On the "quinidine-like action" of some antiarrhythmic agents

The mechanism that causes the clinically well-established antifibrillatory effect of β-adrenoceptor blocking drugs is still subject to debate. The blockade of β-adrenoceptors readily explains their usefulness in the treatment of arrhythmia evoked by an increased tone of the sympathetic nervous system, but other disturbances of cardiac rhythm, e.g. caused by digitalis, are also influenced by drugs like propranolol. Several authors therefore believe that propranolol owes its antiarrhythmic properties at least in part to its so-called "quinidine-like" or cardiodepressive action.

So far, the expression "quinidine-like" has been arbitrarily employed for various kinds of drugs with both antiarrhythmic and cardiodepressive action. However, it has been demonstrated recently that the effects of quinidine and propranolol on the action potential (Tritthart, Fleckenstein & others, 1969) and on calcium fluxes in isolated heart muscle (Silva Graça & van Zwieten, 1972) are quite different for the two drugs, so that the expression "quinidine-like" can hardly be applied to propranolol. It is generally assumed that the antiarrhythmic effect of quinidine is caused by a significant increase of the heart's refractory period. Concomitantly, it might be expected that antiarrhythmic agents with so-called "quinidine-like" action would also prolong the refractory period in a similar manner. To test this hypothesis, we examined the influence of quinidine, propranolol((±)-, (+)- and (−)-isomers in separate experiments), DL-INPEA (*N*-isopropyl-*p*-nitrophenylethanolamine) and lidocaine on the relative refractory period (RRP) in electrically driven, isolated left auricles of guinea-pigs. In the concentrations used, quinidine, (±)-propranolol and lidocaine depressed contractile force by approximately 35% of its initial value, while DL-INPEA was practically devoid of negative inotropic properties (*cf.* Silva Graça & van Zwieten, 1972).

The left auricles were dissected as described by Hoditz & Lüllmann (1964) and placed in a circulation system that contained Muralt-Tyrode solution at 30°. The solution was perfused at a rate of 225 ml min^{-1} and continuously gassed with 5% CO_2 in O_2. Supramaximal stimuli (1·5 × threshold; duration of each pulse 1 ms; frequency of stimulation 1 Hz) were obtained from a Grass S4H stimulator and applied via electrodes placed on the surface, 2 mm apart from each other. Extra stimuli (monopolar, cathodal square waves, duration 1 ms each) of three times the threshold value were obtained from a second Grass S4H device. They were triggered via a Hewlett Packard 132 A dual beam oscilloscope on the time base, starting on "basic stimulus out".

The interval between normal and extra stimuli was determined by means of a Hewlett Packard 5325 Universal Counter. Janse (1971) has shown that at least 20 "basic" pulses should occur between two extra stimuli to prevent changes in RRP owing to a rise in frequency. This condition being fulfilled, RRP was determined with intervals of 5 min for 45–60 min. After equilibration for 30 min following dissection, RRP was measured under control circumstances and shown to be constant for at least 1 h (Fig. 1). The mean RRP for control auricles amounted to 125·4 ± 2·6 ms (mean ± s.e., n = 46).

To test the influence of drugs, superfusion was continued with Tyrode solution that contained the compound to be studied. Drugs used: quinidine sulphate (Merck AG, Darmstadt); (±)-, (+)- and (−)-propranolol hydrochloride (Rhein Pharma GmbH, Heidelberg); DL(±)-INPEA hydrochloride (Selvi and Cy, Milano); lidocaine hydrochloride (Astra AB, Södertälje, Sweden).

Quinidine (5×10^{-5}M) caused a continuous increase in RRP that had not reached equilibrium after 1 h of incubation (Fig. 1). RRP reached about 2·25 times the initial level after 45 min. (±)-Propranolol (10^{-5}M) was much less active than quinidine, although in the concentrations used the negative inotropic actions of both drugs were

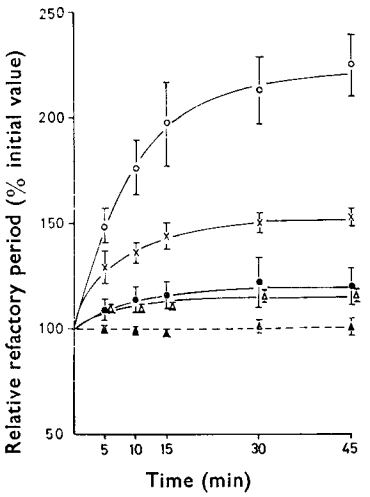

FIG. 1. Influence of quinidine, (±)-propranolol, DL-INPEA and lidocaine on the relative refractory period (RRP) of electrically driven guinea-pig left auricles. Frequency 1 Hz. The control value of the RRP was taken equal as 100% and all subsequent values expressed as percentage of that at t = 0, the time when drug treatment was started. Each point on the curves represents the mean (± s.e.) for at least 4 different auricles. ▲——▲ controls, △——△ lidocaine, ●——● (±)-propranolol, ×——× DL-INPEA, ○——○ quinidine.

similar. After 45 min, the difference in RRP was significant at $P < 0{\cdot}0025$ (Student's *t*-test). Approximately the same modest increase was brought about by either (+)-propranolol, (−)-propranolol or lidocaine (10^{-5}M). DL-INPEA (5×10^{-5}M) was more active than (±)-propranolol (10^{-5}M) ($P < 0{\cdot}01$ after 45 min), although INPEA in this relatively high concentration did not influence contractile force.

Our findings clearly indicate that even at relatively high concentrations propranolol and also lidocaine hardly influence RRP, although both drugs are generally said to possess "quinidine-like" properties. A modest increase in RRP owing to exposure to INPEA has also been described by Wagner & Schümann (1970). The influence of quinidine on RRP is well known. INPEA, however, is said to possess no "quinidine-like" properties.

It seems obvious that there is no relation whatsoever between cardiodepressive action and the influence on RRP for the drugs studied. Furthermore, the present findings, like those described previously by Tritthart & others (1969) and by Silva Graça & van Zwieten (1972), suggest that the expression "quinidine-like" used to characterize certain properties of propranolol and lidocaine cannot be applied generally and requires further specification. A relation between the "quinidine-like" action of certain β-adrenoceptor blocking agents and their antifibrillatory properties seems unlikely, if it is assumed that an increase in the RRP is the cause of quinidine's antiarrhythmic action.

Our findings would suggest that the β-adrenoceptor blocking action of propranolol and also changes in the rate of conduction explain the drug's protective effect against cardiac arrhythmia, rather than the so called "quinidine-like" action.

For the reasons given above we propose that the expression "quinidine-like" should not be used to characterize certain aspects of β-adrenoceptor blocking agents.

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REFERENCES

HODITZ, H. & LÜLLMANN, H. (1964). *Pflügers Arch. ges. Physiol.*, **280**, 22–29.
JANSE, M. J. (1971). M.D. Thesis, Amsterdam.
SILVA GRAÇA, A. & VAN ZWIETEN, P. A. (1972). *J. Pharm. Pharmac.*, **24**, 367–373.
TRITTHART, H., FLECKENSTEIN, A., FLECKENSTEIN, B., HERBST, A. & KRAUSE, H. (1969). *Arch Pharmak.*, **264**, 317–318.
WAGNER, J. & SCHÜMANN, H. J. (1970). *Experientia*, **26**, 163–164.

Selective inhibition of angiotensin-induced contractions of smooth muscle by indomethacin

Angiotensin has been shown to release prostaglandin-like substances from the dog kidney (McGiff, Crowshaw, & others, 1970; Aiken & Vane, 1971).

Indomethacin is known to be a potent inhibitor of prostaglandin synthesis (Vane, 1971) and will abolish prostaglandin release from the dog spleen (Ferreira, Moncada & Vane, 1971). Indomethacin has also been shown to cause a direct relaxation of rabbit isolated ileum, an action which appears related to its ability to inhibit prostaglandin synthesis (Ferreira, Herman & Vane, 1972).

In view of these observations it was considered pertinent to examine the effect of indomethacin on the ability of angiotensin to contract smooth muscle. Indomethacin will antagonize the contractions of a number of smooth muscle preparations to a variety of other agonists (Northover, 1967), an action that appears to be related to an inhibition of the entry of calcium ions into the muscle cells (Northover, 1971).

We have examined indomethacin for its effect on the increases in tension, produced by angiotensin, of isolated preparations of guinea-pig ileum and aorta, rat ileum, colon and fundus strip and rabbit aortic strip. Indomethacin (28–112 μM), kept in contact with the preparations for a minimum period of 20 min caused a selective blockade of angiotensin contractions in all tissues with the exception of the rat colon, where it was without effect.

In the guinea-pig ileum, indomethacin (56 μM) caused a $67{\cdot}1 \pm 4{\cdot}0\%$ ($n = 7$) reduction of a submaximal contraction to angiotensin. The corresponding reductions for the other agonists were $16{\cdot}8 \pm 3{\cdot}5\%$ ($n = 6$) for acetylcholine; $19{\cdot}3 \pm 4{\cdot}7\%$ ($n = 7$) for histamine and $31{\cdot}7 \pm 2{\cdot}3\%$ ($n = 6$) for bradykinin. Similar results were obtained with the rat ileum and the rat fundus strip.

On the guinea-pig ileum indomethacin (56 μM) depressed the responses to all effective concentrations of angiotensin with a $61{\cdot}8 \pm 2{\cdot}0\%$ ($n = 6$) depression of the maximum response (Fig. 1a) whereas the only effect seen on the dose response curve for acetylcholine was a small ($20{\cdot}3 \pm 4{\cdot}7\%$; $n = 5$) depression of the maximum response (Fig. 1b).

The same concentration of indomethacin caused a similar depression of the angiotensin dose-response curve on the rabbit aortic strip with a $38{\cdot}5 \pm 3{\cdot}3\%$ ($n = 6$) depression of the maximum response but was without effect on the dose response curve for noradrenaline on the preparation.

These reductions of angiotensin responses did not appear to be due to tachyphylaxis since no decreases in sensitivity to angiotensin were observed in adjacent pieces of tissue dosed concurrently.