Anti-anginal drugs and the vasodilator response to myocardial hypoxia

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Anti-anginal drugs decrease the work of the heart (Petta & Zaccheo, 1971) and promote the formation of a collateral circulation (Russell Rees & Redding, 1969). They may also have a beneficial effect on myocardial metabolism (Parratt, 1969). It is possible that their overall spectrum of activity is influenced by yet another action—the modification of the normal vasodilator response to hypoxia. This could occur with several of the more recently introduced anti-anginal drugs, since they have been shown to potentiate the dilator effects of adenosine (Raberger & Kraupp, 1971), which itself may be a mediator of physiological dilatation (Rubio, Berne & Katori, 1969).

Myocardial blood flow was measured in anaesthetized cats using a heat clearance technique (McInnes & Parratt, 1969). Vasodilator responses were obtained to reactive hyperaemia, systemic hypoxia and by intravenous infusions of adenosine (0·25 mg/kg min). Reactive hyperaemia was produced by applying tension to a loose snare round the anterior interventricular artery for 10 or 30 s. After release of the snare, blood flow remained elevated for about 2 min. Systematic hypoxia was induced by artificial respiration with 5–10% oxygen in nitrogen. It was found that marked increases in blood flow occurred when the arterial pO_2 fell below 40 mmHg.

Dipyridamole (1 mg/kg, i.v.) itself produced a shortlasting increase in myocardial blood flow, which returned to control levels after 5 min. After dipyridamole, the vasodilator effects of adenosine were markedly potentiated. This effect lasted about 45 min. No changes were observed in the dilator effects of systemic hypoxia or of reactive hyperaemia.

These results do not support the suggestion that anti-anginal drugs with a dipyridamole-like action would influence the normal vasodilator response to myocardial hypoxia.

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The effects of quazodine on myocardial blood flow in developing myocardial infarcts

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Acute ligation of a major branch of the left coronary artery in dogs markedly decreases local blood flow in the area supplied by the ligated vessel; this is partly the result of the conversion of the normal local vasodilator effect of adrenaline to vasoconstriction (Grayson, Irvine & others, 1968). In cats, the effect of noradrenaline on myocardial blood flow is much reduced following coronary artery ligation whereas the effect of isoprenaline is unchanged (Moore & Parratt, 1971). Quazodine (MJ 1988; 6,7-dimethoxy-4-ethylquinazoline) which possesses a spectrum of pharmacological activity similar to that of the β-adrenoceptor stimulants and the methylxanthines, markedly increases myocardial blood flow and contractility both in dogs (Carr, Cooper & others, 1967) and in cats (Parratt & Winslow, 1971). The purpose of this study was to determine if these effects were also present in the ischaemic myocardium and in the early stages of experimental cardiac failure.

Myocardial blood flow was assessed, in cats anaesthetized with sodium pentobarbitone, by a heat clearance technique (McInnes & Parratt, 1969). The effects of intravenous infusions of quazodine (0·5 mg/kg min^{-1}) on systemic blood pressure, heart rate, cardiac output and myocardial blood flow were determined up to 4 h after acute ligation of the anterior descending branch of the left coronary artery. In normal animals quazodine decreased systolic pressure by a mean of 7 ± 2 mmHg (from a mean control level of 135 ± 7 mmHg) and diastolic blood pressure by 14 ± 2 mmHg (from a mean control level of 92 ± 5 mmHg).

Heart rate was increased by 28 ± 3 beats/min (from 196 ± 7 beats/min), cardiac output by 44 ± 5 ml/kg body weight min (from 168 ± 16 mg/kg min) and local myocardial blood flow by a mean of 220%. Quazodine had similar effects in the infarcted animals, decreasing systemic pressure by 13 ± 3 mmHg (from 124 ± 6 mmHg) and diastolic pressure by 20 ± 3 mmHg (from 83 ± 6 mmHg). Heart rate was increased by 30 ± beats/min (from 201 ± 12 beats/min), cardiac output by 22 ± 5 ml/kg body weight min (from 133 ± 20 ml/kg body weight min) and myocardial blood flow by a mean of 34%. In the infarcted animals therefore quazodine produced a more marked decrease in systemic arterial pressure but the effects on cardiac output and on myocardial flow were considerably less than those observed in normal cats. Nevertheless, the degree of myocardial stimulation and the increase in coronary perfusion induced by quazodine, in animals with an ischaemic myocardium, suggest that it warrants further investigation in experimental cardiogenic shock.

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Muscle tremor produced by sympathomimetic bronchodilators

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Adrenaline, stimulation of the splanchnic nerves, and a variety of procedures that cause the reflex release of catecholamines from the adrenal medullae produce a decrease in the tension and an increase in the rate of relaxation of the maximal twitches of the slow-contracting soleus muscle of the anaesthetized or decerebrate cat. The effect is the result of a direct action on the muscle fibres, and is independent of concomitant cardiovascular changes (Bowman & Zaimis, 1958). The increased rate of relaxation means that the overall duration of the twitch is reduced, and this effect results in a pronounced decrease in the tension and degree of fusion when subtetanic contractions are evoked at frequencies of stimulation (5–15 Hz) that include the physiological range for this muscle. Adrenaline was effective in doses as low as 0·01 μg/kg intravenously. In different animals, noradrenaline was 50 to 200 times less potent.

Several sympathomimetic bronchodilators (isoprenaline, salbutamol, orciprenaline, terbutaline) have been shown to produce the same effect, and the use of relatively selective agonists and antagonists (sotalol, butoxamine, practolol) indicated that the adrenoceptors involved are β-receptors and that they resemble those of the bronchi (β_2 receptors) more than those of the heart (β_1 receptors). The same effect, occurring in the slow-contracting units of human muscles (Marsden & Meadows, 1968), probably accounts for the tremor that occurs in patients with phaeochromocytoma and that often accompanies the use of sympathomimetic bronchodilators. The cyclic AMP phosphodiesterase inhibitors, 3-acetamido-6-methyl-8-n-propyl-*syn*-(4,3-a) pyrazine (ICI 58,301), 3-acetamido-5-methyl-8-n-propyl-*syn*-triazolo (4,3-a) pyrazine (ICI 61,129), and 2-amino-6-methyl-7-oxo-8-n-propyl-*syn*-triazolo (4,3-) pyrazine (ICI 63,197), potentiated adrenaline and isoprenaline in their actions on the soleus muscle. ICI 63,197, effective in a dose of 50 μg/kg intravenously, was the most potent in this respect, whereas ICI 61,129, even in doses up to 10 mg/kg, was only very weakly effective. These compounds show the same rank order of potency in phosphodiesterase inhibiting activity (Somerville, Rabouhans & Smith, 1970), and the results are therefore compatible with the possibility that the effects of β-receptor agonists on the soleus muscle are mediated by cyclic adenosine 3′,5′ monophosphate, which in turn may be involved in the relaxation mechanism of the muscle.

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