Sympathomimetic Activity of Guanethidine

SIR,—A report by Abercrombie and Davies (1963) indicated that guanethidine possesses direct sympathomimetic activity in addition to its catecholamine-depleting activity. Abboud and Eckstein (1962) reported that the vasodilator activity of guanethidine may be due to stimulation of β-adrenergic receptors. However, these investigators were not able to show significant changes in heart rate after guanethidine in animals treated with reserpine. In order to explore more fully this proposed sympathomimetic activity of guanethidine, the following experiments were made.

Mongrel dogs of either sex previously treated with reserpine were anaesthetised with 15 mg./kg. of pentobarbitone sodium and prepared for recording the following parameters. Femoral arterial blood pressure was recorded from the cannulated left femoral artery via a Statham pressure transducer on a Grass polygraph. Right femoral arterial blood flow was measured by placement of a Medicon flo-probe (2 mm. I.D.) around the vessel and recorded on the polygraph via a Medicon model FM-6 electromagnetic flowmeter. Chronotropic and inotropic activity were measured by suturing a Walton-Brodie strain gauge arch to the right ventricle after thoracotomy at the fourth intercostal space. The chest was sutured closed and the animal allowed to resume respiration by over-inflation of the lungs and induction of negative intrathoracic pressure. A 20 to 30 min. period elapsed before the administration of drugs.

TABLE I

EFFECT OF GUANETHIDINE, 15 MG./KG., ON CARDIAC ACTIVITY IN DOGS GIVEN RESERPINE BEFORE AND AFTER PRONETHANOL (NETHALIDE)

	Per cent of control response																	
	0·5 min.			1·0 min.			2·0 min.			3·0 min.			5·0 min.			10·0 min.		
Treatment	C	I	P	C	I	P	C	I	P	C	I	P	C	I	P	C	I	P
None	+37	+62	−28	+50	+30	−26	+54	+59	−24	+52	+59	−17	+46	+11	0	+23	−28	−17
Pronethanol 5 mg./kg., i.v.	+3	−14	−47	+1	−17	−22	+3	−20	+15	−5	−20	+34	−5	−17	+94	0	−11	+92

C, chronotropic activity; I, inotropic activity; P, peripheral blood flow calculated as peripheral resistance units; minus value indicates vasodilatation.

In a series of animals pre-treated with reserpine, guanethidine sulphate (15 mg./kg.) produced a biphasic blood pressure response. There was an initial and transient depressor response, of approximately 40 mm. Hg, lasting from 1 to 3 min. followed by a more sustained pressor response, of approximately 80 mm. Hg, lasting as long as 45 min. Accompanying the depressor response there were marked increases in both the chronotropic and inotropic activity of the myocardium, and a vasodilatation as seen in Table I. These effects decreased as the blood pressure reverted toward a pressor response.

To assess the possibility of β-receptor activity, pronethanol (5 mg./kg.), a specific β-receptor blocking agent, was injected intravenously before giving guanethidine. The effects on heart rate, ventricular force, and femoral blood flow are summarised in Table I. There was no change in the depressor response to guanethidine, however, the pressor response was markedly reduced. In addition, the chronotropic response was blocked and a negative inotropic response prevailed.

From these observations, it appears that guanethidine, in addition to its catecholamine-depleting activity, does possess some direct sympathomimetic action. However, the β-receptor mediated responses of heart rate and myocardial force of contraction appear to be dissociated from the peripheral vascular effects of this agent.

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Cardiotonic Activity Amongst Polyene Antifungal Antibiotics

SIR,—The cardiotonic activity of hamycin and trichomycin, two polyene antifungal antibiotics, has been already reported (Arora, 1962, Arora and Sinha, 1963, Ozaki, Kataoka, Maesawa, Tshima and Kubo, 1954). Nystatin and lagosin, two more polyene antifungal antibiotics, revealed the presence of a similar activity.

Ten experiments were made with nystatin and lagosin on the perfused frog heart in which failure was induced by raising the venous pressure in steps of 1 cm. (Burn, 1952). Cardiac outflow was simultaneously recorded through a cannula in the aorta. Nystatin was perfused in a concentration of 2×10^{-5} g./ml. and lagosin in a concentration of 6×10^{-6} g./ml. With either drug, perfusion was followed by a marked increase in the amplitude of contraction as well as an increase in the cardiac outflow. This was followed by an increase in the diastolic tone and a decrease in the cardiac outflow, terminating in systolic arrest of the ventricles in 20 to 30 min. Effects were comparable with a concentration of 2×10^{-5} g./ml. of ouabain although the systolic contracture was not as complete as with nystatin or lagosin. Control experiments with propylene glycol for nystatin and ethanol for lagosin failed to produce the effects seen with these drugs.

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