stimulation, but did not antagonize noradrenaline. The guinea-pig oesophagus responded to vagal stimulation with a twitch followed by a contracture; MJ-1999 (200 μg/ml.) antagonized the contracture but not the twitch, whereas propranolol (10 μg/ml.) antagonized both. The effects of MJ-1999 on the guinea-pig vas deferens and oesophagus resemble those of hexamethonium (Birmingham & Wilson, 1963; Bartlet, 1968) and confirm its lack of local anaesthetic action.

MJ-1999 was kindly supplied by Dr. G. R. McKinney, Mead Johnson Research Centre, U.S.A., and propranolol by I.C.I. Ltd.

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Comparison of propranolol and I.C.I. 50,172 on isoprenaline-induced increase in skin temperature in man

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Propranolol and I.C.I. 50,172 both block adrenoceptive β-receptors in the heart, whereas only propranolol blocks those in the smooth muscle of peripheral blood vessels (Dunlop & Shanks, 1968). These compounds have been compared, therefore, for their effects on isoprenaline-induced increase of skin temperature in man.

Six normal subjects aged 21–48 years were given propranolol 80 mg, I.C.I. 50,172 200 mg and placebo by oral administration at weekly intervals. The drugs and the placebo were given in random order based on a latin square design, under double blind conditions. Two hours later the skin temperature responses to isoprenaline inhalation from " Medihaler IsoForte " aerosols were recorded by means of copper-constantan thermocouples (voltage output 40 μV/° C). These were attached to the cheek, over the sterno-clavicular joint, to the volar surface of the forearm and to the dorsum of the hand. They were connected to Grass polygraph Model 7P1-preamplifiers calibrated within a range of 24°–40° C. The number of " puffs " of isoprenaline necessary to obtain a consistent temperature increase over cheek or sternum or both had previously been determined for each subject. Temperatures were recorded before and for 10 min after inhalation. Heart rate was monitored simultaneously by electrocardiographic recording on the same Grass polygraph.

The results demonstrated a significant rise of mean skin temperature over the cheek (0·5° C, S.E.M. 0·14, $t=3{\cdot}57$, $P<0{\cdot}02$) when isoprenaline was inhaled following placebo administration, but changes in temperature in the other areas were not significant. Propranolol abolished the increase in mean cheek temperature after isoprenaline inhalation (0·18° C, S.E.M. 0·09, $t=2{\cdot}0$) but I.C.I. 50,172 did not (0·65° C, S.E.M. 0·15, $t=4.33$, $P<0{\cdot}01$). The differences in response between placebo and propranolol, and between I.C.I. 50,172 and propranolol were significant ($P<0{\cdot}01$ and $<0{\cdot}05$ respectively).

There was a significant increase in mean heart rate after isoprenaline inhalation following ingestion of placebo (17·7 beats/min, S.E.M. 3·9, $t=4·53$, $P<0·01$) but not after propranolol. There was a small increase in heart rate following I.C.I. 50,172 (6·0 beats/min, S.E.M. 1·2, $t=5·0$, $P<0·01$) but this was significantly less than that following placebo ($P<0·05$).

Oral administration of I.C.I. 50,172 (200 mg) therefore significantly reduces the tachycardia but not the increase in skin temperature produced by isoprenaline inhalation. Propranolol (80 mg) abolishes both responses.

I.C.I. Laboratories kindly supplied the tablets of propranolol, I.C.I. 50,172 and placebo, and Riker Laboratories the " Medihaler " dispensers used in this study. J.H. is supported by a research grant from the Board of Governors of St. Bartholomew's Hospital.

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The effect of some catecholamine β-receptor blocking compounds on the toxicity to the heart of ouabain

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Data concerning the relevance of blockade of catecholamine β-receptors to the anti-digitalis effect of β-receptor blocking agents are rather contradictory. Several authors claim that the protective action of these compounds against digitalis-induced arrhythmias results only from their " non-specific " (local anaesthetic, quinidine-like) activity (Lucchesi, 1965; Somani & Lum, 1965), while others suggest that an anti-adrenergic mechanism might also be involved (Dohadwalla, Freedberg & Vaughan Williams, unpublished; Barrett & Cullum, 1968; Raper & Wale, 1968). It was therefore of interest to study the anti-digitalis and " non-specific " anti-arrhythmic effects of some recently introduced β-receptor blocking agents such as oxprenolol, I.C.I. 50,172 and (−)-propranolol.

Oxprenolol has recently been reported to be a potent β-receptor blocking agent with some local anaesthetic activity (Brunner, Hedwall & Meier, 1968). I.C.I. 50,172 was also found to possess β-receptor blocking potency with marked cardio-selectivity, but without local anaesthetic properties (Barrett, Crowther, Dunlop, Shanks & Smith, 1967; Dunlop & Shanks, 1968). The β-receptor blocking activity of oxprenolol is in the range of that of (±)-propranolol, whereas I.C.I. 50,172 proved to be 2–4 times (*in vivo*) or about 60–70 times (*in vitro*) less potent than (±)-propranolol (Barrett, unpublished; Dunlop & Shanks, 1968; Jackson, 1968).

The anti-digitalis effect was studied in urethane-anaesthetized guinea-pigs, as described by Vaughan Williams & Sekiya (1963). The local anaesthetic potency was determined in desheathed sciatic nerves of the frog, and the direct cardiac actions were studied in isolated rabbit atria. Oxprenolol (0·75–6 mg/kg intravenously) greatly increased the dose of ouabain required to produce extrasystoles and completely prevented the appearance of ventricular fibrillation. I.C.I. 50,172 protected against ouabain-induced fibrillation; the dose required, however, was about 2–3