·21)	>60	+1·0	+0·4	+2·9	+1·92	+4·18	+0·71
15 (3·63)	<60	−2·6	+1·0	+1·8	+2·54	−3·1	−0·3
20 (4·83)	<60	−0·6	−2·24	−1·26	−3·66	−1·61	+0·18
	>60	−2·6	−1·2	+10·7	+19·5	−12·4	−14·5
200 (48·3)	<60	+10·3	+4·9	+3·36	+8·22	+4·78	+6·5
	>60	+5·25	+3·98	−13·8*	−8·16	+4·32	+10·2
1,200 (290)	<60	+3·34	+0·43	−10·2‡	−21·2‡	+9·45‡	+6·18*
	>60	+6·12	−1·3	−35·2‡	−43·9‡	+14·9‡	+11·6‡
2,400 (580)	<60	+0·14	+1·8	−2·0	−4·3	+32·7‡	+17·5†
	>60	−2·84	−9·5‡	−40·5‡	−50·3‡	+17·7*	+15·3*
(−)-Propranolol 1·0 mg/l. ($0·34 \times 10^{-5}$M)	>60	−0·95	−9·8‡	−28‡	−25·4‡	−5·0*	−3·8*

Statistical significance: * $P < 0·05$; † $P < 0·01$; ‡ $P < 0·001$.

with the frog sciatic nerve preparation in addition, both because anti-arrhythmic drugs recently studied have been shown to be potent local anaesthetics by the latter method, and because there could be a real difference between the relative sensitivity to drugs of fine afferent terminals and of large myelinated nerve trunks. The results are presented in Fig. 3. Procaine was used as a standard, and the effect of (−)-propranolol was determined in addition.

The concentrations of each drug required to produce stable reductions in the height of the action potential were plotted on a logarithmic scale. As described

TABLE 2. *Effects on frequency, conduction velocity, threshold and contractions*

Bretylium concentration mg/l. (M × 10^{-5})	Time of exposure (min)	% difference from control: Spontaneous frequency	Maximum driven frequency	Conduction velocity	Electrical threshold	Contractions
5	10	+5·0		+5·3*	−1·9*	+10·9
(1·21)	120	+3·6		0·0	0·0	+5·9
20	10	+8·6†	+3·7	+6·1‡	−4·4	+16·8†
(4·83)	120	+6·1	0·0	+1·1	+0·4	+3·6
200	10	+8·5†	+1·5	+9·8	−8·2*	+17·9†
(48·3)	120	−1·7	−2·4	−2·5	−0·5	+12·2†
1,200	10	+18·8†	+8·0*	+6·1*	−2·8	+24·4‡
(290)	120	−8·5*	+13·3†	−22·9†	+13·7†	+3·5
2,400	10	+9·8	+36	+9·1	−4·8	+30
(580)	120	−13·3	−68	−27·2	+19·5	0·0
(+)-Propranolol						
1 mg/l.	10	0·0	−0·8	−1·9	+19·6	−2·5
(0·34 × 10^{-5}M)	120	−17·4*	−23·1	−21·1*	+93·0†	−14·2*

Statistical significance: * $P<0.05$; † $P<0.01$; ‡ $P<0.001$.

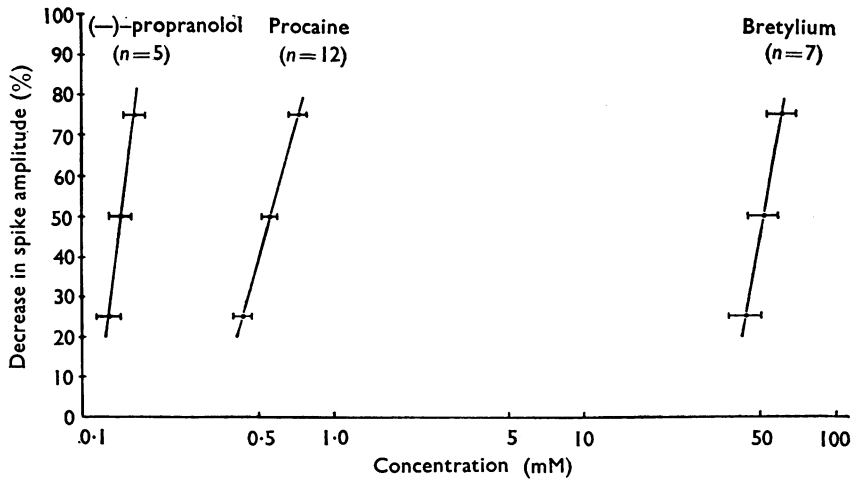

FIG. 3. Comparison of local anaesthetic activity of bretylium, procaine and (−)-propranolol. Ordinate, Reduction in height of action potential of frog sciatic nerve as % decrease from control. Abscissa, Log concentration (mM).

above, the actual effects of increasing concentrations were measured, and the concentrations required to produce 25%, 50% and 75% reductions were obtained by interpolation. The activity of bretylium was 1/90 that of procaine, and 1/300 that of (−)-propranolol, on a molar basis.

Protection against ouabain-induced arrhythmias

Acute effects

The first indication of the development of arrhythmia in response to ouabain infusion is the appearance of unequal intervals between beats, associated with prolongation of the P-R interval on the e.c.g. (Fig. 4A). The intravenous injection of bretylium 20 mg/kg at this point increased the heart rate and restored a regular rhythm (in five out of five experiments). When the infusion of ouabain was continued, however, ectopic extrasystoles appeared, indicated by abnormal QRS complexes, and ventricular fibrillation always eventually occurred, which was not prevented by further injections of bretylium. Since the early effects of bretylium are sympathomimetic, associated with release of noradrenaline, it was possible that the reversion to a regular rhythm was a consequence of stimulation of β-receptors. In another series of experiments, when the early phase of ouabain-induced arrhythmia had become established, a small dose of adrenaline was injected intravenously, and the

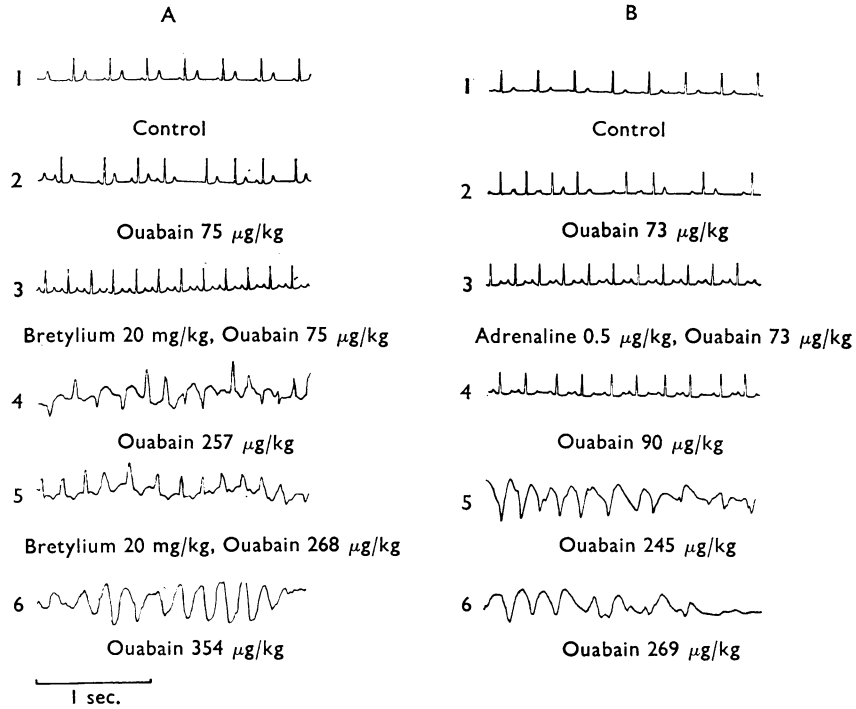

FIG. 4. Effect of bretylium on ouabain induced arrhythmias in guinea-pigs. Each record shows the electrocardiogram taken at the time when the amount of ouabain stated below it had been infused in the manner described under **Methods.** Bretylium and adrenaline were injected into the intravenous cannula supplying the infusion.

arrhythmia reverted to a regular rhythm, as had happened after the injection of bretylium (Fig. 4B). A similar result was obtained with adrenaline 0·5 μg/kg and isoprenaline 0·1 μg/kg. It was of interest to note that when the ouabain infusion was continued after these injections of catecholamines, its toxicity was increased, in agreement with previous findings (Sekiya & Vaughan Williams, 1963).

Prevention of arrhythmias by pretreatment with bretylium

Two series of experiments were carried out to test the effectiveness of bretylium 30 mg/kg administered subcutaneously 24 hr before the commencement of an ouabain infusion, followed by a further 30 mg/kg 4 hr before. In the first series the animals were obtained from local dealers, and all control animals (thirty) developed ventricular fibrillation in response to ouabain infusion, but two out of ten animals pretreated with bretylium did not. In the second series, the guinea-pigs had been delivered by caesarean section, and were guaranteed free from certain pathogens. Two out of twenty control animals in this series did not develop ventricular fibrillation, but three out of ten bretylium-pretreated animals also did not fibrillate. The results of both series were pooled and have been presented in Table 3. Pretreatment with bretylium increased the amount of ouabain required to produce all categories of arrhythmia and cardiac arrest. The increase in the dose needed to induce the first sign of arrhythmia (unequal intervals between atrial beats) was statistically significant, as was the reduced incidence of ventricular fibrillation ($P<0·01$).

In a third series of experiments bretylium, 20 mg/kg, was given intravenously only 10 min before the start of the infusion. All the animals in this series were "pathogen-free". Here again the pretreatment significantly increased the dose of ouabain required before the appearance of unequal atrial intervals ($P<0·001$), but no protection was given against ventricular arrhythmias. On the contrary, all the acutely pretreated animals developed ventricular fibrillation ($n=13$), whereas only eighteen out of twenty controls fibrillated. In contrast, acute pretreatment with as little as 0·75 mg/kg of (−)-propranolol had a significant protective action ($P<0·001$) (Table 3).

TABLE 3. *Effect of bretylium on the toxicity to the heart of ouabain, given by infusion*

Treatment	*n*	Amount of ouabain (μg/kg i.v.) required to produce: Unequal intervals	Ectopic extra-systoles	Idio-ventricular rhythm	Ventricular fibrillo-flutter	Cardiac arrest
Control	50	78·7±6·6 (48/50=96%)	181·1±6·9	214·9±7·8	258·5±8·5 (48/50=96%)	314·5±9·0
Bretylium 2×30 mg/kg s.c. (24 and 4 hr before ouabain)	20	95·6±11·3‡ (16/20=80%*)	194·6±13·7	222·9±12·9	256·8±10·4 (15/20=75%*)†	326·7±13·6
(−)-Propranolol 0·75 mg/kg i.v. (5 min before ouabain)	10	84·1±18·1	245·4±25·4‡	263·3±23·0‡	323·8±37·3‡ (4/10=40%)†	341·6*±23·1

The values given are the means and standard errors of the amounts of ouabain required to produce the stated effects. The incidence of the effects is given in brackets, when this was less than 100%. Statistical significance of the difference from control: * $P<0·05$; † $P<0·01$; ‡ $P<0·001$.

Discussion

Recent reports have indicated that bretylium has anti-arrhythmic properties in animals (Leveque, 1965 ; Bacaner, 1968a) and man (Bacaner, 1968b ; Castaneda & Bacaner, 1969). Many anti-arrhythmic drugs are also local anaesthetics, including β-receptor blockers (Gill & Vaughan Williams, 1964 ; Morales-Aguilerá & Vaughan Williams, 1965), and since bretylium was reported to possess local anaesthetic activity (Boura & Green, 1959) it was possible that bretylium might also have quinidine-like actions on isolated cardiac muscle (Vaughan Williams, 1958). It was found, however, that a concentration of 20 mg/l. of bretylium, higher than would be experienced clinically, had no such effects, in confirmation of the results of Boyd, Chang & Rand (1961), and even 200 mg/l. only caused a small reduction in the rate of rise of the action potential. Although concentrations of 1,200 mg/l. and 2,400 mg/l. ultimately reduced the rate of rise of the action potential, conduction velocity and maximum driven frequency, and increased the electrical threshold, these effects were not associated with any reduction in contractions.

During the first 30–60 min at all concentrations of bretylium studied (5–2,400 mg/l.) contraction heights were increased, conduction velocity and rate of rise of the action potential were faster, and the electrical threshold was reduced. These effects were consistent with the known initial sympathomimetic action of bretylium. Gilmore & Siegel (1962) detected an increase in circulating noradrenaline during the early hypertensive phase of bretylium action ; increased noradrenaline release was observed by Hertting, Axelrod & Patrick (1962) in experiments with (^{3}H)-noradrenaline. Further, the sympathomimetic actions of bretylium can be blocked by dibozane and dichloro-isoproterenol (Yelnovsky & Mortimer, 1961), and its vasoconstrictor action can be abolished by phenoxybenzamine (Cooper, Fewings, Hodge & Whelan, 1963).

Pretreatment with bretylium 30 mg/kg given 24 and again 4 hr before an ouabain infusion, caused a statistically significant reduction in the incidence of ventricular fibrillation in anaesthetized guinea-pigs. Immediate pretreatment with bretylium, however, increased ouabain toxicity, an effect which would again be consistent with its early sympathomimetic action.

The local anaesthetic potency of bretylium, measured by depression of the action potential height in frog nerve, was 1/90 that of procaine and 1/300 that of (−)-propranolol, on a molar basis.

Since bretylium has no quinidine-like or non-specific actions at clinically possible concentrations, its mode of action as an anti-arrhythmic needs to be explained, especially in view of the conclusions of Lucchesi (1965) and of Benfey & Varma (1966) that β-receptor blockade was irrelevant to the anti-arrhythmic actions of pronethalol and propranolol, on the ground that these could be fully accounted for on the basis of their quinidine-like effects. On the other hand, recent evidence has indicated that β-receptor blockade does contribute to protection against arrhythmias induced by ouabain (Barrett & Cullum, 1968 ; Raper & Wale, 1968 ; Dohadwalla, Freedberg & Vaughan Williams, 1969) or by acetylcholine (Hashimoto, Chiba, Tanaka, Hirata & Suzuki, 1968). Surgical removal of cardiac sympathetic nerves raises the fibrillation threshold in the cat (Szekeres, Méhes & Papp, 1961 ; Papp & Szekeres, 1967), and it is possible that the anti-arrhythmic action of bretylium could be due to depression of activity in sympathetic nerves. Leveque (1965) observed

that bretylium did not exhibit maximum anti-arrhythmic effectiveness until after 4 hr. He also reported (1964) that guanethidine possessed anti-arrhythmic properties (although Bacaner (1968a), using another method, concluded differently).

The level of sympathetic stimulation is only one factor in the production of arrhythmias, and its removal may not alone be sufficient to prevent or correct severe arrhythmias. Erlij & Mendez (1964) showed that ventricular fibrillation induced by digitalis could often be prevented by a combination of sympathectomy and adrenalectomy, and similar results were obtained by Boyajy & Nash (1966). Bretylium blocks sympathetic nerves but not the release of catecholamines from the adrenal medulla. Propranolol and several other compounds are both sympatholytic by virtue of their blockade of β-receptors, and have direct quinidine-like actions as well. The latter, however, may be associated with depressed contractions. Bretylium caused no diminution in contractions even at high concentrations.

REFERENCES

BACANER, M. B. (1968a). Quantitative comparison of bretylium with other antifibrillatory drugs. *Am. J. Cardiol.*, **21**, 504–512.

BACANER, M. B. (1968b). Treatment of ventricular fibrillation and other acute arrhythmias with bretylium tosylate. *Am. J. Cardiol.*, **21**, 530–543.

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.

BENFEY, B. G. & VARMA, D. R. (1966). Antisympathomimetic and antifibrillatory effects of pronethalol and propranolol. *Br. J. Pharmac. Chemother.*, **26**, 3–8.

BOGER, D. C. & LEVEQUE, P. E. (1968). The anti-arrhythmic effect of (−)N-(1-phenylethyl)guanidine. *Archs int. Pharmacodyn. Thér.*, **175**, 129–135.

BOURA, A. L. A. & GREEN, A. F. (1959). The actions of bretylium: adrenergic neurone blocking and other effects. *Br. J. Pharmac. Chemother.*, **14**, 530–548.

BOYAJY, L. D. & NASH, C. B. (1966). Alteration of ouabain toxicity by cardiac denervation. *Tox. appl. Pharmac.*, **9**, 199–208.

BOYD, H., CHANG, V. & RAND, M. J. (1961). The local anaesthetic activity of bretylium in relation to its action in blocking sympathetic responses. *Archs int. Pharmacodyn. Thér.*, **81**, 10–23.

BRICK, I., HUTCHISON, K. J., MCDEVITT, D. G., RODDIE, I. C. & SHANKS, R. G. (1968). Comparison of the effects of I.C.I. 50172 and propranolol on the cardiovascular responses to adrenaline, isoprenaline and exercise. *Br. J. Pharmac.*, **34**, 127–140.

CASTANEDA, A. R. & BACANER, M. (1969). Prophylactic suppression of postoperative arrhythmias with bretylium tosylate in open heart surgery. *Am. J. Cardiol.*, **23**, 107.

COOPER, C. J., FEWINGS, J. D., HODGE, R. L. & WHELAN, R. F. (1963). Effects of bretylium and guanethidine on human hand and forearm vessels and on their sensitivity to noradrenaline. *Br. J. Pharmac. Chemother.*, **21**, 165–173.

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

ELLIS, C. H., BARNES, M. & COZZI, M. (1968). Antiarrhythmic actions of bretylium. *Fed. Proc.*, **27**, 406.

ERLIJ, D. & MENDEZ, R. (1964). The modification of digitalis intoxication by excluding adrenergic influences on the heart. *J. Pharmac. exp. Ther.*, **144**, 97–103.

GILL, E. W. & VAUGHAN WILLIAMS, E. M. (1964). Local anaesthetic activity of the β-receptor antagonist pronethalol. *Nature, Lond.*, **201**, 199.

GILMORE, M. S. & SIEGEL, J. H. (1962). Mechanism of the myocardial effects of bretylium. *Circulation Res.*, **10**, 347–353.

HASHIMOTO, K., CHIBA, S., TANAKA, S., HIRATA, M. & SUZUKI, Y. (1968). Adrenergic mechanism participating in induction of atrial fibrillation by ACH. *Am. J. Physiol.*, **215**, 1183–1191.

HERTTING, G., AXELROD, J. & PATRICK, R. W. (1962). Actions of bretylium and guanethidine on the uptake and release of (^{3}H)-noradrenaline. *Br. J. Pharmac. Chemother.*, **18**, 161–166.

JACKSON, I. M. (1968). Beta adrenergic receptor blockade by ICI 50172. *J. Physiol. Lond.*, **198**, 28*P*.

LEVEQUE, P. E. (1964). Guanethidine as an anti-fibrillatory agent. *Nature, Lond.*, **203**, 1389.

LEVEQUE, P. E. (1965). Anti-arrhythmic action of bretylium. *Nature, Lond.*, **207**, 203–204.

LEVEQUE, P. E. (1966). Bethanidine: a new antifibrillatory agent. *Archs int. Pharmacodyn. Thér.*, **163**, 422–426.

LEVY, J. V. (1968). Myocardial and local anaesthetic actions of β-adrenergic receptor blocking drugs: relationship to physicochemical properties. *Eur. J. Pharmac.*, **2**, 250–257.

LUCCHESI, B. R. (1965). The effects of pronethalol and its *dextro* isomer upon experimental cardiac arrhythmias. *J. Pharmac. exp. Ther.*, **148**, 94–99.

MORALES-AGUILERÁ, A. & VAUGHAN WILLIAMS, E. M. (1965). The effects on cardiac muscle of β-receptor antagonists in relation to their activity as local anaesthetics. *Br. J. Pharmac. Chemother.*, **24**, 332–338.

NAYLER, W. G., CHAN, J. & LOWE, T. E. (1968). Beta adrenergic antagonists, including ICI 50172, and the control of cardiac arrhythmias. *Med. J. Aust.*, **1**, 1128.

PAPP, J. GY & SZEKERES, L. (1967). Influence of stretch and dynamic functional state of the myocardium on tendency of the heart to arrhythmia. *Acta Physiol. Acad. Sci. Hung.*, **32**, 163–174.

RAINES, A., MOROS, D. & LEVITT, B. (1968). The effect of guanethidine on ouabain-induced ventricular arrhythmia in the cat. *Archs int. Pharmacodyn. Thér.*, **174**, 373–377.

RAPER, C. & WALE, J. (1968). Propranolol, MJ 1999 and CIBA 39089 Ba in ouabain and adrenaline-induced cardiac arrhythmias. *Eur. J. Pharmac.*, **4**, 1–12.

SEKIYA, A. & VAUGHAN WILLIAMS, E. M. (1963). A comparison of the antifibrillatory actions and effects on intracellular cardiac potentials of pronethalol, disopyramide and quinidine. *Br. J. Pharmac. Chemother.*, **21**, 473–481.

SZEKERES, L., MÉHES, J. & PAPP, J. (1961). Mechanism of increased susceptibility to fibrillation of the hypothermic mammalian heart in situ. *Br. J. Pharmac. Chemother.*, **17**, 167–175.

SZEKERES, L. & VAUGHAN WILLIAMS, E. M. (1962). Antifibrillatory action. *J. Physiol., Lond.*, **160**, 470–482.

VAUGHAN WILLIAMS, E. M. (1958). The mode of action of quinidine on isolated rabbit atria interpreted from intracellular records. *Br. J. Pharmac. Chemother.*, **13**, 276–287.

VAUGHAN WILLIAMS, E. M. (1964). The mode of action of antifibrillatory drugs. *Proc. 2nd Int. Pharmac. Cong., Pharmacology of Cardiac Functions*, vol. 5, pp. 119–132. London: Pergamon Press.

VAUGHAN WILLIAMS, E. M. (1966). Mode of action of beta-receptor antagonists on cardiac muscle. *Am. J. Cardiol.*, **18**, 399–405.

VAUGHAN WILLIAMS, E. M. (1967). Chemosensitivity of cardiac muscle. *J. Physiol., Lond.*, **189**, 119–137.

VAUGHAN WILLIAMS, E. M. & SEKIYA, A. (1963). Prevention of arrhythmias due to cardiac glycosides by block of β-sympathetic receptors. *Lancet*, **1**, 420–421.

YELNOVSKY, J. & MORTIMER, L. C. (1961). A brief study of the sympathomimetic cardiovascular effects of bretylium. *Archs int. Pharmacodyn. Thér.*, **130**, 200–206.

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