Changes in baroreflexes induced by L-dopa

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L-Dopa commonly reduces the blood pressure in Parkinsonian patients. This hypotension is seldom sufficiently severe to produce symptoms.

We have investigated the mechanism of hypotension induced by L-dopa by comparing the baroreflex responses before treatment, during therapy with maximum tolerated doses of L-dopa alone, and during treatment with maximum tolerated doses of L-dopa given in combination with L-alpha methyldopahydrazine 300 mg/day, which blocks the conversion of L-dopa to catecholamines outside the central nervous system.

The intra-arterial blood pressure responses to Valsalva's manoeuvre and postural change were investigated in 18 patients before treatment. The investigations were repeated in all patients during L-dopa therapy, and in 10 patients recordings were also obtained during the combined regimen of L-dopa plus L-alpha methyldopahydrazine 2 h after receiving the drugs. Results of the Valsalva's manoeuvre were expressed as a 'constrictor index' (Reid *et al.*, 1971). The index fell from $0{\cdot}485 \pm 0{\cdot}077$ to $0{\cdot}312 \pm 0{\cdot}051$ (mean $\pm$ S.E. of mean) while taking L-dopa alone, this impairment in baroreflex function being significant ($P<0{\cdot}001$). With L-alpha methyldopahydrazine in combination with L-dopa the mean index was $0{\cdot}472 \pm 0{\cdot}076$ (not significantly different from pretreatment values).

The supine blood pressures were significantly reduced from 157/86 (mean) before treatment to 146/75 (mean) on L-dopa alone ($P<0{\cdot}05$) and 147/75 (mean) on L-dopa in combination with L-alpha methyldopahydrazine ($P<0{\cdot}001$). Treatment with L-dopa alone led to a significant ($P<0{\cdot}05$) reduction of the blood pressure during 35° head up tilt, from 157/94 (mean) to 142/83 (mean). With L-alpha methyldopahydrazine plus L-dopa, the blood pressures returned towards pretreatment values, though this trend did not attain statistical significance.

The plasma concentration of L-dopa was estimated in 7 patients during both treatment regimens. One and a half hours after their noon dose, the concentrations ranged from 0·15 to 2·44 μg/ml between patients, but the values for each patient were not significantly influenced by the addition of L-alpha methyldopahydrazine.

It is concluded that the impairment of baroreflex function by L-dopa is mediated, at least in part, at the periphery. In contrast, mechanisms operating within the central nervous system may contribute to the lowering of supine blood pressure in patients receiving L-dopa.

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REFERENCE

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Isoprenaline-induced tachycardia in man

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Conolly, Davies, Dollery & George (1971) reported that an intravenous infusion of a low dose of isoprenaline caused an increase in the dose of isoprenaline,

administered as an intravenous bolus injection, that was required to produce a 20 beat/min increase in the heart rate in man. We have performed three types of experiment to examine further the effect of isoprenaline on the heart rate in healthy adult human volunteers.

Initially, the tachycardia produced by logarithmically spaced doses of isoprenaline was studied, each dose being given by continuous intravenous infusion for four min. Dose-response curves were thus constructed with time intervals between them of 24, 12, 6, 12 and 24 min. The infusion of isoprenaline was stopped, and after a further interval a final dose-response curve was constructed. There was no reduction in the heart rate reached during the isoprenaline infusions, regardless of the interval between the dose-response curves. At the end of the experiment, after more than 15 min without isoprenaline, the heart rate remained higher than before any isoprenaline was given (mean increase 10 beats/min).

Intravenous bolus injections of graded doses of isoprenaline were given at 5 min intervals before and after an intravenous infusion of isoprenaline 0·75 μg/min for 45 min. On the second occasion, both the heart rates before injection and the peak heart rates tended to be higher at the greater dose levels than at first, but the increases in heart rate were slightly reduced. None of these changes is statistically significant. These results are shown in Table 1.

TABLE 1. *Mean heart rates (beats/min)* $\pm$ S.E.M. n=3

Isoprenaline dose (μg)	1·5		6·0	
(a) Effect of isoprenaline infusion	Before	After	Before	After
Peak rate	70$\pm$6·1	70$\pm$1·2	91$\pm$4·7	93$\pm$3·3
Increase	14$\pm$2·5	9·7$\pm$2·2	32$\pm$2·8	29$\pm$1·2
(b) Effect of work load (kpm/min)	200	400	200	400
Peak rate	100$\pm$4·7	113$\pm$7·7	118$\pm$4·5	133$\pm$6·4
Increase	13$\pm$1·4	9·7$\pm$1·5	27$\pm$2·3	25$\pm$3·3

Finally, intravenous bolus injections of isoprenaline were given during exercise on a bicycle ergometer at work loads of 200 and 400 kilopond metres/min. At the higher load, the peak heart rate after injection was higher than at the lower load, but the increase produced by each dose of isoprenaline was less. These results are also shown in Table 1. In other experiments, isoprenaline produced a higher peak heart rate on exercise than when given in the supine position at rest, but the actual increase in heart rate was greater at rest than during exercise.

We have not found any evidence of resistance to isoprenaline in terms of the dose needed to produce a given peak heart rate. However, the dose required to produce a given increment in heart rate is raised if the pre-isoprenaline heart rate is increased, and this is seen when the effects of isoprenaline are compared at rest, during exercise, at different levels of exercise, or after previous administration of isoprenaline.

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