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A comparison of the effects of bretylium, lignocaine and propranolol on experimental cardiac arrhythmias

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Propranolol and lignocaine are widely used in the treatment of cardiac arrhythmias in man. On the basis of observations in animals it has been suggested that there are two ways in which propranolol may abolish experimental cardiac arrhythmias. Its effect on arrhythmias induced by a catecholamine has been attributed to blockade of beta receptors for catecholamines, while its effect on ouabain-induced arrhythmias has been attributed to a local anaesthetic effect similar to that of quinidine and procaine (Barrett & Cullum, 1968). Recently it has been suggested that bretylium has anti-arrhythmic properties (Bacaner, 1968). We have compared the effects of these three drugs on two types of experimental arrhythmias.

In dogs anaesthetized with morphine and pentobarbitone and respired with room air and 1% halothane increasing doses of adrenaline (0·2–6·4 μg/kg) were given by intravenous injection until a period of ventricular ectopic beats, lasting at least 10 sec, was produced. The adrenaline challenge was repeated after propranolol (0·05 μg/kg) and increasing doses of lignocaine (0·8 to 6·4 μg/kg), using four and five dogs respectively for each drug. Lignocaine was much less effective than propranolol in abolishing these arrhythmias. In seven dogs a fixed dose of bretylium tosylate was given and the adrenaline challenge repeated at hourly intervals. In two dogs the intravenous injection of bretylium (10 mg/kg) had no effect on the arrhythmia. In four out of five dogs bretylium (20 mg/kg) protected from the arrhythmia when tested two or more hours later. The adrenaline arrhythmias were potentiated during the first hour after bretylium administration.

Ventricular or nodal tachycardia was produced in dogs anaesthetized with morphine and pentobarbitone, by the intravenous injection of ouabain. After establishment of the arrhythmia the test compound was infused intravenously. In three dogs the mean dose of propranolol to abolish the arrhythmia was 1·9 mg/kg and in three given lignocaine, 3·0 mg/kg when infused at 0·2 mg/kg per min and 2·2 mg/kg when infused at 1·0 mg/kg per min. The intravenous infusion of bretylium at a rate of 0·2 mg/kg per min resulted in the restoration of sinus rhythm after 15·9 mg/kg and in three others intravenous infusion of bretylium (20 mg/kg) over twenty minutes resulted in the return of sinus rhythm, at 12, 41 and 52 min respectively after starting the infusion.

These studies indicate that lignocaine and bretylium can abolish experimental cardiac arrhythmias. The mode of action of bretylium on these arrhythmias is obscure as it does not appear to possess quinidine-like or local anaesthetic activities (Papp & Vaughan Williams, 1969).

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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).