The effects of intravenous injections of vinblastine or vincristine on the responses of the rat heart to nerve stimulation and to drugs.

T. BENNETT* & SHEILA M. GARDINER
(introduced by A.T. BIRMINGHAM)

Department of Physiology, The Medical School, University of Nottingham, NG7 2RD and The School of Agriculture, University of Nottingham

Intravenous injection of vinblastine (3 mg/kg) depletes noradrenaline (NA) levels in the rat heart, and reduces cardiac binding of ^{3}H-NA (Keen & Livinston, 1970, 1971; Cheney, Hanin, Massarelli, Trabucchi & Costa, 1973; Hanbauer, Kopin, Maengwyn-Davies, Thoa & Weise, 1973; Hanbauer, Jacobowitz & Kopin, 1974). There is evidence to suggest that this effect may be due to destruction of noradrenergic nerve terminals (Bennett, Cobb & Malmfors, 1973: Hanbauer *et al.*, 1974). It has been claimed that the action of vinblastine on noradrenergic neurons is not possessed by its chemical analogue, vincristine (Cheney *et al.*, 1973). Furthermore, neither vinblastine nor vincristine administered intravenously appear to affect cholinergic neurons (Cheney *et al.*, 1973). The effects of these drugs on the response of the rat heart to nerve stimulation, to NA and to acetylcholine (ACh), have now been investigated.

Male Wistar rats weighing between 250 and 300 g were used: vinblastine sulphate or vincristine sulphate was dissolved in Kreb's solution (1 mg/ml) and injected into a tail vein to give a dose of 3 mg/kg. The rats were killed 30 h later; the left atrium was removed and set up in a 100 ml organ bath (containing Kreb's solution at 37° C bubbled with 95% oxygen and 5% carbon dioxide) and connected to an isometric recording system. The quiescent preparation was driven by transmural electrical pulses (4 Hz, 2 ms, 6 V); nerve stimulation was effected by increasing the strength of the stimulating pulses to 100 V (Blinks, 1966) for 15 seconds. Noradrenergic responses were observed in the presence of atropine (5×10^{-6} M), cholinergic responses were observed in the presence of propranolol (5×10^{-7} M).

Thirty hours after treatment with vinblastine (3 mg/kg) there was a 70% reduction in the positive inotropic effect of noradrenergic nerve stimulation ($n = 7$; $P < 0.025$), and, although there was a marked reduction in the force of contraction of the left atrium, its sensitivity to NA was increased 12-fold ($n = 8$; $P < 0.001$). Vincristine (3 mg/kg) caused a 65% reduction in the effect of noradrenergic nerve stimulation ($n = 7$; $P < 0.05$, and a 42-fold increase in sensitivity to NA ($n = 8$; $P < 0.001$); as with vinblastine, the absolute force of contraction of the atrium was markedly reduced. Neither drug caused a significant change in the effects of cholinergic nerve stimulation nor in the response to ACh ($n = 10$).

The present findings corroborate the report of differential effects of vinblastine and vincristine on noradrenergic and cholinergic neurons (Cheney *et al.*, 1973), but indicate that both drugs can affect noradrenergic neurons.

We are indebted to Eli Lilly & Co. (Basingstoke) for the generous donations of vinblastine and vincristine.

References

BENNETT, T., COBB, J.L.S. & MALMFORS, T. (1973). Fluorescence histochemical and ultrastructural observations on the effects of intravenous injections of vinblastine on noradrenergic nerves. *Z. Zellforsch. mikrosk. Anat.*, **141**, 517-527.

BLINKS, J.R. (1966). Field stimulation as a means of effecting the graded release of autonomic transmitters in isolated heart muscle. *J. Pharmac. exp. Ther.*, **151**, 221-235.

CHENEY, D.L., HANIN, I., MASSARELLI, R., TRABUCCHI, M. & COSTA, E. (1973). Vinblastine and vincristine: a study of their action on tissue concentrations of epinephrine, norepinephrine and acetylcholine. *Neuropharmacology*, **12**, 233-238.

HANBAUER, I., JACOBOWITZ, D.M. & KOPIN, I.J. (1974). Effects of vinblastine on noradrenergic axons. *Br. J. Pharmac.*, **50**, 219-225.

HANBAUER, I., KOPIN, I.J., MAENGWYN-DAVIES, G.D., THOA, N.B. & WEISE, V.K. (1973). Effects of vinblastine on catecholamine–biosynthetic enzymes in heart, sympathetic ganglion and adrenal glands of rats. *Br. J. Pharmac.*, **48**, 106-112.

KEEN, P. & LIVINGSTON, A. (1970). Decline of tissue noradrenaline under the influence of a mitotic inhibitor. *Nature, New Biol.*, **227**, 967-968.

KEEN, P. & LIVINGSTON, A. (1971). Intraneuronal transport of noradrenaline in the rat. *Mem. Soc. Endocrinol.*, **19**, 671-679.