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The effect of amiodarone, a new anti-anginal drug, on cardiac muscle

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Summary

1. Amiodarone (2-butyl, 3-(4-diethylaminoethoxy, 3,5-diiodo, benzoyl) benzofuran hydrochloride), an anti-anginal drug which causes coronary dilatation and depresses myocardial oxygen consumption, was found to protect anaesthetized guinea-pigs against ouabain-induced ventricular fibrillation.

2. A 5% (73·4 mM) solution of amiodarone had no local anaesthetic action on guinea-pig skin.

3. Amiodarone, 20 mg/kg (29·4 μmol/kg) given daily for 6 weeks intraperitoneally, had no effect on the resting potential or action potential height, and only a small effect on the maximum rate of depolarization, of isolated rabbit atrial or ventricular muscle fibres as shown by intracellular recording. It caused a considerable prolongation of the action potential in both tissues.

4. Simultaneous administration of thyroxine (5 μg ; 6·26 nmol), given daily for 3 weeks intraperitoneally, prevented the prolongation by amiodarone of the duration of the action potential.

5. Treatment of rabbits with 20 mg/kg of amiodarone daily intraperitoneally for 6 weeks had no effect on the weight of the thyroid gland, but was associated with a reduction in body growth rate.

6. Treatment of rabbits with 10 mg/kg (60·3 μmol/kg) of potassium iodide (equal in its iodine content to that of 20 mg/kg of amiodarone), given daily for 6 weeks intraperitoneally, had no effect on body growth rate or the duration of cardiac action potentials.

7. It was concluded that amiodarone had effects on cardiac action potentials similar to those which occur after thyroidectomy.

Introduction

The drug amiodarone (Cordarone, Labaz 3428 ; 2-butyl, 3-(4,diethylaminoethoxy, 3,5-diiodo, benzoyl) benzofuran hydrochloride (Fig. 1)) according to clinical trials benefits patients with angina pectoris (Vastesaeger, Gillot & Rasson, 1967 ; Hueber & Kotzaurek, 1968 ; Barzin & Fréson, 1969 ; Jouve, Medvedowsky & Benyamine, 1969 ; Deleixhe & Delrée, 1969). Its pharmacological actions have been reviewed by Charlier, Deltour, Baudine & Chaillet (1968). Briefly, the drug increased coronary flow, reduced myocardial oxygen consumption, caused an atropine-resistant bradycardia, and antagonized several effects of catecholamines and

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sympathetic stimulation. It did not seem, however, that the anti-anginal actions could be attributed solely to the circulatory effects, because the latter were brief, and the benefit to patients was not optimal until they had been receiving treatment for several days. The present investigation was undertaken to determine whether treatment with amiodarone would lead to any alterations in the properties of cardiac muscle.

Methods

Protection against ouabain induced arrhythmias

The method used was that described by Vaughan Williams & Sekiya (1963) as modified by Papp & Vaughan Williams (1969b). Guinea-pigs of either sex were given 1·6 g/kg of urethane intraperitoneally, and were respired artificially. Body temperature was maintained at 37° C. The electrocardiogram was recorded for 5 s every 2 min and ouabain 3·6 μg was infused over 30 s from a motor-driven syringe every 2 minutes.

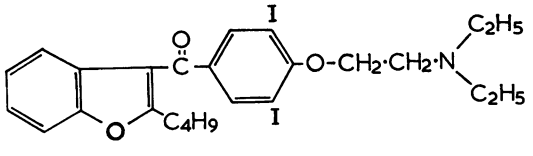
Local anaesthesia

The guinea-pig wheal method of Bülbring and Wajda (1945) was employed. Amiodarone was injected intradermally as a 5% (73·4 mM) solution in distilled water.

Intracellular potentials

These were recorded as described by Szekeres & Vaughan Williams (1962) and Papp & Vaughan Williams (1969a) with glass microelectrodes from the internal surface of isolated rabbit atria suspended horizontally in a bath through which nutrient solution, kept at 32° C, flowed continuously. Contractions were recorded with a RCA 5734 transducer. Conduction velocity was calculated from records obtained with bipolar surface electrodes placed on the left and right atrium. The left atrium was stimulated with 1 ms shocks, of at least twice threshold voltage. The nutrient solution contained (mM): NaCl, 125 ; KCl, 5·6 ; $CaCl_2$, 2·15 ; $NaHCO_3$, 25 ; and glucose, 11, and was gassed with 95% oxygen and 5% carbon dioxide ; pH 7·4.

Ventricular action potentials were recorded from strips 1·5–2·0 cm in length, 2–3 mm wide, cut from the free wall of the right ventricle. They were stimulated by platinum plates (0·5 × 2·0 cm) fixed parallel to, but not touching, the strip, one on each side. The stimulus frequency was 1 Hz, duration 2 ms, strength twice threshold.



Amiodarone

FIG. 1. Structure of amiodarone. The drug was used as the hydrochloride.

Drugs used

Amiodarone hydrochloride (Cordarone, Labaz 3428); (−)-thyroxine, sodium salt (B.D.H.); Strophanthin-G (ouabain) (B.D.H.); urethane (Hopkin and Williams); atropine sulphate (B.D.H.); potassium iodide (Analar, B.D.H.). Results are presented as means ± S.E. The statistical significance of differences was calculated by Student's *t* test and the χ^2 test was used for the evaluation of results concerning ventricular fibrillation.

Results

Acute experiments in guinea-pigs

Within a minute after intravenous administration of amiodarone to anaesthetized guinea-pigs a bradycardia was noted, which was fully developed within 5 min (Table 1), and was not abolished by 1 mg/kg of atropine sulphate. When the heart rate had become stable, an infusion of ouabain from a motor driven syringe was started, and the doses were noted at which various abnormalities of cardiac rhythm became apparent on the electrocardiogram. The results show that acutely administered amiodarone provided significant protection against ouabain-induced arrhythmias but not against cardiac arrest (Table 2).

Local anaesthesia. Amiodarone was devoid of a local anaesthetic action. Even a 5% (73·4 mM) solution injected intradermally did not modify the responses of guinea-pigs to pin-pricks.

Experiments in rabbits

Growth rates. Three groups of rabbits were given daily intraperitoneal injections of 20 mg/kg (29·4 μmol/kg) of amiodarone for 6 weeks, 3 weeks and 1 week, respectively. The mean initial weight of the first group was 806 ± 41 g (n=14), and the mean weight 6 (range 5–7) weeks later was 1,533 ± 57 g. The mean daily growth rate (calculated separately for each animal) was 18·25 g. The mean of the heart weight (wet weight) after 6 weeks' treatment with amiodarone was 0·2180 ± 0·0048% of the final body weight, which was significantly less than the control value of 0·2519 ± 0·0030% (n=12, P<0·001). In the rabbits treated for 3 weeks and 1 week with amiodarone, the daily growth rates during treatment were 23·5 ± 1·3 g and 21·0 ± 1·0 g, respectively.

Spontaneous and maximum driven frequencies, electrical threshold and conduction velocity. Six weeks' treatment of rabbits with amiodarone, 20 mg/kg (29·4 μmol/kg) given daily intraperitoneally, significantly reduced the spontaneous frequency of the

TABLE 1. *Changes in heart rate 5 min after intravenous amiodarone*

Amiodarone		Control heart rate per min	n	% Change from controls
Dose	Heart rate/min			
6·25 mg/kg (9·17 μmol/kg)	265·6 ± 34·5	271·0 ± 33·2	5	−2·2 ± 1·5
12·5 mg/kg (18·35 μmol/kg)	267·2 ± 11·0	302·9 ± 14·0	10	−11·6 ± 1·3
25 mg/kg (36·7 μmol/kg)	223·7 ± 6·4	279·4 ± 14·6	10	−19·3 ± 2·6
50 mg/kg (73·4 μmol/kg)	223·6 ± 10·6	317·2 ± 19·7	10	−28·5 ± 2·9

TABLE 2. *Effect of amiodarone on toxicity of infused ouabain*

Dose of amiodarone (5% (73·4 mM) solution in dist. water) i.v. 5 min before infusion of ouabain	*n*	Unequal intervals	Ectopic beats	Ventricular rhythm	Ventricular flutter-fibrillation	Cardiac arrest
Control	30	88·5±4·8	204·7±10·6	226·0±11·8	240·7±11·7 (29/30)	311·2±12·7
Amiodarone 6·25 mg/kg (9·17 μmol/kg)	5	94·1±3·2	188·2±12·9	210·6±15·1	222·8±13·0 (5/5)	296·4±17·1
Amiodarone 12·5 mg/kg (18·35 μmol/kg)	10	102·9±7·0 (7/10)**	237·5±22·3 (9/10)	241·5±15·8 (8/10)	245·0±12·2 (8/10)	312·0±22·7
Amiodarone 25 mg/kg (36·7 μmol/kg)	10	147·9±42·1 (4/10)***	247·1±19·0 (9/10)	294·8±13·7* (7/10)**	308·2±17·9* (5/10)***	341·0±18·3
Amiodarone 50 mg/kg (73·4 μmol/kg)	10	119·7±7·3 (5/10)***	245·3±19·3 (9/10)	288·0±23·3 (4/10)***	330·4±55·3 (2/10)***	347·0±26·9

The figures give the mean amounts of ouabain infused in μg/kg ± S.E. at the time the stated effects were observed. The incidence of the effect is given in brackets when this was less than 100%, the amount of ouabain thus referring only to those animals in which the effect was observed. Significance of difference from control: * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

TABLE 3. *Parameters of intracellularly recorded action potentials in rabbit atria*

	Resting potential (mV)	Action potential (mV)	Maximum rate of rise (V/s)	Mean rate of rise (V/s)	Time for repolarization to 50% (ms)	Time for repolarization to 90% (ms)
Control (*n*=73)	63·4±0·4	87·9±0·6	83·9±1·7	49·7±1·1	49·1±0·8	104·3±0·8
Amiodarone 6 weeks (*n*=69)	65·1±0·6	87·6±0·7	70·8±1·5	43·9±1·0	71·6±0·7	139·3±0·9
Significance of difference from control	NS	NS	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
Control (*n*=30)	62·7±0·8	89·5±0·6	96·3±2·4	60·0±1·8	47·5±1·1	99·8±1·8
Amiodarone 3 weeks (*n*=38)	65·4±0·6	88·9±0·6	91·8±2·1	52·6±1·8	67·6±1·5	123·5±2·0
Significance of difference from control	NS	NS	NS	$P<0.01$	$P<0.001$	$P<0.001$
Amiodarone 1 week (*n*=30)	63·8±0·7	88·9±1·0	99·9±2·2	58·6±2·3	61·7±1·0	110·9±1·2
Significance of difference from control	NS	NS	NS	NS	$P<0.001$	$P<0.001$

Amiodarone was given in a daily dose of 20 mg/kg (29·4 μmol/kg) intraperitoneally for the period stated.
The atria were removed at the end of treatment and studied *in vitro*.
n indicates the numbers of fibres from which the means were calculated.

isolated atria *in vitro* at 32° C. Atria from control rabbits contracted at a frequency of $134{\cdot}28 \pm 2{\cdot}61$/min as compared with atria from treated rabbits which had a frequency of $110{\cdot}71 \pm 1{\cdot}77$ ($P<0{\cdot}001$). The maximum driven frequency of the former was $401{\cdot}78 \pm 8{\cdot}01$ per min as compared with $360{\cdot}42 \pm 6{\cdot}46$ per min ($P<0{\cdot}001$) for the latter. On the other hand, changes in conduction velocity ($0{\cdot}51 \pm 0{\cdot}04$ m/s in atria from controls, $0{\cdot}55 \pm 0{\cdot}044$ in atria from treated rabbits) and electrical threshold ($1{\cdot}74 \pm 0{\cdot}13$ V in atria from controls; $2{\cdot}23 \pm 0{\cdot}39$ V in atria from treated rabbits) were not statistically significant ($P=0{\cdot}9$ and $0{\cdot}3$ respectively).

Cardiac intracellular potentials. Amiodarone, 20 mg/kg (29·4 μmol/kg) given daily intraperitoneally for six weeks, had no effect on the resting potential of rabbit atria isolated at the end of the treatment. In contrast to the action of other anti-arrhythmic drugs, it also had no effect on the action potential height, and although the rate of the rise was reduced significantly in comparison with that of controls, the change was small and the mean maximum rate of rise of 71 V/s observed was at the lower end of normal limits. The most outstanding change produced by amiodarone in intracellular potentials was a very great increase in the duration of the action potential. After 6 weeks' treatment the mean times from the peak of the potential to 50% and 90% repolarization were prolonged by 22·4 ms (45%) and 35 ms (33·5%), respectively. Details of alterations in the intracellular potentials after 6 weeks', 3 weeks' and 1 week's treatment with amiodarone are presented in Table 3. The prolongation of the action potential was the main effect, being highly significant even after one week's treatment, whereas the mean rate of rise of the action potential was significantly altered only after 3 weeks' treatment. The rabbits used for the 6 weeks' experiments and their controls were members of a different

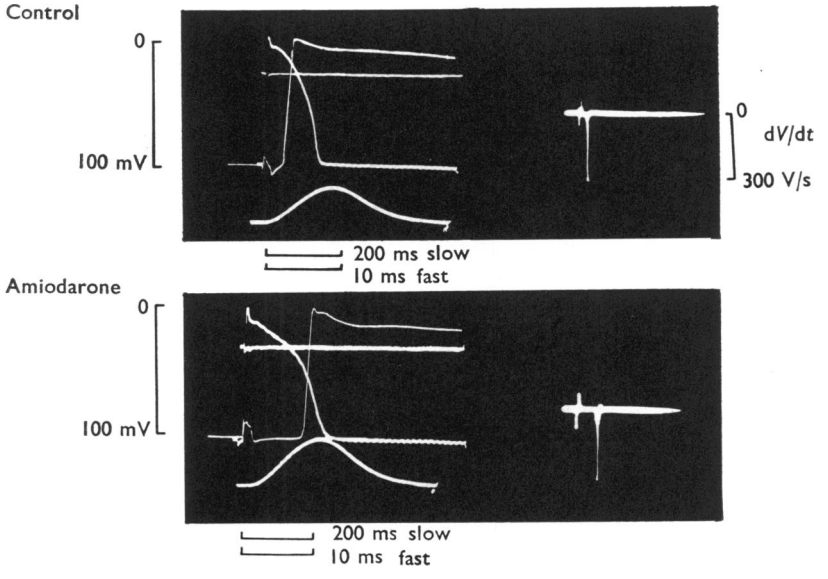


FIG. 2. Effect of six weeks' treatment with amiodarone, 20 mg/kg (29·4 μmol/kg) daily, intraperitoneally on rabbit ventricles isolated at the end of treatment and studied *in vitro*. Left: the horizontal line indicates the resting potential; the superimposed traces depict intracellular potentials at slow and fast sweep speeds. Bottom trace: contraction. Right: pulse depth is proportional to rate of rise of intracellular potential. In the lower picture the greater interval between the stimulus artifact and the differentiated spike is not due to a reduced conduction velocity but to the fact that the intracellular electrode was in a more distant fibre.

TABLE 4. *Effect of amiodarone on action potentials in rabbit ventricular fibres*

	Resting potential (mV)	Action potential (mV)	Maximum rate or rise (V/s)	Mean rate of rise (V/s)	Time for repolarization to 50% (ms)	Time for repolarization to 90% (ms)
Control	70·8±1·9 (45)	100·6±4·1 (45)	356·1±9·9 (42)	140·8±7·9 (39)	133·4±2·4 (45)	171·6±1·8
Amiodarone (6 weeks)	73·7±2·6 (51)	97·1±3·9 (51)	371·8±11·0 (46)	146·3±7·3 (36)	169·8±4·5 (51)	222·5±3·4 (51)
Significance of difference from control	NS	NS	NS	NS	$P<0·001$ ($t=8·27$)	$P<0·001$ ($t=15·05$)

Amiodarone was given daily in a dose of 20 mg/kg (29·4 μmol/kg) intraperitoneally. The ventricles were removed at the end of treatment and studied *in vitro*. The figures in brackets indicate the numbers of fibres from which the means were calculated.

TABLE 5. *Effect of potassium iodide and of amiodarone supplemented by thyroxine, on action potentials recorded from rabbit atria isolated at the end of treatment*

	Resting potential (mV)	Action potential (mV)	Maximum rate of rise (V/s)	Mean rate of rise (V/s)	Time for repolarization to 50% (ms)	Time for repolarization to 90% (ms)
Control ($n=45$)	62·9±0·3	89·3±0·6	91·5±2·1	56·7±1·3	48·8±0·8	101·6±1·4
Iodine 6 weeks ($n=51$)	66·9±0·7	91·5±0·8	92·5±1·7	54·7±1·5	47·2±2·1	99·2±1·1
Significance of difference from control	$P<0·001$	$P<0·01$	NS	NS	NS	NS
Amiodarone 6 weeks L-thyroxine 3 weeks ($n=48$)	64·2±0·5	89·6±0·7	91·2±1·7	53·4±1·3	52·0±0·6	106·7±1·1
Significance of difference from control	NS	NS	NS	NS	NS	$P<0·01$

For details of doses see text.

batch from those used for the three and one week series. Results obtained in the two control series were slightly different, but this had no bearing on the conclusions drawn.

Ventricular potentials. The effect of amiodarone, 20 mg/kg (29·4 μmol/kg) given for 6 weeks intraperitoneally, on ventricular potentials was similar to that on atrial potentials (Table 4 and Fig. 2). There was no significant change in resting potentials, or in the heights or rates of rise of action potentials. The electrical threshold of control ventricular strips was 10·5 V ($n=5$) and of strips from amiodarone treated rabbits 12 V (difference not significant).

Effects of iodine and thyroxine. Amiodarone (HCl) contains 37·2% iodine by weight, so that if the drug were completely de-iodinated *in vivo*, a 20 mg dose (29·4 μmol) would be equivalent to an iodine intake of 7·44 mg. A group of five rabbits with a mean initial weight of $512 \pm 17{\cdot}7$ g was given daily intraperitoneal injections of 10 mg/kg (60·3 μmol/kg) of potassium iodide (representing 7·65 mg iodine/kg) for 38–41 days. The mean daily growth rate was $28{\cdot}8 \pm 1{\cdot}0$ g, and the mean of the heart weights (wet weight) after treatment was $0{\cdot}242 \pm 0{\cdot}0057\%$ of the body weight, which may be compared with control values of $0{\cdot}2519 \pm 0{\cdot}003\%$ ($n=12$) in the current series of experiments, and of $0{\cdot}2353 \pm 0{\cdot}0065\%$ ($n=23$) previously reported (Freedberg, Papp & Vaughan Williams, 1970).

Iodine treatment had no effect on spontaneous frequency ($130{\cdot}2 \pm 3{\cdot}8$ beats/min in controls; $127{\cdot}4 \pm 2{\cdot}3$ in iodine series) or maximum driven frequency ($406{\cdot}6 \pm 20{\cdot}7$ in controls; $409 \pm 8{\cdot}1$ in iodine series) of atria isolated at end of the treatment. No significant changes were produced in conduction velocity or rate of depolarization and there was no prolongation of the action potential (Table 5). There was a small but statistically significant increase in resting and action potential voltages in the iodine series as compared with their controls; nevertheless, the resting potentials of the atria of treated animals were well within the normal range observed in recent experiments (Papp & Vaughan Williams, 1969b, c).

It was recently shown that prolongation of the cardiac action potential occurred 6 weeks after thyroidectomy in rabbits (Freedberg *et al.*, 1970), and the possibility had to be considered that amiodarone might act by reducing cardiac metabolism. A group of five rabbits with a mean initial weight of 753 g was given intraperitoneal injections of 20 mg/kg (29·4 μmol/kg) of amiodarone for 6 weeks. From the end of the third week they were also injected daily with 5 μg (0·00626 μmol) L-thyroxine subcutaneously, a dose which may be considered insufficient to produce a hyperthyroid state or even to suppress endogenous thyroxine production (Brown-Grant, 1955), since rabbits normally secrete approximately (6 μg/kg)/day of thyroxine, so that, as the mean weight of the rabbits in the present experiments at the start of thyroxine injections was 1,139 g, they should have been secreting about 7 μg/day of thyroxine. The mean daily growth rate of the animals given thyroxine and amiodarone simultaneously was $31{\cdot}2 \pm 0{\cdot}9$ g, which may be compared with a control daily growth of 31·8 g recently observed (Freedberg *et al.*, 1970).

The effects of the combined thyroxine and amiodarone treatment on intracellular potentials are presented in Table 5 and it is clear that all the changes which amiodarone alone would have produced, with the exception of a small prolongation of the action potential, were completely abolished by the simultaneous administration of thyroxine. In the atria, removed at the end of treatment, the mean spon-

taneous frequency was 127·8 per min (130·2 per min in controls), the maximum driven frequency 369 per min (389/min in controls), conduction velocity 0·55 m/s (0·53 m/s in controls) and electrical threshold 1·62 V (1·67 V in controls). The mean wet weight of hearts taken from treated animals was 0·236% of body weight, as compared with 0·235% in controls.

Effect of amiodarone on thyroid weight

Seven rabbits with a mean weight of 651 ± 26·1 g were given 20 mg/kg (29·4 μmol/kg) of amiodarone intraperitoneally daily for 38–44 days. Their mean daily growth rate was 19·1 ± 0·9 g, similar to that of the series already described, and their mean weight at the end of treatment was 1,444·7 ± 72·0 g. The mean heart weight was 0·2255 ± 0·0049% of the body weight.

The mean weight of the thyroid glands of these animals was 244·4 ± 13·6 mg/kg body weight. In seven untreated rabbits, with a mean body weight of 1,536·7 ± 34·7 g, the mean thyroid weight was 247·3 ± 16·9 mg/kg body weight. It was evident, therefore, that amiodarone caused no change in the weight of the thyroid gland.

Discussion

Amiodarone, a benzofuran derivative, has been reported to have beneficial effects on patients with established angina pectoris in twenty clinical trials, of which that carried out by Vastesaeger *et al.* (1967) on more than five hundred cases treated for up to 2 years may be taken as representative. The mode of action of the drug appears to be complex, and extensive pharmacological investigations have been summarized by Charlier *et al.* (1968). Although amiodarone increased coronary flow, this acute action could not wholly account for its beneficial effects in angina pectoris, since clinical improvement was not fully manifest for several days. Oxygen utilization by the heart was reduced by amiodarone, and the oxygen saturation of coronary sinus blood was raised. Amiodarone induced a pronounced bradycardia in dogs (Charlier *et al.*, 1968), unaffected by atropine, and associated with a brief and small reduction in mean arterial blood pressure and no significant alteration of cardiac output (3–9%). We have confirmed that amiodarone caused an acute atropine-resistant bradycardia in guinea-pigs.

Amiodarone reduced responses to sympathetic stimulation and to injected catecholamines (Charlier *et al.*, 1968). Effects mediated by α- and β-adrenoceptors were both reduced, but never abolished, and it was clear that amiodarone was not acting by simple competitive blockade.

Most drugs with anti-arrhythmic properties reduce the height and rate of rise of the action potential, but do not affect the resting potential of cardiac muscle, and either do not change the duration of the action potential at all or prolong it to a trivial extent in comparison with increases produced in the duration of the effective refractory period (Szekeres & Vaughan Williams, 1962). The anti-arrhythmic action of propranolol and several other β-adrenoceptor blocking drugs may partly be attributed to such "quinidine-like" effects, but it is clear that their sympatholytic action does also contribute to their anti-arrhythmic properties even against ouabain-induced arrhythmias (Dohadwalla, Freedberg & Vaughan Williams, 1969). Likewise adrenergic neurone blocking drugs without non-specific actions on the cardiac

membrane also protect against ouabain arrhythmias (Papp & Vaughan Williams, 1969b). It was, therefore, of interest to find that amiodarone, which had no local anaesthetic activity even in 5% (73·4 mM) solution, unlike many anti-arrhythmic drugs (Gill & Vaughan Williams, 1964; Morales-Aguilerà & Vaughan Williams, 1965), had a significant protective effect against ouabain-induced ventricular fibrillation. Since this was an acute effect, it may be attributed to the sympatholytic properties of amiodarone, and must be distinguished from the effects of more prolonged treatment. An anti-arrhythmic action of amiodarone in other types of experimentally induced cardiac arrhythmias also was observed by Charlier, Delaunois, Bauthier & Deltour (1969).

Treatment of rabbits for several weeks with amiodarone had an unusual action on cardiac intracellular potentials, both atrial and ventricular, in that the drug interfered with repolarizing currents to a much greater extent than it affected depolarization, whereas quinidine, propranolol and most other anti-arrhythmic drugs do the reverse. After 20 mg/kg (29·4 μmol/kg) of amiodarone given intraperitoneally daily for three weeks, the atrial action potential was prolonged by 23·7% without any significant change in the maximum rate of depolarization and after six weeks' treatment repolarization was delayed by 33·5%, but the rate of rise of the action potential, though significantly less than that of the controls, was nevertheless 71 V/s—on the border of normal limits. There was no significant change in resting or action potential voltages. In ventricular muscle the results were similar.

Alterations in cardiac potentials resembling the above have been observed in rabbits after thyroidectomy (Freedberg *et al.*, 1970). ^{131}I-labelled amiodarone is taken up by the thyroid gland (Deltour, Bekaert, Broekhuysen & Charlier, 1962) and partly de-iodinated (Broekhuysen, Laruel & Sion, 1969). In humans given 600 mg amiodarone daily for up to three months, plasma bound iodine increased above 30 μg/100 ml because the drug or its metabolites are partly fixed to plasma proteins. The presence of iodide raises total blood iodine to even higher values, sufficient to saturate the thyroid and block completely the uptake of radioactive iodine. The thyroxine-iodine, however, was not increased above normal limits (5·2 μg/100 ml controls; 6·5 μg/100 ml treated). In our experiments treatment of rabbits for six weeks with daily injections of potassium iodide equivalent to the iodine content of 20 mg/kg of amiodarone did not alter the duration or rate of rise of the action potential. Amiodarone itself has no thyroxine-like activity (Broekhuysen, Deltour & Ghislain, 1969).

There is no evidence that amiodarone produces any signs of general hypothyroidism in humans or animals, and there is no change in blood cholesterol in either. Amiodarone did, however, have effects on cardiac metabolism, increasing all the ratios $\frac{\text{ATP}+\text{CrP}}{\text{ADP}+\text{Creatine}}$, $\frac{\text{CrP}}{\text{Cr}}$ and $\frac{\text{ATP}+\text{CrP}}{\text{Inorganic P}}$ in the cardiac muscle of treated animals (Broekhuysen *et al.*, 1969). Amiodarone, 10 mg/kg, decreased cardiac oxygen consumption by 27%, in association with increased coronary flow (Charlier *et al.*, 1968), but 50 mg/kg reduced oxygen consumption of the whole animal by 12·7%, a reduction so small that it could be attributed to the fall in cardiac oxygen consumption alone, implying very little change in oxygen utilization by other tissues. Our experiments relate mainly to isolated cardiac muscle, and have indicated that 6 weeks' treatment with amiodarone produced an effect on intracellular potentials

which was similar to that observed 6 weeks after thyroidectomy (Freedberg *et al.*, 1970), and which could be prevented so far as atrial potentials were concerned, by administration of a dose of thyroxine equivalent to less than the normal daily thyroxine secretion, which is 6 μg/kg (Brown-Grant, 1955). Rabbits are known to metabolize thyroxine rapidly, being able to eliminate half of a 50 μg dose in 29 h (Brown-Grant & Tata, 1961). The changes in cardiac membrane activity produced by amiodarone were thus prevented by a very small dose of thyroxine, and the drug may have been blocking the effect of endogenous thyroxine, or the changes produced may merely have been secondary to a reduction by amiodarone of cardiac metabolism in parallel, as it were, to thyroxine-dependent pathways.

The present experiments indicate that amiodarone did not cause any depression of thyroid function, because the weights of the thyroid glands of animals treated with 20 mg/kg of amiodarone daily intraperitoneally for 6 weeks were exactly the same as those of untreated animals.

It may tentatively be concluded, therefore, that amiodarone exerts a depressant effect on metabolic turnover which has some cardio-specificity, and that this has two secondary consequences. First, the incidence of pain in patients with angina pectoris is reduced, without a diminution of cardiac output. Second, the duration of the cardiac action potential is prolonged, leading to a reduced probability of cardiac arrhythmia.

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