Short communications

Action of L-α-methyldopahydrazine on the blood pressure of patients receiving levodopa

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The blood pressure and pulse rate have been compared in a 'double blind, cross over' study involving twenty patients with idiopathic Parkinsonism receiving maximum tolerated dosage of levodopa with and without an extracerebral decarboxylase inhibitor, L-α-methyldopahydrazine. The supine and erect systolic pressures were significantly higher and the erect pulse rate significantly lower during administration of L-α-methyldopahydrazine. The implications of these observations are discussed.

Administration of levodopa to Parkinsonian patients may result in hypotension (Yahr, Duvoisin, Hoehn, Schear & Barrett, 1969; Markham, Treciokas & Ansel, 1970; Godwin-Austen, Tomlinson, Frears & Kok, 1969; McDowell, 1970). In a recent double blind, cross over study, the mean erect and supine systolic pressures of twenty Parkinsonian patients during treatment with levodopa were 19·3 and 10·7 mmHg (1 mmHg≡1·333 mbar) lower than the corresponding values on placebo. These differences were statistically significant at the 1% and 5% levels respectively (Calne, Brennan, Spiers & Stern, 1970).

Levodopa itself is pharmacologically inert, its actions depending on the formation of metabolites, in particular the catecholamines dopamine, noradrenaline and adrenaline. From observations on urinary catabolites, it appears that administration of levodopa results in the formation of much more dopamine than noradrenaline or adrenaline (Calne, Karoum, Ruthven & Sandler, 1969). Four explanations have been put forward to explain the hypotension produced by levodopa: (1) dopamine may act as a 'false transmitter' at peripheral sympathetic nerve endings (Yahr *et al.*, 1969); (2) there may be reduced tissue concentrations of noradrenaline because dopamine can displace noradrenaline from its storage sites in sympathetic nerve endings (Calne *et al.*, 1970); (3) dopamine has a vasodilator action on the renal and mesenteric vascular beds which could result in hypotension (McNay, McDonald & Goldberg, 1965; McNay & Goldberg, 1966; Eble, 1964; Ross & Brown, 1967); (4) changes in catecholamine concentrations within the central nervous system can cause hypotension (Henning & Rubenson, 1970). These hypothetical mechanisms are not mutually exclusive and it is possible that several may contribute to the hypotension induced by levodopa.

Extracerebral decarboxylase inhibitors block the conversion of levodopa to catecholamines outside the brain and have therefore been used to distinguish between the peripheral and central actions of levodopa (Henning & Rubenson, 1970; Watanabe, Chase & Cardon, 1970). In order to investigate the possible contribution of changes in catecholamine concentrations in the peripheral nervous system, we have compared the blood pressure and pulse rate in Parkinsonian patients receiving maximum tolerated doses of levodopa with and without an extracerebral decarboxylase inhibitor, L-α-methyldopahydrazine.

Material and Methods.—Twenty patients with idiopathic Parkinsonism were investigated. There were eight men and twelve women of ages ranging from 35 to 72 years (mean 59·8). They were treated according to two drug regimens administered in a double blind, cross over design. Regimen A comprised L-α-methyldopahydrazine (MK 486, 300 mg per day) plus levodopa in maximum tolerated dosage (mean 0·67 g/day). Regimen B comprised levodopa alone, in maximum tolerated dosage (mean 2·97 g/day). All patients had been taking levodopa routinely for at least 3 months before entering the study. Many were receiving anticholinergic drugs (benzhexol, benztropine or orphenadrine), the dosage of which was not altered.

Each drug regimen was administered to outpatients over six weeks. One 'blind' physician measured all pulse rates and blood pressures at fortnightly intervals. The pulse rates were recorded by palpation of the radial artery and the blood pressures by means of a sphygmomanometer (1 mmHg≡1·333 mbar). At each atten-

dance measurements were made after lying for 1 min, lying for 3 min and after standing for 1 minute.

Further details of the design have been described elsewhere, together with clinical results of each drug regimen (Calne, Reid, Vakil, Rao, Petrie, Pallis, Gawler, Thomas & Hilson, 1971) and the blood concentrations of levodopa achieved (Allen, Calne, Davies & Reid, 1971).

Results.—The first set of measurements taken at each attendance, after lying for 1 min, were discarded as they merely represented an initial manoeuvre performed to acclimatize the patient to the recording environment. The blood pressure and pulse rate obtained after lying for 3 min were designated the 'supine' values and the results after standing for 1 min the 'erect' values. For each patient the mean values over the three successive fortnightly attendances on each regimen were calculated. The mean value for all patients on each regimen was then determined.

The statistical significance of the mean differences of the recordings while on the two regimens was tested by a paired *t* test. Allowance was made for the effect of order of administration as nine patients started on regimen A before regimen B and eleven patients began on regimen B then crossed over to regimen A.

The cardiovascular observations together with the results of statistical analysis are summarized in Table 1. In comparing regimen A with regimen B three differences achieve significance at the 5% level: (i) the supine systolic blood pressure was 5 mmHg higher on regimen A, (ii) the erect systolic blood pressure was 7 mmHg higher on regimen A, (iii) the erect pulse rate was four beats/min lower on regimen A. Taking the patients' ages into account, the postural changes in pulse rate and systolic blood pressure were normal on both regimens.

Discussion.—Before attempting to interpret these cardiovascular observations it is relevant to mention that there was no significant difference in the blood concentrations of levodopa 1·5 h after drug administration on each regimen (Allen *et al.*, 1971), in spite of the differences in maximum tolerated dosage. Similarly there was no significant difference between the therapeutic effects of levodopa on each regimen.

The conclusion can therefore be drawn that L-α-methyldopahydrazine increased the systolic blood pressure without significantly changing the 1·5 h blood concentrations of levodopa or its therapeutic activity. The reduction in the erect pulse rate is presumably a reflex consequence of the changes in blood pressure.

By itself, L-α-methyldopahydrazine has no effect on the blood pressure in man (Sjoerdsma, Vendsalu & Engleman, 1963). Other workers have reported that hypo-

TABLE 1. *Summary of cardiovascular observations*

	Regimen A Levodopa plus L-α-methyldopahydrazine	Regimen B Levodopa	Difference Regimen A—Regimen B
Systolic pressure (mmHg)			
Supine	124·1	119·0	5·4*
Erect	117·6	110·6	7·2*
Difference (supine—erect)	6·6†	8·4†	−2·3
Diastolic pressure (mmHg)			
Supine	77·4	75·8	1·7
Erect	78·3	75·0	3·3
Difference (supine—erect)	0·8	0·7	−1·7
Pulse rate beats/min			
Supine	82·9	85·2	−2·2
Erect	89·9	93·7	−3·9*
Difference (supine—erect)	−7·1†	−8·7†	−1·8

These results are mean values of three measurements in each of twenty patients, taken at fortnightly intervals.
* Represents a significant difference at the 5% level.
† Represents a significant difference at the 1% level.

tension induced by levodopa still occurs in patients receiving L-α-methyldopahydrazine (Watanabe *et al.*, 1970) and in rats the blood pressure is actually reduced by administering this extracerebral decarboxylase inhibitor with levodopa (Henning & Rubenson, 1970). From such observations it has been suggested that the hypotensive action of levodopa is achieved by mechanisms within the central nervous system. In contrast, our results are more in accord with the view that peripheral actions of dopamine contribute to the hypotension induced by levodopa. However, they do not exclude the possibility of a hypotensive action mediated by alteration of brain amines. Complex interactions between dopamine, noradrenaline and 5-hydroxytryptamine are likely to occur in the central nervous system when levodopa is administered and it is quite possible that an extracerebral decarboxylase inhibitor might modify blood concentrations of 5-hydroxytryptamine precursors. The enzyme which is inhibited by L-α-methyldopahydrazine, L-aromatic aminoacid decarboxylase, is responsible for conversion of 5-hydroxtryptophan to 5-hydroxytryptamine in addition to decarboxylation of levodopa to dopamine. Furthermore noradrenaline may, in different regions of the central nervous system, exert both excitatory and inhibitory actions (Bloom, Costa & Salmoiraghi, 1965) so the consequences of a widespread alteration in the concentration of brain amines are difficult to predict.

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REFERENCES

ALLEN, J. G., CALNE, D. B., DAVIES, C. A. & REID, J. L. (1971). The relationship of plasma concentrations of levodopa to clinical response in Parkinsonism. *Br. J. Pharmac.*, in the Press.

BLOOM, F .E., COSTA, E. & SALMOIRAGHI, G. C. (1965). Anesthesia and the responsiveness of individual neurons of the cat's caudate nucleus to acetylcholine, norepinephrine and dopamine, administered by microelectrophoresis. *J. Pharmac. exp. Ther.*, **150**, 244–252.

CALNE, D. B., KAROUM, F., RUTHVEN, C. R. J. & SANDLER, M. (1969). The metabolism of orally administered L-dopa in Parkinsonism. *Br. J. Pharmac.*, **37**, 57–68.

CALNE, D. B., BRENNAN, J., SPIERS, A. S. D. & STERN, G. M. (1970). Hypotension caused by L-dopa. *Br. med. J.*, **1**, 474–475.

CALNE, D. B., REID, J. L., VAKIL, S. D., RAO, S., PETRIE, A., PALLIS, C. A., GAWLER, J., Thomas, P. K. & Hilson, A. (1971). Idiopathic Parkinsonism treated with an extracerebral decarboxylase inhibitor. *Br. med. J.*, **3**, 729–732.

EBLE, J. N. (1964). A proposed mechanism for the depressor effect of dopamine in the anaesthetised dog. *J. Pharmac. exp. Ther.*, **145**, 64–70.

GODWIN-AUSTEN, R. B., TOMLINSON, E. B., FREARS, C. C. & KOK, H. W. L. (1969). Effects of L-dopa in Parkinson's disease. *Lancet*, **2**, 165–168.

HENNING, M. & RUBENSON, A. (1970). Central hypotensive effect of L-3,4,dihydroxyphenylalanine in the rat. *J. Pharm. Pharmac.*, **22**, 553–560.

MCDOWELL, F. H. (1970). Orthostatic hypotension. In: *L-dopa and Parkinsonism*, ed. Barbeau, A. & McDowell, F. H., pp. 263–264. Philadelphia: Davis.

MCNAY, J. L., MCDONALD, R. H. JUN. & GOLDBERG, L. I. (1965). Direct renal vasodilation produced by dopamine in the dog. *Circulation Res.*, **16**, 510–157.

MCNAY, J. L., & GOLDBERG, L. I. (1966). Comparison of the effects of dopamine, isoproterenol, norepinephrine and bradykinin on canine renal and femoral blood flow. *J. Pharmac. exp. Ther.*, **151**, 23–31.

MARKHAM, C. H., TRECOIKAS, L. & ANSEL, R. D. (1970). Blood pressure in Parkinsonian patients receiving L-dopa. In: *L-dopa and Parkinsonism*, ed. Barbeau, A. & McDowell, F. H., pp. 255–262. Philadelphia: Davis.

ROSS, G. & BROWN, A. W. (1967). Cardiovascular effects of dopamine in the anaesthetised cat. *Am. J. Physiol.*, **212**, 823–828.

SJOERDSMA, A., VENDSALU, A. & ENGLEMAN, K. (1963). Studies on the metabolism and mechanism of action of methyldopa. *Circulation*, **28**, 492–502.

WATANABE, A. M., CHASE, T. N. & CARDON, P. V. (1970). Effect of L-dopa alone and in combination with an extracerebral decarboxylase inhibitor on blood pressure and some cardiovascular reflexes. *Clin. Pharmac. Ther.*, **11**, 740–746.

YAHR, M. D., DUVOISIN, R. C., HOEHN, M. M., SCHEAR, M. J. & BARRETT, R. E. (1969). Treatment of Parkinsonism with levodopa. *Archs Neurol.*, **21**, 343–354.

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