GRAYSON, J. & MENDEL, D. (1961). Myocardial blood flow in the rabbit. *Am. J. Physiol.*, **200**, 968–974.
MCINNES, LINDA & PARRATT, J. R. (1969). Studies on the mode of action of hexobendine, a prospective anti-anginal drug. *Br. J. Pharmac.*, **37**, 272–282.
PERLROTH, M. G. & HARRISON, D. C. (1969). Cardiogenic shock: a review. *Clin. Pharmac.*, **10**, 449–467.
TAYLOR, S. H., SUTHERLAND, G. R., MACKENZIE, G. J., STAUNTON, H. P. & DONALD, K. W. (1965). The circulatory effects of intravenous phentolamine in man. *Circulation*, **31**, 741–754.

Cardiovascular effects of pentazocine in rabbits

M. FOGARTY, D. GILL, P. HILL* and J. PETTIT (introduced by P. J. CANNON), *Department of Pharmacology, University College, Dublin*

After the intravenous injection of pentazocine in man some workers (Lal, Savidge & Chhabra 1969) have recorded a transient fall in arterial pressure followed by a rise to levels higher than those of the control period. Others (Jewitt, Maurer & Hubner, 1970) did not observe the initial fall but noted a transient reduction in cardiac output followed by a prolonged rise in systemic and pulmonary arterial pressures. These haemodynamic changes are unexplained.

In decerebrate rabbits or in rabbits anaesthetized with chloralose–urethane, rapid intravenous injection of pentazocine in doses of 0·5, 1·0 and 2·0 mg/kg also caused a transient fall and subsequent rise in arterial pressure. The degree and duration of the fall in pressure were related to the dose given and were greater and longer lasting after cutting the vagus and sympathetic in the neck. In conscious animals, doses of pentazocine (1–2 mg/kg intravenously) caused an increase in heart rate, prolongation of the QT interval, a marked reduction in voltage with widening of the QRS complex and abnormalities of the T wave. Ventricular tachycardia occurred in two animals.

Pentazocine reduced the force of contraction of the heart isolated from the rabbit, the dose required to produce a 50% reduction being approximately 350 μg; with this dose the maximum effect occurred within 30 s and wore off gradually over 6–7 min. The heart rate was slowed but this effect was less marked and of shorter duration than the effect on contractile force. Coronary flow was measured as a drop rate; this slowed very briefly, recovering completely within 30 s.

Apart from its effects on the heart, pentazocine also had local anaesthetic properties and acted as a non-competitive anatagonist of acetylcholine and histamine on the guinea-pig ileum.

It is suggested that the cardiovascular effects of intravenous pentazocine in the intact animal are due to a direct depressant action of the drug on the myocardium modified by secondary reflex sympathetic activity.

REFERENCES

JEWITT, D. E., MAURER, B. J. & HUBNER, P. J. B. (1970). Increased pulmonary arterial pressures after pentazocine in myocardial infarction. *Br. med. J.*, **1**, 795.
LAL, S., SAVIDGE, R. S. & CHHABRA, G. P. (1969). Cardiovascular and respiratory effects of morphine and pentazocine in patients with myocardial infarction. *Lancet*, **1**, 379.

Cardiovascular actions of Wy 21901, a new hypotensive and anti-arrhythmic agent

B. J. ALPS*, E. S. JOHNSON and A. B. WILSON, *Department of Pharmacology, Wyeth Institute of Medical Research, Taplow*

β-Adrenoceptor blocking drugs are well known as anti-arrhythmic agents, and have

been used in the treatment of hypertension by virtue of their action in altering cardiac function (Prichard & Gillam, 1969; Zacharias & Cowen, 1970). In clinical use the onset of the blood pressure fall with propranolol is delayed and treatment is associated with an increase in vasoconstrictor tone. It would seem likely that these disadvantages could be overcome by a reduction in this reflex vasoconstrictor response.

Wy 21901 (3-[2-(4-benzamidopiperid-1-yl)ethyl] indole hydrochloride) is a member of a series of potent hypotensive agents (Archibald, 1968) active in conscious or anaesthetized, normotensive or hypertensive animals and possessing cardio-inhibitory and α-adrenoceptor blocking properties (Alps, Hill, Johnson & Wilson, 1970). In conscious cats Wy 21901 (2·5–10 mg/kg, orally) was a more potent hypotensive agent than guanethidine. In cats anaesthetized with pentobarbitone Wy 21901 (0·1–3·2 mg/kg intravenously) induced a significantly greater ($P<0·01$) and more persistent decrease in blood pressure than the standard cardio-inhibitory drug propranolol (0·1–12·8 mg/kg intravenously). Like propranolol, Wy 21901 caused bradycardia, reduced myocardial contractile force and decreased cardiac output, but in contrast its hypotensive action was sustained, whereas that caused by propranolol seldom lasted longer than 3 min. Lignocaine (0·1–12·8 mg/kg intravenously) caused an almost identical decrease in force of myocardial contraction as propranolol and Wy 21901, but unlike these compounds it had no significant effect on heart rate or blood pressure.

In cats anaesthetized with halothane, Wy 21901 abolished adrenaline-induced arrhythmias and was more potent than lignocaine and approximately equipotent with propranolol. Wy 21901 was more potent than lignocaine or propranolol in abolishing ouabain-induced atrial or ventricular arrhythmias in cats anaesthetized with pentobarbitone. In addition ouabain-induced ventricular fibrillation was reversed by a single intravenous dose of Wy 21901 (1–2 mg/kg) in all of five experiments.

In experiments on the peripheral vasculature, Wy 21901 caused a dose-related increase in blood flow in the perfused hind-quarters of the anaesthetized cat and the perfused hind-limb of the anaesthetized red patas monkey. In addition, the constrictor responses caused by lumbar sympathetic chain stimulation, or noradrenaline (intra-arterially or intravenously) were reduced. Propranolol in identical conditions caused a marked decrease in hind-limb blood flow and did not affect the constrictor responses either to nerve stimulation or noradrenaline. The reflex increase in vascular resistance with propranolol provides an explanation for the transient nature of its blood pressure fall. In contrast, these results indicate that the sustained nature of the hypotensive action of Wy 21901 is related to its α-adrenoceptor blocking actions in the periphery.

REFERENCES

ALPS, B. J., HILL, MADELINE, JOHNSON, E. S. & WILSON, A. B. (1970). Autonomic blocking properties of Wy 21901. *Br. J. Pharmac.*, **40**, 153P.

ARCHIBALD, J. L. (1968). A new class of indole antihypertensive agents. *Chim. Therap.*, **3**, 397.

PRICHARD, B. N. C. & GILLAM, P. M. S. (1969). Treatment of hypertension with propranolol. *Br. med. J.*, **1**, 7–16.

ZACHARIAS, F. J. & COWEN, K. J. (1970). Controlled trial of propranolol in hypertension. *Br. med. J.*, **1**, 471–474.