Thus practolol (4 mg intravenously) appears to abolish certain ventricular dysrhythmias occurring during anaesthesia without depressing cardiac action.

Blood levels of practolol following intravenous administration

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Blood concentrations of the cardioselective β-adrenoceptor blocking agent practolol (I.C.I. 50172, Eraldin) have been studied in normal volunteers following oral administration. Concentrations in blood were correlated with the percentage inhibition of exercise tachycardia. The peak concentration in blood occurred 1·5–3 h after the oral administration and decayed thereafter with a half life of 10 ± 2 h (Fitzgerald & Scales, 1968).

In the present study intravenous practolol was administered to six volunteer hypertensive patients. The decay curve can only be explained by the use of a three compartmental mathematical model. The initial short half-life of 5 min is due to a rapid tissue equilibration and the later long half-life component of 12 h may be the result of entero-hepatic recirculation. These results are supported by results in animals (Scales & Cosgrove, 1970).

The blood levels required to produce over 30% inhibition of isoprenaline tachycardia (4 μg/min) are greater than 0·5 μg/ml, exercise tachycardia (100 W, 2 min) are over 1 μg/ml. Levels of 1 μg/ml can only be maintained by the administration of 20 mg intravenously at 10 min intervals. A single injection of 20 mg only gives levels above 1 μg/ml for about 5 min.

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Vascular actions of clonidine in man

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Clonidine, an imidazoline derivative, has been recently introduced for the treatment of hypertension. Animal studies indicate an action on sympathetic centres. Surprisingly, the peripheral action on blood vessels is constrictor, probably the result of stimulation of α-adrenoceptors. The drug has been given to man intravenously, but little information is available on the direct effects on human blood vessels.

Clonidine (250–500 ng/min) was infused into a brachial artery of each of twelve normal volunteers, and the effects on hand or forearm blood flow were recorded. There was a prompt dose-related vasoconstriction lasting for the period of the infusion (in one instance for 30 min). This constriction was abolished completely by α-adrenoceptor blocking agents and occurred in the skin vessels rather than the

muscle vessels of the forearm. The drug did not alter the response of hand blood vessels to noradrenaline in the one subject tested.

Clonidine (150 μg) was infused intravenously into four supine subjects at the rate of 25–30 μg/min. There was no pressor response, but all subjects showed a progressive fall in mean arterial pressure. There was, however, an initial increase in hand vascular resistance which was followed by a fall. Intravenous and intra-arterial noradrenaline were given before and after the clonidine, and the effects on arterial blood pressure and hand blood flow measured. The clonidine increased the effects of noradrenaline.

In view of one report of reduced vascular constrictor and dilator responses in cats after chronic clonidine administration, we have studied the vascular and pressor responses to intravenous and intra-arterial noradrenaline before and during oral therapy with clonidine in two hypertensive patients. There was a small increase in the effects of noradrenaline during treatment, but it was less than that seen during bethanidine therapy.

A new method for studying the pharmacology of the superficial veins in conscious man

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A technique has been developed by which it is possible to quantitate the effect of drugs infused directly into the superficial veins of conscious man. Changes in compliance of a dorsal hand vein are estimated by following the size of the vein when it is distended by application of a sphygmomanometer cuff on the upper arm at a standard congesting pressure of 45 mmHg (which gives a pressure of approximately 30 mmHg in the vein). Vein size is measured by a simple optical technique in which a microscope is focused on a skin marker dot over the distended vein and then refocused when the vein has emptied; the distance moved by the microscope is measured on a vernier scale (Nachev, Collier & Robinson, 1970).

Drugs were made up in physiological saline and infused at 0·25 ml/min into the vein approximately 1 cm upstream from the point of measurement. Skin and room temperature were kept constant throughout each experiment.

The venous compliance during infusion of saline alone showed no significant change throughout each experiment and was constant from day to day in any one subject. Noradrenaline produced a dose dependent venoconstriction with a linear log dose-response relationship. The threshold was usually 2–4 ng/min and maximum constriction was produced by 64 ng/min. Adrenaline also produced venoconstriction with similar or slightly less potency. 5-Hydroxytryptamine also caused venoconstriction in a similar dose range but the log dose-response curves tended to be steeper.

Histamine, acetylcholine or isoprenaline produce neither constriction nor dilatation of the resting vein in doses ranging from 2–256 ng/min. However, when the vein was previously constricted by a constant infusion of noradrenaline, each of these drugs produced a dose dependent venodilatation; with the vein 50% constricted the dose required to achieve complete relaxation varied from 32–64 ng/min. The dilator effects of histamine, acetylcholine and isoprenaline could be prevented by prior infusion of mepyramine (5 μg in 10 min), atropine (5 μg in 10 min) or propranolol (10 μg in 10 min) respectively.