Br. J. Pharmac. (1973), **48**, 183–193.

The effects on cardiac muscle and nerve of a fluorinated decahydroquinoline derivative, L7810, rapidly absorbed after oral administration

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Summary

1. L7810 (4-carbamoyloxy-1-(4-(4-fluorophenyl)-4-oxobutyl) decahydroquinoline, has a local anaesthetic action on frog nerve 1·75 times that of procaine.

2. L7810 protected anaesthetized guinea-pigs against ouabain-induced ventricular fibrillation and increased the lethal dose of ouabain.

3. L7810 reduced the rate of rise of intracellularly recorded action potentials in rabbit isolated atria ; the resting potential was not affected, but the duration of the action potential was prolonged.

4. Unlike most drugs with local anaesthetic properties L7810 did not depress contractions in isolated atria but increased them.

5. L7810 reduced the spontaneous frequency, maximum follow frequency and conduction velocity of rabbit isolated atria.

6. L7810 had no blocking action on the chronotropic or positive inotropic actions of isoprenaline on isolated atrial muscle.

7. In anaesthetized dogs L7810 caused a small dose-related bradycardia, and a large dose-related decrease in peripheral vascular resistance. There was no blockade of the effects of isoprenaline on heart rate or peripheral blood flow.

Introduction

There are three main ways in which antidysrhythmic drugs affect cardiac muscle (Vaughan Williams, 1970). The first class of action, exhibited by quinidine, procaineamide, lignocaine and other compounds which also have local anaesthetic properties on nerve, is to reduce the maximum rate of depolarization, without alteration of resting potential or duration of action potential (Vaughan Williams, 1958 ; Szekeres & Vaughan Williams, 1962). The second class of action is antisympathetic (Dohadwalla, Freedberg & Vaughan Williams, 1969 ; Papp & Vaughan Williams, 1969), either by neurone blockade or by competition for β-adrenoceptors. The third class of action is a prolongation of the plateau of the action potential (Freedberg, Papp & Vaughan Williams, 1970 ; Singh & Vaughan Williams, 1970a, b). Several drugs have more than one of these effects, e.g. the β-adrenoceptor blocking drugs propranolol, alprenolol and oxprenolol are all more potent local anaesthetics than procaine. Lignocaine, which has class 1 actions only (Singh &

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Vaughan Williams, 1971), is rapidly destroyed by the liver (Harrison & Alderman, 1971) which reduces the danger of overdosage but is an impediment to its being given orally.

No antidysrhythmic drug at present available is free from undesirable side-effects of one kind or another and there is a particular need for a compound reliably absorbed after oral administration which could be used prophylactically or as maintenance therapy after correction of dysrhythmias by other drugs. The present experiments were undertaken to investigate the mode of action of a new compound, L7810 (4-carbamoyloxy-1-(4-(4-fluorophenyl)-4-oxobutyl) decahydroquinoline (Fig. 1), which is rapidly absorbed after oral administration. In acute experiments the drug was effective against dysrhythmias induced by barium chloride, coronary ligation, adrenaline, digitalis, acetylcholine and aconitine (Charlier, unpublished). The drug has also been found to inhibit hypertensive responses to various catecholamines in dogs and rats (Charlier, Colot, Delaunois, Polster, Beersaerts & Bacq, 1972) and to protect dogs from adrenaline-induced shock (Barac & Bacq, 1973).

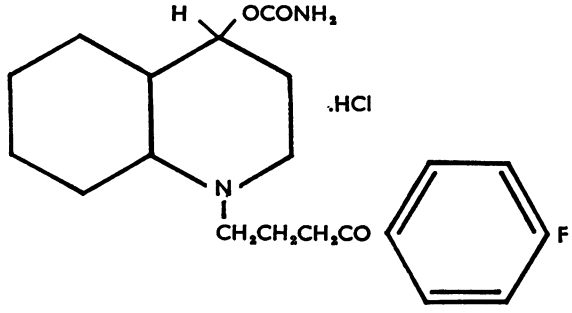

FIG. 1. Structure of L7810.

We have investigated whether the drug has any blocking action on cardiac or peripheral β-adrenoceptors in dogs, or has class 1 or class 3 actions on intracellularly recorded rabbit atrial potentials.

Methods

Protection against ouabain-induced arrhythmias

The method used was that described by Vaughan Williams & Sekiya (1963) as modified by Dohadwalla *et al.* (1969). Guinea-pigs of either sex were anaesthetized with 1·6 g/kg of urethane intraperitoneally and were respired artificially. Body temperature was maintained at 37° C by a heated plate under the animal. 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 of nerve

Frog sciatic nerves were placed in a three compartment chamber at room temperature. They were stimulated in moist air at one end and action potentials were recorded from the other. The segment of nerve in the central compartment was bathed in frog Ringer containing various concentrations of procaine or of L7810.

The solution contained (mM): NaCl, 120 ; KCl, 1·88 ; $CaCl_2$, 1·08 ; $NaHCO_3$, 2·38 ; Tris (Sigma) buffer, at pH 7·5, 10 ml/litre. The height of the fastest wave of the action potential was measured before and after exposure for 30 min to each concentration of the drug used.

Isolated atria. Intracellular potentials and other measurements

The method was as previously described (Vaughan Williams, 1958 ; Szekeres & Vaughan Williams, 1962). Single fibres were penetrated from the internal surface of isolated rabbit atria suspended horizontally in a bath through which modified Locke solution at 32° C was recirculated by an external oxygenator. Mean values of all parameters were measured according to defined criteria (Vaughan Williams, 1959). Contractions were recorded with a RCA 5734 transducer and conduction velocity was calculated from the interval between a stimulus (2 ms, strength at least twice threshold) to an electrode on the left atrium and an action potential recorded from the surface of the right atrium with a bipolar electrode. Similar preparations were used for measurement of maximum driven frequency, electrical threshold and blockade of the chronotropic and inotropic actions of isoprenaline.

The solution contained (mM): NaCl, 125 ; KCL, 5·6 ; $CaCl_2$, 2·16 ; $NaHCO_3$, 25 ; glucose, 11·0 ; and was gassed with 95% O_2 5% CO_2 ; pH was 7·4.

In vivo *experiments on dogs*

Dogs were anaesthetized with pentobarbitone 30 mg/kg, an endotracheal tube was introduced, and artificial respiration was maintained with a Palmer suck-and-thrust pump. Additional pentobarbitone was administered intravenously from a motor-driven syringe at a rate of 5 (mg/kg)/h ; in a few dogs this was not quite sufficient to prevent a lightening of anaesthesia (indicated by tight abdominal muscles) and then an additional 5 mg/kg was administered as a single injection. Through a mid-line abdominal incision the aorta, just above the bifurcation but below the inferior mesenteric artery (i.m.a.), was cleaned and encircled by a cuff-type electromagnetic flow-probe (S.E. Laboratories, #275) of a size to fit closely ; the exact site was determined by the position of arterial branches. The inferior mesenteric artery was cannulated in a retrograde direction with fine polythene tubing and the abdominal incision was closed around the latter and the leads to the probe. The vagi were cut and both carotids were tied and cannulated with polythene tubing fitted to pressure transducers (Consolidated Electrodynamics 4-327-L221). The cannula in the right carotid was used to record mean pressure ; that in the left, which was usually advanced into the left ventricle, recorded phasic pressure changes. In all except one of the experiments the chest was opened between 5th and 6th ribs and a strain-gauge was stitched to the left ventricle. The chest was then closed by sutures. All outputs were displayed on a Devices M8 recorder. One of the channels recorded the lead II electrocardiogram.

Intra-arterial injections of isoprenaline were made into the inferior mesenteric artery at 4 min intervals each successive dose being 1·8 times the previous dose. When a dose was reached which increased aortic blood flow approximately three-fold further injections of isoprenaline were made intravenously at 4 min intervals until an increase in heart rate of about 70 beats/min had been obtained. In some experiments responses to i.a. noradrenaline were also measured.

An automated programme with a 4 min cycle switched on the paper-drive of the M8 at 0–5, 15–30, 35–40, 45–50, 120–125, 230–235 s from the start. Intra-arterial injections were given at the end of the 5th second, so that the first 5 second record served as a preinjection control. The peak increase in blood flow always occurred between 15–25 s after the injection. A slightly different programme (0–5, 25–30, 35–40, 45–50, 55–60, 120–125, 230–235 s) was used to record responses to intravenous isoprenaline because peak increases in heart rate always occurred between 20 and 45 s after the injection.

Peripheral blood-flow conductance was calculated from the simultaneous records of mean arterial blood pressure and aortic blood flow and was expressed as (ml/mmHg)/minute.

Dose-response curves, after sets of intra-arterial and intravenous injections of isoprenaline or noradrenaline, were obtained before and after i.v. injections of various doses of L7810.

Drugs used were: L7810, 4-carbamoyloxy-1-(4-(4-fluorophenyl)-4-oxobutyl) decahydroquinoline (LABAZ), procaine hydrochloride (B.D.H.), isoprenaline sulphate (Burroughs Wellcome), (−)-noradrenaline bitartrate (Koch-Light Labs.), urethane (Hopkin & Williams), strophanthin G (Ouabain, B.D.H.), pentobarbitone sodium B.P.

The statistical significance of differences was calculated from Student's *t* test.

Results

Protection against ouabain

In three series of experiments intravenous injections of 0·3 mg/kg ($n=10$), 1·0 mg/kg ($n=10$) and 3·0 mg/kg ($n=10$) respectively of L7810 were injected intravenously 5 min before the start of intermittent intravenous infusion of ouabain. The electrocardiogram was monitored continuously on an oscilloscope screen, as well as being recorded automatically for 5 s every 2 min, and the amount of ouabain infused was noted when: (a) irregularities of sinus rhythm occurred; (b) ventricular ectopic beats started; (c) persistent ventricular tachycardia commenced (i.e. without intervening intervals of sinus rhythm); (d) the ventricles fibrillated; (e) the heart stopped. The results, together with the effects of 37 control ouabain infusions, are presented in Table 1. It is clear that a prior dose of 3 mg/kg conferred a

TABLE 1. *Effect of L7810 on ouabain toxicity in anaesthetized guinea-pigs*

Dose of L7810 mg/kg (mol $\times 10^{-7}$/kg)	No. of animals	Dose of infused ouabain (μg/kg) required to produce: 1 Irregular sinus rhythm	2 Ventricular extra-systoles	3 Persistent ventricular tachycardia	4 Ventricular fibrillation	5 Cardiac arrest
0·0	37	90·0± 4·7	197·2± 9·5	234·8±11·4	249·3±11·3	311·8±11·6
0·3 (0·76)	10	78·9± 9·8	198·8±31·6	291·0±25·9*	315·0±28·2* (7/10)*	371·2±19·1
1·0 (2·52)	10	75·5±16·7	152·8±11·4	240·2±19·0	260·6±18·5 (5/10)†	325·6±20·8
3·0 (7·55)	10	114·0±19·4	198·2±22·7	316·6±31·4†	347·5±27·6 (8/10)‡	402·7±19·6‡

Statistical significance of difference. *=$P<0·05$; †=$P<0·01$; ‡=$P<0·001$. The incidence of ventricular fibrillation is given in parentheses in column 4. The dose of ouabain is the mean dose producing fibrillation in the susceptible animals.

highly significant degree of protection against the toxicity of ouabain, of which the lethal dose was increased by 29%. There was one curious feature about the results. In the controls ouabain caused ventricular fibrillation in 36 out of 37 animals at a mean dose (±S.E.M.) of 249·3±11·3 μg/kg in those animals which fibrillated. The incidence of ventricular fibrillation was reduced to 7/10 by the prophylactic dose of 0·3 mg/kg of L7810 and to 5/10 by 1·0 mg/kg, both results being statistically significant by a χ^2 test. Yet after 3·0 mg/kg L7810, ouabain caused ventricular fibrillation in 8/10 animals in spite of the fact that the dose of ouabain needed to produce the fibrillation was 39% greater ($P<0·001$) than that necessary to induce fibrillation in the controls. The possible significance of this finding is discussed later.

Local anaesthesia of nerve

L7810 was found to have a strong local anaesthetic effect on nerve with a mean (±S.E.M.) activity 1·75±0·11 times that of procaine (range 1·44 to 2·1, $n=7$).

Intracellular potentials

From the above result it would be expected that L7810 would have a 'class 1' action on cardiac muscle, defined as a depression of the maximum rate of depolarization without change of resting potential or duration of the action potential. The effect of various concentrations of L7810 on intracellularly recorded potentials was studied (Fig. 2) in isolated atria from five rabbits and the results are summarized

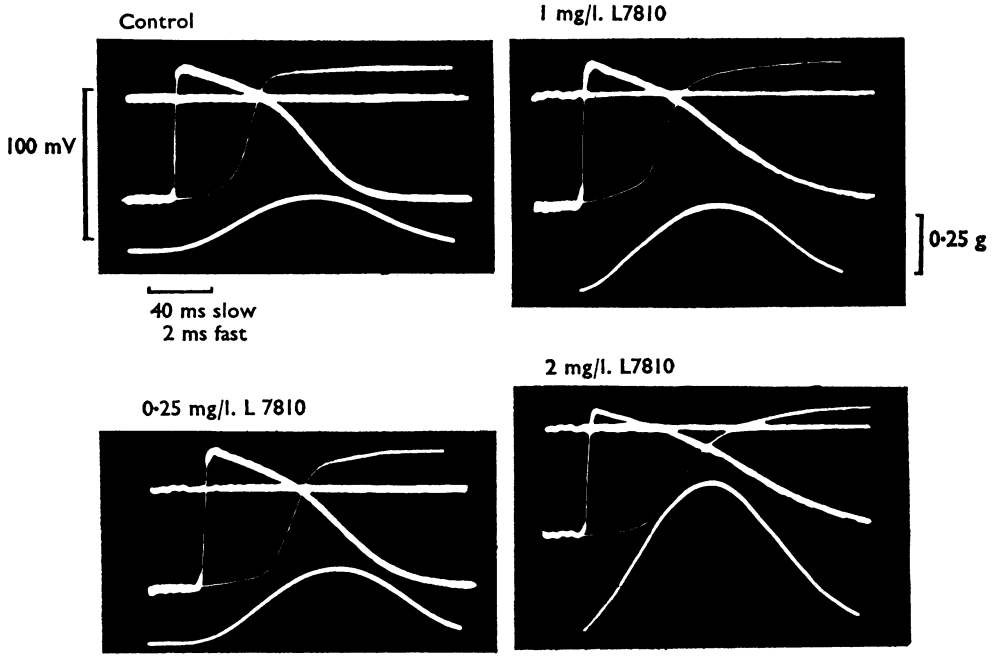

FIG. 2. Effect of L7810 on intracellular potentials and contractions of isolated rabbit atria. In each frame, the upper records from a microelectrode depict the zero potential (horizontal trace) and intracellular potentials at slow and fast sweep speeds. The lower trace records contractions. L7810 reduced the rate of rise of the action potential and the overshoot but increased contractions.

in Table 2. Control records were obtained from several different fibres in each preparation before exposure to the drug (for one hour) but, since there was no significant difference between the control records from different rabbits, for simplicity of presentation the mean of the controls from all the animals is given in the Table.

TABLE 2. *Effect of L7810 on intracellular potentials in rabbit isolated atria*

Conc. of L7810 mg/l. ($M \times 10^{-6}$)	No. of fibres	Resting potential mV	Difference from control	Action potential mV	Difference from control	MRD V/S	Difference from control	Time to 90% repolarization ms	Difference from control
0·0	46	73·45 ±0·74		93·71 ±0·76		76·55 ±3·19		122·38 ±2·10	
0·25 (0·63)	28	71·77 ±1·19	−1·68	89·32 ±1·66	−4·39†	50·17 ±5·27	−26·38‡	126·25 ±2·48	+3·87
1·0 (2·52)	17	74·54 ±1·44	+1·09	89·42 ±1·87	−4·28†	48·77 ±6·19	−27·78‡	157·33 ±5·53	+34·94‡
2·0 (5·04)	19	65·26 ±2·11	−8·20‡	79·91 ±2·08	−13·80‡	28·85 ±5·19	−47·71‡	162·03 ±4·33	+39·6‡

Statistical significance of differences from control. †=$P<0{\cdot}01$; ‡=$P<0{\cdot}001$. MRD=Maximum rate of depolarization.

The two lower concentrations of L7810 (0·63 and $2{\cdot}52 \times 10^{-6}$M) did not affect the resting potential, but reduced the overshoot potential. The highest concentration used (still only $5{\cdot}04 \times 10^{-6}$M) reduced the resting potential also which is not a usual effect with local anaesthetic-type drugs unless very high concentrations are employed. Even the lowest concentration caused a very big reduction in maximum rate of depolarization. None of the concentrations used caused any change in the duration of repolarization to within 50% of the diastolic potential (i.e. there was no flattening or broadening of the ' plateau '), and so these measurements have not been recorded in the Table. Both of the highest concentrations used, however, significantly prolonged the tail of the action potential.

Effect of L7810 on contractions and electrical threshold

It was apparent from the above experiments that L7810 was an extremely active drug of the class 1 type. Many such compounds often also depress contractions but their activity varies considerably in this respect. The effects of L7810 on the contractions and the electrical threshold are shown in Fig. 3 in which percentage changes have been plotted against the logarithm of the concentration. At the highest concentration used (10^{-5}M) electrical threshold was raised, an action typical of a local anaesthetic-type of antidysrhythmic drug. At the lower concentrations, however, electrical threshold was unaltered and contractions were *increased* by all the concentrations used; this implies that L7810 has other actions in addition to its class 1 effects.

Spontaneous frequency, maximum driven frequency and conduction velocity

The effect of L7810 on the above is shown in Figure 4. In contrast to the effects on contraction and electrical threshold there was a simple linear relationship to the log (concentrations) implying that, so far as these parameters were concerned, the class 1 action of L7810 was its predominant effect.

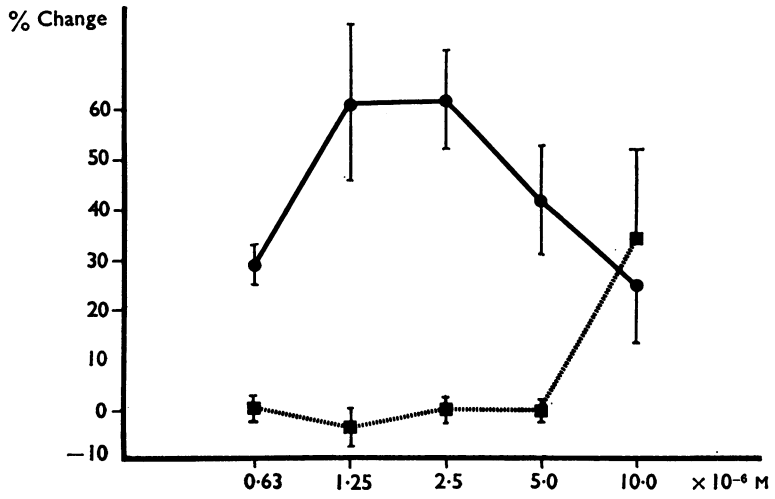

FIG. 3. Effect of L7810 on contractions (●) and electrical threshold (■) in isolated rabbit atria. Ordinates: % increases from control period after 40 min exposure to L7810. Abscissae: concentration of L7810.

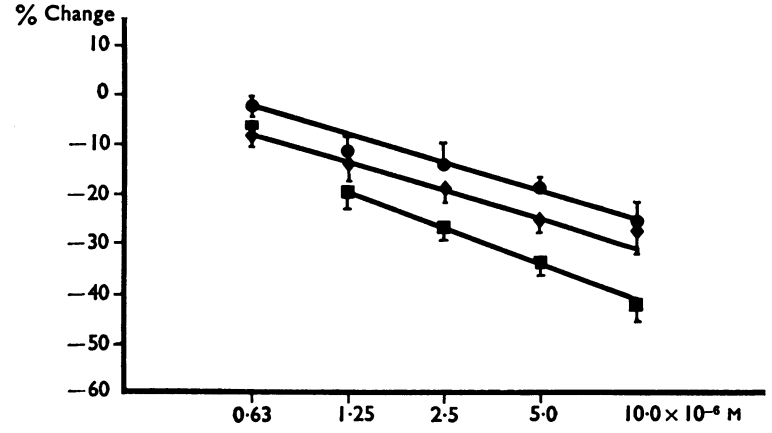

FIG. 4. Effect of L7810 on the spontaneous frequency (◆), maximum frequency at which a stimulus (×2 threshold) could be followed (■) and on conduction velocity (●). Ordinates: % decreases from control. Abscissae: concentration of L7810.

Effect of L7810 on the chronotropic action of isoprenaline in vitro

The peak effects of various concentrations of isoprenaline on the spontaneous frequency of isolated atria before and after exposure (for 40 min) to L7810 are shown in Figure 5. It was apparent that L7810 had no significant β-receptor blocking action. It was not possible to construct a comparable curve for the effects of isoprenaline on contraction because of the non-linear relation between contractions and log (concentration) of L7810 itself (Figure 3).

Effects of L7810 in vivo *in dogs*

The effects of intravenous injections of L7810 (from 0·63 to 25 mol$\times 10^{-7}$/kg) were investigated in six dogs. In three of them to which a small dose was given the effect of a larger dose given 1–1·5 h later was also studied. In every experiment

L7810 caused a fall in blood pressure and, although the response varied from dog to dog, it was dose-related as can be seen from Figure 6.

It was anticipated, from the fact that L7810 *increased* contractions *in vitro*, that this *in vivo* hypotensive effect would be due to peripheral vasodilatation rather than to a cardiodepressant action. The peripheral blood flow conductance was calculated from the aortic blood flow and the mean arterial pressure and in five out of six dogs L7810 caused a dose-related increase in blood flow conductance

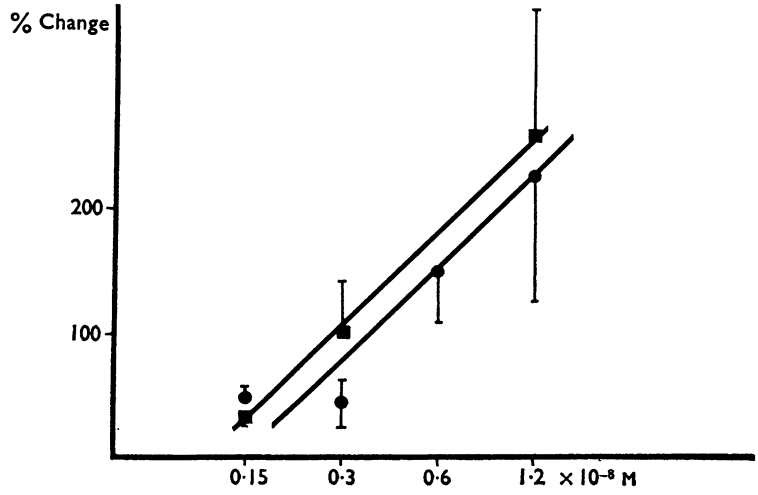

FIG. 5. Effect of L7810 on increases in frequency of spontaneously beating isolated atria provoked by isoprenaline. Isoprenaline before L7810, ●——●. Isoprenaline after L7810, ■——■. Ordinates: increase in frequency. Abscissae: concentration of isoprenaline. L7810, $2{\cdot}5 \times 10^{-6}$M caused no significant blockade.

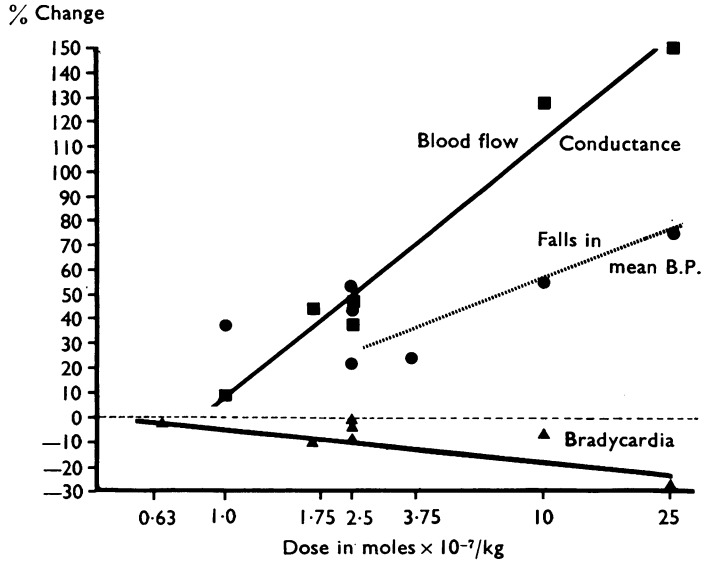

FIG. 6. Effect of L7810 on spontaneous heart rate, peripheral blood flow conductance and mean arterial pressure in vagotomized ,artificially-ventilated dogs anaesthetized with pentobarbitone. Ordinates: % changes (increase of blood-flow conductance, fall of mean B.P., reduction of heart rate). Abscissae: dose of L7810 mol$\times 10^{-7}$/kg.

(Figure 6). In the sixth dog there was no significant change in conductance in response to an injection of $2{\cdot}5\times10^{-7}$ mol/kg of L7810.

In contrast to the *in vitro* findings, L7810 did reduce the force of ventricular contractions measured by strain gauge but it was not clearly dose-related. For example, a dose of 10^{-6} mol/kg had no effect whereas a dose of $1{\cdot}75\times10^{-7}$ mol/kg depressed contractions by 41%. The maximum depression of contractions observed (of 46% in response to $2{\cdot}5\times10^{-6}$ mol/kg) was nevertheless associated with an *increase* of peripheral blood flow conductance of +150%. It would appear, therefore, that the hypotension must have been primarily due to vasodilatation though a negative inotropic action could have contributed to it to some extent.

Log-dose/response curves were constructed for increases in peripheral blood flow conductance in response to intra-arterial injections of isoprenaline and for increases in heart rate in response to intravenous injection, before and after the administration of L7810. The drug caused no blockade of these effects and, in this respect, the *in vivo* and *in vitro* results were in agreement.

L7810 caused a slight bradycardia, which was dose-related, though the slope was obviously much less steep than for blood-flow conductance (Figure 6). Here again, the *in vivo* and *in vitro* results were in agreement.

Discussion

A need exists for an antidysrhythmic drug rapidly and reliably absorbed after oral administration. One such compound, Kö 1173, the pharmacological effects of which have recently been reported (Allen, Kofi Ekue, Shanks & Zaidi, 1970; Singh & Vaughan Williams, 1972a) is at present undergoing clinical trial. The present paper is concerned with another, L7810.

The main positive findings were that L7810 protected guinea-pigs against ouabain-induced dysrhythmias and increased the lethal dose of ouabain. It was a local anaesthetic, with 1·75 times the activity of procaine on frog nerve, and it reduced the maximum rate of depolarization of intracellularly recorded action potentials in isolated rabbit atria. In the latter respect it was one of the most active compounds, on a molar basis, that we have yet studied and is comparable to alprenolol (Singh & Vaughan Williams, 1970c). L7810 also reduced spontaneous frequency, maximum driven frequency and conduction velocity in a dose-related manner; effects consistent with its class 1 action. It had no effect on the 'plateau' (50% repolarization time) of the action potential but significantly prolonged the tail of the action potential at a concentration of 10^{-6}M. L7810 had no β-receptor blocking activity either *in vitro* or *in vivo*. In sum, on the basis of the classification of antidysrhythmic actions outlined in the introduction, L7810 had high class 1 activity, moderate class 3 and no class 2 action.

Drugs with direct membrane effects have often, though not necessarily or proportionately (Vaughan Williams & Szekeres, 1961; Singh & Vaughan Williams, 1972b), a negative inotropic action on cardiac contractions. L7810, however, *increased* the magnitude of the contractions of isolated rabbit atria at all the concentrations used (up to 10^{-5}M). The only other compound we have studied in which a depressant action on maximum rate of depolarization was associated with a positive inotropic action was papaverine (Vaughan Williams & Szekeres, 1961).

In vivo, in a dog preparation designed to minimize reflex responses to hypotension, L7810 had a strong hypotensive action. Blood flow measurements indicated that this was due to peripheral vasodilatation. Although L7810 also caused some reduction of the force of ventricular contractions measured with a strain gauge, this was not the cause of the hypotension. The largest reduction of force (−46% after an injection of $2{\cdot}5\times10^{-6}$ mol/kg of L7810) was nevertheless associated with an *increase* of blood flow conductance of +150%. The reductions of force on the strain-gauge were not dose-related (e.g. 10^{-6} mol/kg had no effect) and were perhaps secondary to reduced coronary flow during the hypotension.

It seemed possible that L7810 might have α-adrenoceptor blocking activity, for which some evidence has already been obtained by Charlier *et al.* (1972) and an attempt was made to investigate this in 4 dogs by measuring the reductions of blood flow after intra-arterial injections of noradrenaline. The log dose-response curves before and after L7810, however, were not sufficiently parallel to permit any conclusions and the data were not included in the results section. There are so many ways in which a hypotensive effect may be produced that the analysis of this action may require a considerable investigation.

Another feature of the action of L7810 which will require further investigation is its positive inotropic effect *in vitro*. In anaesthetized guinea-pigs the highest dose of L7810 used ($7{\cdot}6\times10^{-6}$ mol/kg), although it greatly increased the amount of infused ouabain required to produce ventricular fibrillation, failed to reduce the *incidence* of the fibrillation as much as expected from the effect of lower doses. It was thought possible that L7810 might be causing noradrenaline release which would explain both the positive inotropic effect *in vitro* and the higher-than-expected incidence of ventricular fibrillation. Blood was taken from anaesthetized guinea-pigs and assayed for noradrenaline on the blood pressure of pithed rats. In the first series of experiments, evidence was obtained that the blood noradrenaline level was raised by L7810 but this result was not confirmed in two further series of experiments so that the data were not included in the results.

In summary, L7810 is a very active antidysrhythmic drug of the class 1 type, with some class 2 action in addition, but has no blocking action on cardiac or peripheral vascular β-adrenoceptors. Unlike most drugs with class 1 actions it is positively inotropic on cardiac contractions *in vitro*, and has a hypotensive action *in vivo*. Both the latter effects could be advantageous in situations in which cardiac dysrhythmia was associated with depressed myocardiac function and so merit further analysis.

REFERENCES

ALLEN, J. D., KOFI EKUE, J. M., SHANKS, R. G. & ZAIDI, S. A. (1970). The effect on experimental cardiac arrhythmias of a new anti-convulsant agent, Kö 1173, and its comparison with phenytoin and procainamide. *Br. J. Pharmac.*, **39**, 183–184.

BARAC, G. & BACQ, Z. M. (1973). Action preventive de la 4-carbamoyloxy-l-(4-(4-fluorophenyl)-4-oxobutyl) decahydroquinoline (L-7810) dans le shock adrénalinique, chez le chien. *J. Physiol. (Paris)* In press.

CHARLIER, R., COLOT, M., DELAUNOIS, G., POLSTER, P., BEERSAERTS, J. & BACQ, Z. M. (1972). Selective anti-adrenergic effects of a fluorodecahydroquinoline. *Abs. Vth Internat. Pharmac. Cong. San Francisco*, p. 40.

DOHADWALLA, A. N., FREEDBERG, A. S. & VAUGHAN WILLIAMS, E. M. (1969). Relevance of β-receptor blockade to ouabain-induced cardiac arrhythmias. *Br. J. Pharmac.*, **38**, 749–757.

FREEDBERG, A. S., PAPP, J. GY & VAUGHAN WILLIAMS, E. M. (1970). The effect of altered thyroid state on atrial intracellular potentials. *J. Physiol. (Lond.)*, **207**, 357–370.

HARRISON, D. C. & ALDERMAN, E. L. (1971). Relations of blood levels to clinical effectiveness of lidocaine. pp. 178–188. in *Lidocaine in the Treatment of Ventricular Arrhythmias*. Ed. Scott, D. B. & Julian, D. G. Edinburgh: E. & S. Livingstone.

PAPP, J. GY. & VAUGHAN WILLIAMS, E. M. (1969). Effect of bretylium on intracellular cardiac action potentials in relation to its anti-arrhythmic and local anaesthetic activity. *Br. J. Pharmac.*, **37**, 380–390.

SINGH, B. N. & VAUGHAN WILLIAMS, E. M. (1970a). The effect of amiodarone, a new anti-anginal drug, on cardiac muscle. *Br. J. Pharmac.*, **39**, 657–668.

SINGH, B. N. & VAUGHAN WILLIAMS, E. M. (1970b). A third class of anti-arrhythmic action. Effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle, of MJ 1999 and AH 3474. *Br. J. Pharmac.*, **39**, 675–687.

SINGH, B. N. & VAUGHAN WILLIAMS, E. M. (1970c). Local anaesthetic and anti-arrhythmic actions of alprenolol relative to its effect on intracellular potentials and other properties of isolated cardiac muscle. *Br. J. Pharmac.*, **38**, 749–757.

SINGH, B. N. & VAUGHAN WILLIAMS, E. M. (1971). Effect of altering potassium concentration on the action of lidocaine and diphenylhydantoin on rabbit atrial and ventricular muscle. *Circulation Res.*, **29**, 286–295.

SINGH, B. N. & VAUGHAN WILLIAMS, E. M. (1972a). Investigations of the mode of action of a new antidysrhythmic drug, Kö 1173. *Br. J. Pharmac.*, **44**, 1–9.

SINGH, B. N. & VAUGHAN WILLIAMS, E. M. (1972b). A fourth class of antidysrhythmic action. Effect of verapamil on ouabain toxicity, on atrial and ventricular intracellular potentials, and on other features of cardiac function. *Cardiovasc. Res.*, **6**, 109–119.

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 in isolated rabbit atria interpreted from intracellular records. *Br. J. Pharmac. Chemother.*, **13**, 276–287.

VAUGHAN WILLIAMS, E. M. (1959). The effect of changes in extracellular potassium concentration on the intracellular potentials of isolated rabbit atria. *J. Physiol. (Lond)*., **146**, 411–427.

VAUGHAN WILLIAMS, E. M. (1970). Classification of anti-arrhythmic drugs. pp. 469–472. In *Symposium on Cardiac Arrhythmias*. Ed. Sandøe, E., Flensted-Jensen, E. & Olesen, K. H. AB Astra. Södertälje, Sweden.

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

VAUGHAN WILLIAMS, E. M. & SZEKERES, L. (1961). A comparison of tests for antifibrillatory action. *Br. J. Pharmac. Chemother.*, **17**, 424–432.

(*Received December* 14, 1972)