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The acute exercise test for the preliminary evaluation of β-receptor blocking drugs in angina pectoris

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It is well established that propranolol is effective in the treatment of angina pectoris. In this study three other β-receptor blocking drugs and propranolol are compared with saline in an acute exercise test to screen them for anti-anginal effect.

Six volunteer patients with angina pectoris exercised on a cycle-ergometer at constant work load before (control) and after the intravenous administration of drug or saline until pain occurred. This was followed by a second post-injection exercise 5 min after pain from the previous one subsided. Exercise tests were performed each week on every patient under standard laboratory conditions. In a run-in period the patient was made familiar with the procedure and the dose was adjusted so that neither a certain maximum for each substance was exceeded nor the pulse rate fell under about 60 beats/min nor other side-effects occurred. Previous studies with oral propranolol (Gillam & Prichard, 1966; unpublished) showed that for maximum relief of anginal pain maximum tolerated doses should be given.

The following substances were used (in brackets average and maximum dose in mg): propranolol (38; 40), practolol (I.C.I. 50172) (153; 160), oxprenolol (60; 60), M.J. 1999 (50; 60) and physiological saline. All injections were made up to 40 ml. and injected over 5 min. All patients received each treatment in random order; the study was double-blind.

Table 1 shows that the duration of the first post-injection exercise was significantly ($P<0.05$) longer after all drugs than after saline. The four β-adrenergic blocking drugs differ in many respects: propranolol and oxprenolol have a local anaesthetic effect. Practolol and oxprenolol show a slight sympathomimetic effect. Only practolol has a differential blocking action, acting predominantly on the β-receptors of the heart. Common property of all is their inhibition of the β-receptors of the

TABLE 1

Substance	Duration of post-injection exercise periods (in % of pre-injection value)			
	1st exercise	P*	2nd exercise	P*
Saline	97 (S.E. 4)		110 (S.E. 8)	
Propranolol	139 (S.E. 12)	<0·05	161 (S.E. 19)	<0·05
Practolol	127 (S.E. 8)	<0·05	148 (S.E. 11)	<0·05
M.J. 1999	137 (S.E. 13)	<0·05	148 (S.E. 19)	>0·1
Oxprenolol	129 (S.E. 9)	<0·05	137 (S.E. 14)	>0·1

* With respect to saline (calculated from the differences in logarithm of duration of exercise before and after injection).

heart. This seems to supply additional evidence that beta receptor inhibition is responsible for the benefit of these drugs in angina and not some other non-specific property.

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Cardiovascular actions of glucagon and secretin

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It has been suggested (Robison, Butcher & Sutherland, 1967) that adenyl cyclase is the β-receptor for catecholamines and that the cardiac effects of catecholamines result from myocardial cyclic 3',5'-AMP accumulation. Glucagon also causes cyclic AMP accumulation in certain tissues and produces cardiac chronotropic and inotropic responses. It seemed of interest to determine the peripheral vascular effects of glucagon and to compare them with isoprenaline. The actions of secretin, which closely resembles glucagon in structure, were also examined.

Cats were anaesthetized with pentobarbitone sodium. Arterial blood flows were measured with non-cannulating electromagnetic flowmeters and drugs were given by close intra-arterial injection, or infusion.

Rapid injections of glucagon (1–10 μg) produced dilatation of mesenteric resistance vessels, constriction of the hepatic arterial vascular bed and no effect on the renal and femoral vasculature. Rapid injections of secretin (1–10 μg) produced dilatation of the mesenteric and femoral vasculature, constriction of the hepatic arterial bed and no effect on the renal vessels. Glucagon and secretin appeared to act directly on the resistance vessels, since the responses developed within a few seconds and were unaffected by appropriate denervation. Their vasodilator actions were unaffected by pre-treatment with propranolol.

Isoprenaline dilated the mesenteric, hepatic and femoral vasculature and was without effect on renal vessels.

Since the pattern of vascular responses induced by glucagon and secretin differed from that of isoprenaline, the vasomotor changes induced by these hormones were probably not mediated by β-receptors.

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The excretion of hydroxyphenyltrimethylammonium in bile

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The biliary excretion of quaternary amines varies greatly from compound to compound. For example, benzomethamine and procainamide ethobromide are