A new type of cardioselective adrenoceptive blocking drug

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The selective adrenoceptive blocking drug practolol is a partial agonist, but unlike propranolol, does not have membrane stabilizing properties (Dunlop & Shanks, 1968). The haemodynamic effects of practolol differ markedly from propranolol but the precise reason for the differences is not clear (Gibson, 1971).

The compound 4-(2-hydroxy-3-isopropylaminopropoxy)phenyl acetamide (ICI 66082) is cardioselective and possesses neither partial agonist nor membrane stabilizing properties. ICI 66082 is as active as propranolol in antagonizing the positive chronotropic response to isoprenaline in cats and dogs and the chronotropic response to stimulation of the cardioaccelerator nerve in the cat. It is less effective than propranolol in antagonizing the isoprenaline vasodepressor response and very much less effective in antagonizing isoprenaline-induced relaxation of bronchial smooth muscle (guinea-pigs) and lipolysis in adipose tissue (rats) (Table 1). ICI 66082 (0·25 mg/kg, I.V.) is specific in as much as it antagonizes the positive inotropic response in dogs to isoprenaline (0·05 μg/kg) but not the inotropic responses to calcium (1·5 ml 10%), acetyl strophanthidin (30 μg/kg) or glucagon (40 μg/kg). Furthermore it does not have significant antihistaminic or anti-cholinergic activity (Table 1).

TABLE 1

	Agonist	Species (tissue)	Response	N**	Propranolol	Practolol	ICI 66082
						POTENCY RATIO	
In vivo	Isoprenaline	Cat	Heart rate	6	1	3	1·2
	Isoprenaline	Dog	Vasodilatation	3	1	29	14
	Isoprenaline	Rat	Lipolysis (epididymal fat)	4	1	32	40
						pA_2 VALUES	
*In vitro**	Isoprenaline	Atrium	Chronotropic	5	8·32 ± 0·09	6·49 ± 0·01	7·27 ± 0·11
	Isoprenaline	Trachea	Relaxation	4	8·46 ± 0·4	4·26 ± 0·04	4·61 ± 0·14
	Acetylcholine	Ileum	Contraction	4	4·58 ± 0·01	3·7 ± 0·7	3·32 ± 0·06
	Histamine	Ileum	Contraction	3	4·98 ± 0·04	3·5 ± 0·08	2·5 ± 0·21

* Guinea-pig bronchial smooth muscle.
** N = Number of experiments.
A comparison of the adrenoceptive and non-adrenoceptive antagonist properties of propranolol, practolol and ICI 66082.

In rats depleted of catecholamines, ICI 66082 (0·02–2 mg/kg, I.V.), in contrast to practolol, does not cause an increase in heart rate, or increase cardiac contractile force and reduce AV conduction time in depleted dogs in doses between 0·25 and 10·24 mg/kg I.V. It resembles practolol in that it depresses neither contractile force in the isolated atrium nor the action potential of the stimulated isolated frog sciatic nerve in concentrations up to 10^{-2}M.

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The action of ICI-66082 on the heart

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The effects of ICI-66082 on the inotropic and chronotropic responses to isoprenaline in the dog heart and on the isometric twitch response of the rabbit papillary muscle have been studied.

Dogs were anaesthetized with chloralose, artificially respired and the chest opened in the mid-line. The inotropic state of the heart was measured as the maximum rate

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of rise of pressure in the left ventricle (dP/dt max) in a preparation in which heart rate and mean aortic pressure were held constant (Furnival, Linden & Snow, 1970). Cardiac reflexes were prevented from occurring by section of vagal and sympathetic nerves to the heart.

ICI-66082 (0·1–2·0 mg/kg) antagonized the increase in heart rate and dP/dt max induced by isoprenaline, an effect which could be overcome by increasing the infusion rate of isoprenaline, e.g. in five dogs an increase in heart rate of 40–50 beats/min was produced by an infusion rate of 1–2 μg/min of isoprenaline in the absence of 66082 and by 10–15 μg/min in the presence of 66082 (dose 0·1 mg/kg). In three dogs ICI-66082 (0·25–4 mg/kg) reduced the control measurement of dP/dt max by a mean value of 661 mmHg/s; this effect is due to β-receptor blockade of circulating catecholamines by ICI 66082 in this preparation, as described previously for propranolol (Harry, Linden & Snow, 1972). In three dogs depleted of catecholamines by reserpine ICI-66082 (up to 3 mg/kg) produced no change in dP/dt max.

In five isolated papillary muscle preparations, set up as described by Harry, Linden & Snow (1971), ICI-66082 (1–1,000 μg/ml) produced no depression of the twitch response to electrical stimulation.

It is concluded that ICI-66082 is a β-adrenoceptor blocking drug, with no intrinsic stimulating action and without negative inotropic activity on the heart in high doses.

This work was supported by grants from the British Heart Foundation, the Medical Research Council and the Wellcome Trust.

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Enhancement by propranolol of gastric acid secretion in response to pentagastrin in conscious dogs.

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In conscious dogs, both β-adrenoceptor agonists (Curwain & Holton, 1972; Curwain, Holton & Spencer, 1972) and burimamide (Black, Duncan, Durant, Ganellin & Parsons, 1972; Curwain, Holton & Spencer, 1973) decrease pentagastrin-induced gastric acid secretion. It has also been shown that β-adrenoceptor agonists decrease, and that propranolol increases (Assem & Feigenbaum, 1972), histamine formation in human leucocytes. If histamine formation is involved in the effect of pentagastrin on the gastric mucosa, as has been suggested by Kahlson & Rosengren (1971), the action of β-adrenoceptor agonists on gastric secretion might be secondary to their action on histamine formation. If this were so, propranolol would be expected to increase histamine formation and hence gastric secretion in response to pentagastrin but not in response to histamine. We have therefore investigated the effects of propranolol on gastric acid secretion in conscious Heidehain pouch dogs.

Secretion was induced by a constant infusion of pentagastrin (1–2 [μg/kg]/h) histamine acid phosphate (1–2 [μg/kg]/min) or bethanechol hydrochloride (0·5–1·0 [μg/kg]/min). Increasing doses (0·1, 0·3, 0·6 and 1·0 mg/kg) of (±) propranolol hydrochloride were injected intravenously at 30–60 min intervals. In some experiments gastric mucosal blood flow was measured by radioactive aniline clearance (Curwain & Holton, 1971, 1973).

In each of four experiments in four dogs, propranolol (0·4–2·0 mg/kg total dose) caused a prolonged increase of 53% ± 22·7% (S.E. of mean) in pentagastrin-induced gastric secretion (mean maximum increase of 81% over control; range 33–120%). Propranolol also increased gastric mucosal blood flow in parallel with the increased secretion.