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.

REFERENCES

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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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