Preliminary Communications

Stimulation of Adrenergic β-Receptors by Orciprenaline

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Propranolol (Inderal), a potent adrenergic β-receptor antagonist (Black *et al.*, 1965), is effective in the treatment of angina pectoris (Gillam and Prichard, 1965 ; Grant *et al.*, 1966 ; Hamer *et al.*, 1966) and various cardiac arrhythmias (Besterman and Friedlander, 1965 ; Rowlands *et al.*, 1965). On rare occasions propranolol may precipitate or aggravate cardiac failure or produce a severe bradycardia (Bath, 1966 ; Stephen, 1966), and in asthmatic patients may produce a marked reduction in ventilatory function (McNeill, 1964). On oral administration propranolol reaches its maximum effect, as judged by reduction of exercise tachycardia, after one to one and a half hours, and has a reduced effect for a further three hours (Shanks, unpublished). After intravenous injection the activity of propranolol in blocking an isoprenaline tachycardia declines by 50% in 40 to 50 minutes in conscious dogs (Black *et al.*, 1965), but in man may last for up to four hours (Mahon, 1965). If untoward side-effects occur in man after the administration of propranolol its duration of action may be too long to allow these effects to wear off spontaneously.

As propranolol is a competitive antagonist its blockade of β-receptors can be overcome by a β-receptor agonist (Black *et al.*, 1965). In man the compound used for this purpose must be relatively free from other actions, and must be available for intravenous administration. Isoprenaline is the ideal compound, as it is the most potent and specific activator of β-receptors (Ahlquist, 1948), and has been widely used in experimental studies in man. However, it is not generally available for intravenous administration in this country, and, so far as we can ascertain, can only be supplied to special order from pharmaceutical firms. Adrenaline and noradrenaline, though stimulating β-receptors, produce marked stimulation of α-receptors with a resultant increase in arterial pressure (Ahlquist, 1948) ; this pressor response is potentiated after propranolol (Glover and Hutchison, 1965 ; Harris *et al.*, 1966). Though adrenaline and noradrenaline are available for parenteral administration in man it is probably best not to use them to overcome the effects of β-receptor blockade, as the increase in arterial pressure may cause further embarrassment to the heart owing to pressure loading and reflex bradycardia.

Recently a drug, orciprenaline (Alupent), has been described which stimulates β-receptors but not α-receptors (Engelhardt *et al.*, 1961). As orciprenaline is available for intravenous administration in this country, we have compared its actions with those of isoprenaline in laboratory animals and in man. The structures of isoprenaline, orciprenaline, and propranolol are given in Fig. 1.

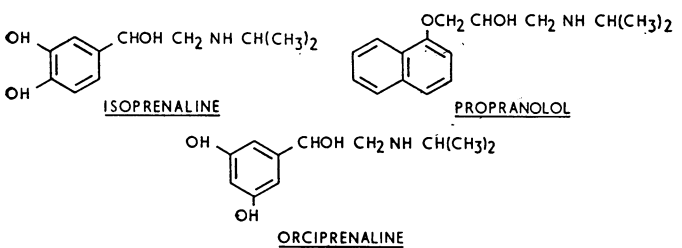

FIG. 1.—Structure of isoprenaline, orciprenaline, and propranolol

METHODS

Cats were anaesthetized by the intravenous injection of chloralose 80 mg./kg. ; spontaneous respiration was assisted by the insertion of a tracheal cannula. Heart rate was recorded by means of a cardiotachometer, and drugs were injected through a polyethylene catheter in a femoral vein.

Dogs were anaesthetized by the intravenous injection of pentobarbitone 30 mg./kg. and artificially respired with room air. Cardiac contractile force was measured by suturing a strain gauge arch to the surface of the right ventricle. Arterial pressure was recorded from a cannula in a femoral artery with an inductive-type differential pressure transducer (New Electronic Products), and heart rate was measured with a cardiotachometer. All responses were recorded on a multichannel tape recorder (Ampex, SP 300), and later displayed on an ink-writing recorder (Elema-Schonander). Drugs were administered through a catheter in a jugular vein, and are expressed in terms of the salt.

Observations were also made on three healthy men who volunteered for the experiments. Catheters (No. 19 Intracath, Bardic) were inserted into the left brachial artery and the right antecubital vein. Saline was continuously infused through these catheters at 4 ml./min. When drugs were infused the dose for one minute was contained in 4 ml. of saline. Forearm blood flow was measured by venous occlusion plethysmography, mercury in rubber strain gauges being used (Whitney, 1963). Arterial blood pressure was measured intermittently via the catheter in the brachial artery by a strain gauge pressure transducer. The length of the arterial catheter was adjusted so that damping was nearly critical. Mean arterial pressure was recorded by electrically integrating the instantaneous pressure signal over five-second periods. Instantaneous heart rate was measured with a cardiotachometer, and mean rate was recorded by integrating the instantaneous rate signal over 30-second periods.

RESULTS

Observations were made in five cats in which the increase in heart rate produced by the intravenous injection of a series of doses of isoprenaline (0.05, 0.1, 0.2, and 0.4 μg./kg.) and orciprenaline (1.6, 3.2, 6.4, and 12.8 μg./kg.) were recorded. The increases in heart rate in each cat and the mean increase produced by each dose of isoprenaline and orciprenaline are given in Fig. 2. These results show that isoprenaline is approximately 40 times more active than orciprenaline in increasing heart rate.

In three dogs the intravenous injection of isoprenaline increased heart rate and cardiac contractile force and reduced diastolic arterial pressure ; orciprenaline had similar effects. The mean changes in three dogs produced by a series of doses of isoprenaline (0.1, 0.4, and 1.6 μg./kg.) and orciprenaline (2.5, 10, and 20 μg./kg.) are given in Fig. 3. These show that on a dose basis isoprenaline is 10 to 20 times more active than orciprenaline in producing positive inotropic and chronotropic effects. The administration of isoprenaline and orciprenaline was repeated after the intravenous injection of propranolol 0.5 mg./kg. ; the results are given in Fig. 3. Propranolol abolished the effects of the two smaller doses of isoprenaline and orciprenaline and reduced the effects of the largest dose of each by the same extent.

The results of the experiments on the human volunteers were in agreement with those on cats and dogs. Fig. 4 shows the averaged results of three experiments on three subjects, in which the responses of forearm blood flow, arterial pressure,

and heart rate to intravenous isoprenaline and orciprenaline were measured. Both drugs caused increases in heart rate, pulse pressure, and forearm blood flow, but little change in mean pressure. The responses to orciprenaline 20 μg./min. were slightly greater than those produced by isoprenaline 0.5 μg./min. but considerably less than those produced by isoprenaline 2 μg./min. The responses to isoprenaline 2 μg./min. were slightly less than those produced by orciprenaline 80 μg./min. This showed that isoprenaline is between 10 and 40 times as potent as orciprenaline. The intravenous infusion of propranolol 200 μg./min. for five minutes prevented the effects of a subsequent infusion of orciprenaline at 80 μg./min.

In the same three subjects the responses of forearm blood flow to the infusion of each drug into the brachial artery were measured. Both drugs caused a transient increase followed by a smaller sustained increase in flow. There was no change in flow in the opposite control forearm. The responses to isoprenaline 0.0125 and 0.05 μg./min. were similar in size to those produced by orciprenaline 0.5 and 2 μg./min. respectively. These results suggested that the potency of isoprenaline was about 40 times that of orciprenaline. The vasodilator action of orciprenaline could be prevented by the prior intra-arterial administration of propranolol.

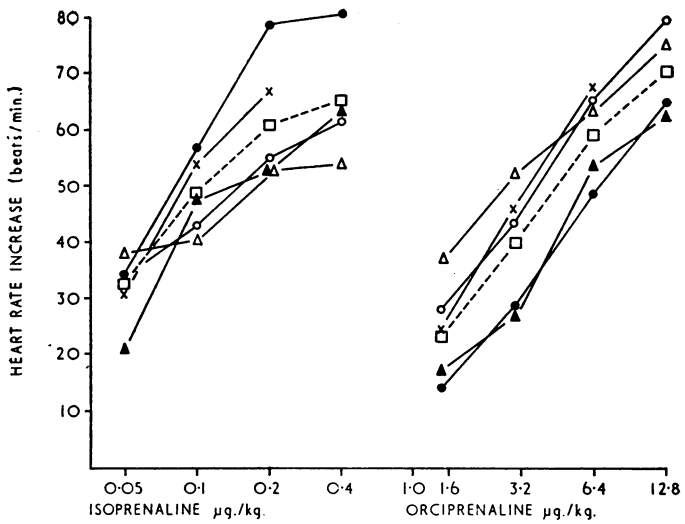

FIG. 2.—Increases in heart rate produced by the intravenous injection of isoprenaline and orciprenaline in five anaesthetized cats. Each set of symbols represents observations in a single cat and □ - - - □ the mean increase for each dose.

DISCUSSION

Stock and Dale (1963) first showed that the administration of pronethalol occasionally aggravated or precipitated heart failure. Similar findings have been reported with propranolol (Stephen, 1966). In man propranolol *reduces* resting heart rate, myocardial contractility, and cardiac output and *increases* heart size, left ventricular end-diastolic pressure, and right atrial pressure (Harris *et al.*, 1966 ; Chamberlain, 1966). These effects, which probably result from blockade of resting sympathetic drive, generally appear to have little adverse effect except when there is severe impairment of cardiac function. In such circumstances heart failure may be produced or made worse. Where this is of rapid onset its early correction by stimulation of β-receptors may be imperative.

The present experiments suggest that orciprenaline is probably the most specific β-receptor stimulant readily available in several countries, including the British Isles, for this role. As propranolol blocks β-receptors competitively, each patient should be treated with orciprenaline by intravenous injection or infusions of increasing amounts until a response—for example, an increase in heart rate—is observed. Rapid digitalization may also be of value, as the positive inotropic action of digitalis is not antagonized by propranolol (Levy and Richards, 1965). A severe bradycardia has been observed in some patients (especially young adults) treated with propranolol, and has been attributed to an unmasking of increased parasympathetic (vagal) activity by the removal of sympathetic drive (Johnstone, 1966 ; Bath, 1966). Atropine has been shown to abolish this bradycardia when occurring during anaesthesia (Johnstone, 1966). If additional cardiac stimulation is required the administration of orciprenaline may be of value.

SUMMARY

The cardiovascular actions of the chemically related amines isoprenaline and orciprenaline were compared in cats, dogs, and humans.

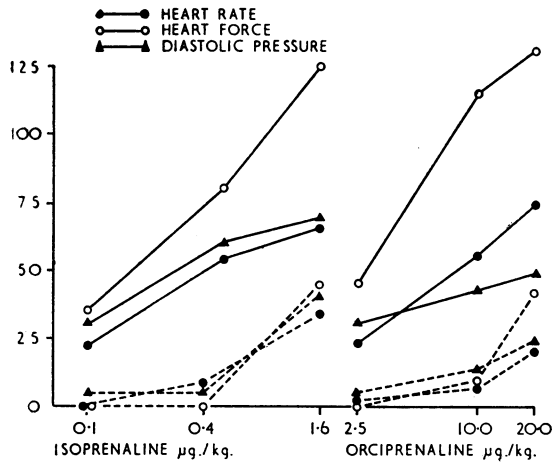

FIG. 3.—Increase in heart rate (beats/min.) and cardiac contractile force (percentage of initial control level) and decrease in diastolic arterial pressure (mm. Hg) produced by the intravenous injection of isoprenaline and orciprenaline. Mean changes in three anaesthetized dogs. Continuous line = observations during control period ; broken line = observations after intravenous injections of 0.5 mg. of propranolol/kg.

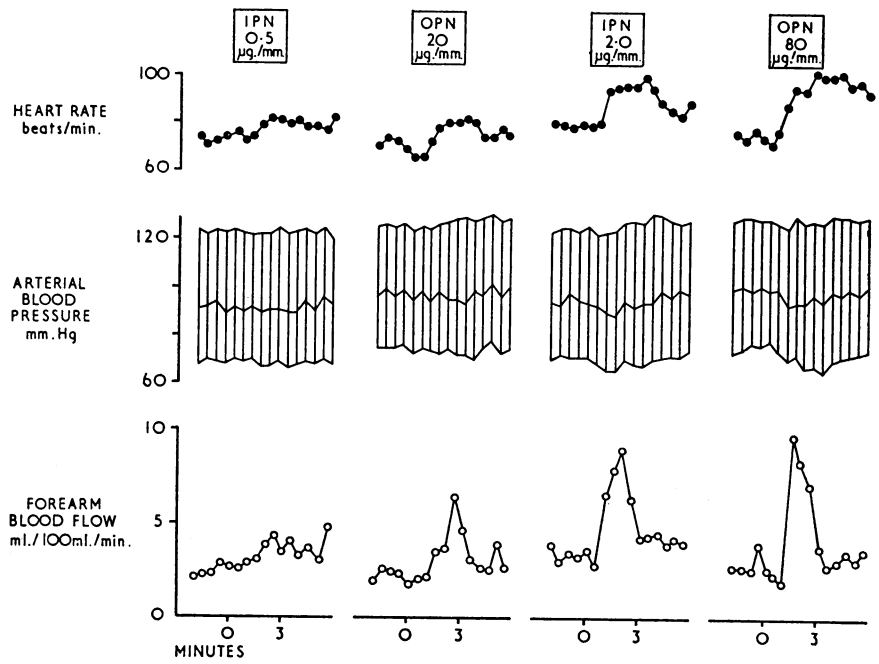

FIG. 4.—Average response in three subjects of heart rate, arterial blood pressure, and right forearm blood flow to intravenous infusion of isoprenaline (IPN) 0.5 and 2 μg./min., and orciprenaline (OPN) 20 and 80 μg./min. Drugs were infused during the periods between the dotted lines.

Both drugs increased heart rate in cats, heart rate and cardiac contractile force in dogs, and heart rate and forearm blood flow in man.

Both drugs acted by stimulating adrenergic β-receptors, as their effects were antagonized by propranolol.

Isoprenaline was found to be about 40 times more active than orciprenaline in cats, 10 to 20 times more active in dogs, and 10 to 40 times more active in humans.

These observations suggest that orciprenaline may be of value in patients in whom side-effects have occurred from blockade of adrenergic β-receptors.

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Medical Memoranda

Initial Cardiac Tamponade in Acute Leukaemia

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Invasion of the pericardium may occur in acute leukaemia (Hayhoe, 1960), and occasionally primary leukaemic pericarditis (Parx, 1961) and haemorrhagic pericarditis (Kosteasph, Xenakes, and Loubros, 1961) have been described. A review of the literature, however, shows that pericardial involvement is extremely rare. To the best of our knowledge cardiac tamponade as an early major manifestation of acute leukaemia has not been described. Recently we saw this phenomenon, and details of the case are given below.

CASE REPORT

A man aged 26 was admitted to hospital with a 10-day history of fever, pain in chest, cough, and dyspnoea. On examination he was acutely orthopnoeic, B.P. 60/45 mm. Hg ; pulse 134/min., slightly irregular ; and there was pulsus paradoxus. Jugular venous pressure 12 cm. The liver was enlarged two fingerbreadths and tender. The apical impulse could not be felt and the area of cardiac dullness was increased. The heart sounds were feeble ; no murmur or friction rub could be heard. Diffuse rales were heard in both lung fields. There were non-tender enlarged lymph nodes and the spleen was just palpable and without tenderness. Laboratory investigations showed haemoglobin 11 g./100 ml. (Haldane), W.B.C. 11,300/cu. mm. (lymphoblasts 35%, lymphocytes 55%, segmented neutrophils 10%), and platelets 90,000/cu. mm.

The diagnosis of acute leukaemia was confirmed by bone-marrow examination. *X*-ray examination of the chest revealed massive pericardial effusion. The E.C.G. showed sinus tachycardia with low-voltage S–T depression and flattening of T waves in all the leads. An emergency pericardiocentesis was performed and 120 ml. of haemorrhagic pericardial fluid was aspirated. Smear examination of aspirated fluid showed plenty of red blood cells and blast cells. He was treated with corticosteroids and mercaptopurine, and pericardiocentesis had to be repeated on three occasions. He had complete symptomatic and haematological remission and was sent home after 45 days.

He returned three months later with a relapse of acute leukaemia. This time he had haematuria, malaena, extensive leukaemic skin infiltrations, progressive anaemia, retinal haemorrhage, and purpura. There were, however, no cardiac signs or symptoms. He stayed in hospital for 60 days and was discharged after remission had been obtained. At the time of writing he was in remission on maintenance doses of corticosteroids.

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