(0·3 mg/kg) or a placebo on their exercise tolerance. The same procedure was repeated after oral administration of propranolol (50 mg 8 hourly), practolol (100 mg 8 hourly) or a placebo. The treadmill is a reproducible test of exercise tolerance providing a situation similar to the normal daily life of the patient.

There was a significant increase in exercise tolerance ($P<0·05$) in the oral and intravenous study with both propranolol and practolol. No distinction could be made on the basis of exercise tolerance between either the drugs or their mode of administration.

A beneficial effect on exercise tolerance is observed in angina pectoris from β-adrenoceptor blockade. In the doses used the effect of propranolol is not related to its local anaesthetic activity, since a similar response was noticed with practolol. Practolol does not affect the bronchi and may be given to patients with obstructive airways disease and as it has a relatively slight effect on contractility may be better tolerated in the presence of cardiac failure.

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The effect of propranolol on the human and canine transmembrane action potential

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Many studies have been reported on the effect of β-adrenoceptor antagonists on the intracellular cardiac potential of the isolated mammalian heart. There is some divergence in the results; Dohadwalla, Freedberg & Vaughan Williams (1969) found no change in the rate of rise of the action potential after (±)-propranolol, whereas Shevde & Spilker (1970) found an increase in the rate of rise in a similar preparation, but only at low concentrations ($1·0\times10^{-6}$M).

Human tissue might provide a more applicable model of the clinical situation. We have used small pieces of human ventricular cardiac tissue excised at corrective cardiac surgery to study the effect of propranolol on transmembrane action potential. Cardiac tissue taken from identical sites in healthy mongrel dogs was also studied.

(±)-Propranolol (3×10^{-5}M) significantly decreased the rate of rise of the action potential in human ventricular tissue with no significant effect on other electrophysical events. There was a similar effect in dog ventricle at the same order of concentration of propranolol, in agreement with the work of Davis & Tempte (1969). There was no increase in rate of rise of the action potential at lower concentrations in either species.

The conclusion of Dohadwalla *et al.* (1969) that the measurement of the rate of rise of the action potential is a sensitive test of the activity of drugs on cardiac muscle is corroborated by our results, which extend the observations to human tissue.

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Comparative effectiveness of lignocaine, quinidine, propranolol and procainamide as antifibrillatory agents

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The effects of quinidine, procainamide, lignocaine and propranolol on the ventricular fibrillation threshold (VFT), irritability and contractility of the isolated perfused heart from the rabbit (Langendorff preparation) were compared. The VFT was measured by the method described previously (MacConaill & Murnaghan, 1967). It consisted of using a single square-wave 10 ms pulse applied during the vulnerable period of late systole, and measuring the minimal current required to produce fibrillation or tachycardia. The diastolic extrasystolic threshold was determined to indicate the degree of irritability and the contractility was measured with a strain-gauge attached to the apex of the heart. The perfusion apparatus was constructed so that any one of three solutions of different composition could be selected by the turn of a tap. Several concentrations of each drug could be tested and control values could be measured after, as well as before, those due to the drug. To indicate the magnitude of the change produced on the VFT by the drug, the VFT change ratio was calculated—VFT during the drug/VFT of the control.

Quinidine (2·5–15 μM) in seventeen trials on nine hearts raised the VFT in seven trials, lowered it in five and lowered it before raising it above the control value in five. The mean±S.E.M. VFT change ratio in the twelve trials where it was raised was 4·68±1·2; in the ten trials where the VFT change ratio was lowered the value was 0·49±0·06. These results with quinidine were reported earlier (Murnaghan, 1969). The respective values with procainamide (30–100 μM) were 1·6±0·17 and 0·61±0·11. With this drug the threshold was lowered in three out of eight trials on four hearts. Propranolol (1–10 μM) gave values of 1·84±0·24 and 0·42±0·04; the threshold was lowered in three out of nine trials on five hearts. With lignocaine (6·6–26·4 μM) the VFT change ratios were 3·06±1·15 and 0·47; the threshold was lowered in only one out of thirteen trials on six hearts. As indicated by the incidence of lowering the VFT, quinidine was the drug most liable to predispose to fibrillation, lignocaine was the least and propranolol and procainamide were intermediate in position. All four drugs reduced the irritability of the heart; quinidine was the most potent, lignocaine and propranolol were moderately so, while procainamide was relatively weak. All drugs except lignocaine depressed cardiac contractility, propranolol being the most potent.

The results are consistent with those obtained clinically which show that lignocaine is an effective anti-arrhythmic agent and posseses the advantage over quinidine that it does not predispose, or rarely predisposes, to ventricular arrhythmia or even fibrillation.

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