Pargyline on blood pressure in spinal and decerebrate cats

SIR,—Acutely administered pargyline produces a slowly developing long-lasting hypertensive effect in spinal cats, but in decerebrate animals, under similar conditions, it has no action on blood pressure.

Five cats were anaesthetised with ether, and cannulae were placed in the right carotid artery, the left external jugular vein and the trachea. Both vagi were cut and the cord sectioned at C-2, the cats being maintained subsequently under artificial respiration. One hr after the ether anaesthesia was discontinued, pargyline hydrochloride was given intravenously in doses of 10 mg/ kg at 30 min intervals for a cumulative dosage of 60 mg/kg. The systolic and diastolic blood pressures were read 15 min before and after each injection. Immediately after each dose, a small hypotensive response of short duration was obtained, but during the course of each experiment pargyline gradually produced a long-lasting hypertensive effect. After 20 mg/kg (Table 1), the mean systolic blood pressure was increased by 26·8 mm Hg, whereas after 60 mg/kg, the increase was 54·8 mm Hg. In this series of experiments, the mean heart rate was not significantly altered although a positive chronotropic trend was apparent according to rank-sum analysis (Rümke & de Jonge, 1964).

Five more cats were decerebrated (Burn, 1952), and maintained subsequently under artificial respiration. In contrast to the results in spinal animals, pargyline did not raise the blood pressure, and a slight, but not statistically significant, depression was obtained (Table 1). Mean heart rates were again not significantly altered, although analysis by the method of de Jonge (Rümke & de Jonge, 1964) indicated a decreasing trend.

TABLE 1. THE EFFECT OF PARGYLINE HYDROCHLORIDE ON BLOOD PRESSURE AND HEART RATE IN SPINAL[1] AND DECEREBRATE[2] CATS. (Readings taken 15 min after injection. Paired mean differences from control values[3] ± s.e.)

Cumulative intravenous dose mg/kg	Spinal cats (n = 5)			Decerebrate cats (n = 5)		
	Blood pressure (mm Hg)		Heart rate beats/min	Blood pressure (mm Hg)		Heart rate beats/min
	Systolic	Diastolic		Systolic	Diastolic	
10	1·8 ± 2·6	2·6 ± 3·7	−6·0 ± 9·4	0·8 ± 2·0	−5·8 ± 1·7	4·8 ± 6·9
20	26·8 ± 8·6*	26·2 ± 15·5	−5·6 ± 13·3	−1·6 ± 2·2	−6·8 ± 4·0	0·4 ± 5·9
30	42·0 ± 11·5*	33·0 ± 9·8*	18·8 ± 17·9	−1·8 ± 3·5	−6·0 ± 4·6	−2·4 ± 6·3
40	47·2 ± 13·0*	38·6 ± 8·8*	21·6 ± 21·1	−4·6 ± 4·4	−9·2 ± 4·5	−9·6 ± 5·5
50	48·8 ± 9·7*	38·6 ± 7·2*	18·0 ± 17·2	−6·8 ± 6·3	−12·2 ± 6·8	−12·0 ± 9·5
60	54·8 ± 10·3*	49·2 ± 9·0*	13·0 ± 18·0	−9·6 ± 9·3	−13·8 ± 6·0	−20·4 ± 12·7

[1] Control values: Blood pressure 97·6/46·6; heart rate 154·8.
[2] Control values: Blood pressure 128·2/86·0; heart rate 199·2.
[3] Analysis by the method of Walker & Lev (1953).
* $P < 0.05$.

Ten cats were then decerebrated according to the method of Smith, Budris & Paul (1963). In five of these animals an insulated, bipolar, twisted, nichrome wire electrode was placed in the medulla at Horsley-Clarke coordinates P12, L2, H-8. Stimulation at this site with square pulses (100/sec; 1 msec duration) resulted in striking hypertensive responses. Three of these preparations were given pargyline and two received iproniazid phosphate intravenously. Pargyline at 40 mg/kg caused a reduction in the pressor response; higher doses, with a maximum of 100 mg/kg, produced further reduction but in no case was the response abolished. Iproniazid had similar effects over the same dosage range. In the other five decerebrate animals, a bipolar shielded electrode was placed on the central end of the cut sciatic nerve. Stimulation (100/sec; 1 msec duration)

produced typical pressor responses. In three of the animals given pargyline, this response was decreased in magnitude by doses of 40 mg/kg. In the two other cats, iproniazid (50 mg/kg) caused similar effects.

These experiments indicate that the presence of the medullary vasomotor centre is necessary to prevent the peripheral hypertensive action of pargyline. Further, reflexly-induced hypertensive responses are reduced by both pargyline and iproniazid.

Pargyline (as well as some other monoamine oxidase inhibitors) may have two antagonistic actions, a peripheral hypertensive effect resulting from an increase in the concentration of circulating catecholamines and a stronger depressant action on vasomotor centres in the central nervous system. The result is a reduction in blood pressure and the postural hypotension which is observed clinically.

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August 5, 1966

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On the neurotoxic effects induced by alkylating agents

SIR,—During some experiments made to evaluate the chemotherapeutic effect of DL-sarcolysine applied topically to a cerebral tumour of the rat, signs of neurotoxicity were observed. We therefore investigated the central effect of several alkylating agents injected intracerebrally in normal rats. The symptoms observed, the relative potency, and some attempts to protect the animals are reported.

Male Sprague-Dawley rats, 160 $\pm$10 g, were kept in Makrolon cages (47 $\times$ 26 $\times$ 15 cm) 6 per cage at a constant temperature of 22° and relative humidity of 60%. They had free access to food (Diet Alal 56 Alal, Milan) and water until the beginning of the experiment.

The intracerebral injection was made under light ether anaesthesia through the squamopetrosal fissure of the temporal area of the skull (Valzelli, 1964).

The drugs were dissolved in distilled water and injected in 0·02 ml volumes. The intracerebral injection of the solvent never induced any appreciable symptoms and the animals completely recovered from anaesthesia in about 10 min. The mortality was calculated after a period of 24 hr.

The drugs used were: DL-sarcolysine, L-sarcolysine, D-sarcolysine, glycine mustard, alanine mustard, cyclophosphamide, chlorambucil, 6-diazo-5-oxo-L-norleucine (DON), azaserine (all from CCNSC, N.I.H. Bethesda), tryptophan mustard (Dr. L. Otis, Stanford Research Institute, Palo Alto, California), degranol (Medimpex, Budapest), mustine, and tretamine (Simes, Milan), phenobarbitone sodium (Bayer), thiourea (Erba, Milan), phenytoin sodium (Recordati, Milan).