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THE ABSORPTION AND METABOLISM OF A STANDARD ORAL DOSE OF LEVODOPA IN PATIENTS WITH PARKINSONISM

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1 The metabolism of a standard oral dose of levodopa was studied in forty-two patients with Parkinsonism. Plasma levodopa and 3-*o*-methyldopa concentrations were estimated at intervals for 8 h after ingestion and the concentration of homovanillic acid (HVA) in the lumbar cerebrospinal fluid (CSF) was measured at 8 hours. Clinical responses 3 months after the test were compared with these findings.

2 Although therapeutic benefit correlated significantly with calculated estimates of both plasma levodopa concentration and CSF HVA at optimal levodopa dose, individual values were widely scattered. There was no significant correlation between toxic effects and plasma levodopa or CSF HVA; and 3-*o*-methyldopa concentrations similarly did not show a significant correlation with either toxic or therapeutic effects.

3 Blood and CSF levels of levodopa or the metabolites measured in this study were not significantly altered by concurrent treatment with either anticholinergic drugs or amantadine nor by previous treatment with levodopa.

Introduction

The therapeutic effect of levodopa in the treatment of Parkinsonism is most simply explained in terms of the replacement of a dopamine deficiency in the Parkinsonian brain by the conversion of dopa to dopamine in the striatum (Birkmayer & Hornykiewicz, 1961; Barbeau, 1962). This hypothesis was the basis of the original trials of levodopa in the treatment of Parkinsonism since it was known that whereas levodopa can cross the blood-brain barrier dopamine cannot. Clinical experience with levodopa therapy supports this hypothesis in certain respects. Thus the individual patient shows increasing benefit with larger doses of levodopa up to a limit imposed by side effects. Concurrent inhibition of extracerebral decarboxylase increases the amount of circulating levodopa available for cerebral metabolism, and results in therapeutic benefit with a much smaller dose of levodopa (Marsden, Parkes & Rees, 1973).

Response to levodopa therefore presumably depends on availability of levodopa to the brain and its subsequent conversion to dopamine. In order to investigate these relationships we have measured plasma levels of levodopa in response to a standard oral dose of levodopa and have considered our findings in relation to the clinical response to levodopa treatment. We have also determined the dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid (CSF) after the same standard oral dose of levodopa as this is to some extent an index of cerebral dopamine turnover. Another metabolite of levodopa is 3-*o*-methyldopa which is present in the plasma of levodopa treated subjects in considerable quantity as it is cleared and metabolized only slowly. Kuruma, Bartholini & Pletscher (1970) suggested that 3-*o*-methyldopa acts as a reservoir from which

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levodopa and hence dopamine may be derived. Although this does not occur appreciably in man (Calne, Reid & Vakil, 1973), plasma 3-*o*-methyldopa after the standard oral dose of levodopa was determined as other relevant effects of 3-*o*-methyldopa are possible (Chalmers, Baldessarini & Wurtman, 1971).

Methods

Forty-two patients were selected for study. They were all attending the Outpatients' Department for treatment of Parkinsonism at The National Hospital (Queen Square), King's College Hospital (Denmark Hill), General Hospital (Nottingham) or The Derbyshire Royal Infirmary. In all cases the nature of the investigation was explained and the full agreement of the patient obtained. Twenty-two patients were investigated who had received no previous treatment with levodopa. Among the twenty patients who were already on treatment were included four patients with post-encephalitic Parkinsonism, patients who showed the 'on/off' response to treatment, and patients who had obtained no therapeutic benefit from treatment.

The investigations were carried out with the patients in hospital. If the patient was receiving levodopa treatment this was stopped more than one week before the investigations were performed. Other medication was continued unchanged. No sulphonamide, salicylate, butyrophenone or phenothiazine was administered before the investigations.

Levodopa (1.5 g) was given to each subject by mouth at 09.00 hours. At 0, 0.5, 1, 2, 4, 6 and 8 h later blood (10 ml) was collected into lithium-heparin tubes. Plasma was separated immediately upon collection, sodium EDTA (1 mg/ml) 0.1 ml/ml plasma added and the plasma stored in the deep freeze. CSF (8 ml) was taken by lumbar puncture 8 h after the oral dose of levodopa because it has been shown that the peak level for amine metabolites in the CSF after oral administration of an amine precursor is at this time (Eccleston, Ashcroft, Crawford, Stanton, Wood & McTurk, 1970). The CSF sample was stored in the deep freeze.

Plasma levodopa and 3-*o*-methyldopa were determined by the method of Curzon, Kantamaneni & Trigwell (1972). CSF HVA was determined as described by Curzon, Godwin-Austen, Tomlinson & Kantamaneni (1970) except that following Pullar, Weddell, Ahmed & Gillingham (1970), 0.1 M borate buffer (pH 6.8) was used instead of phosphate buffer.

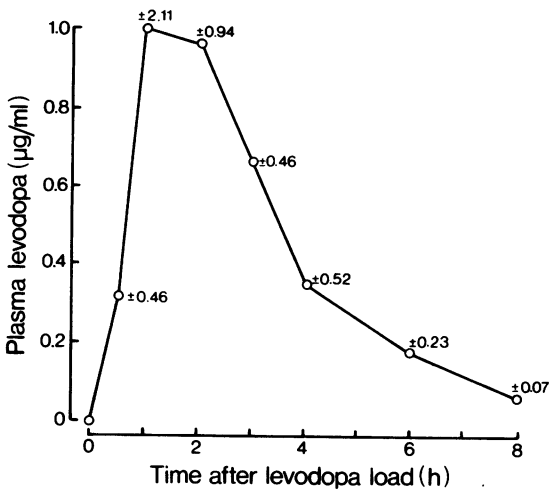

Fig. 1 Plasma levodopa concentrations (mean ± 1 s.d.) after an oral dose of levodopa (1.5 g) to 42 Parkinsonian subjects.

Results

Concentrations of levodopa and its metabolites in body fluids after loading with levodopa

Plasma levodopa. Plasma levodopa concentrations following an oral load of 1.5 g are shown in Figure 1. Mean concentrations were maximal 1-2 h after administration and then fell, reaching half peak values at 3.5 h and negligible concentrations 8 h after loading. Standard deviations were relatively greater during the first hour after loading when plasma levodopa was increasing than during its subsequent fall. Peak concentrations varied widely from subject to subject ranging up to ten times the mean peak concentration. The shape of the plasma levodopa curve also varied widely with peak concentrations occurring between 0.5 and 4 h after loading. Figure 2 illustrates how different the curve may be for different subjects. The peak height of the plasma levodopa curve was measured in each subject and the area beneath the curve ('total plasma levodopa') was calculated. Relationship between these two measurements and clinical features were calculated.

Concurrent treatment with either anticholinergic drugs or amantadine was not associated with any significant difference in peak levodopa concentration or total plasma levodopa (Table 1).

Previous treatment with levodopa did not appear to affect the absorption or metabolism of the standard dose of levodopa (although those on

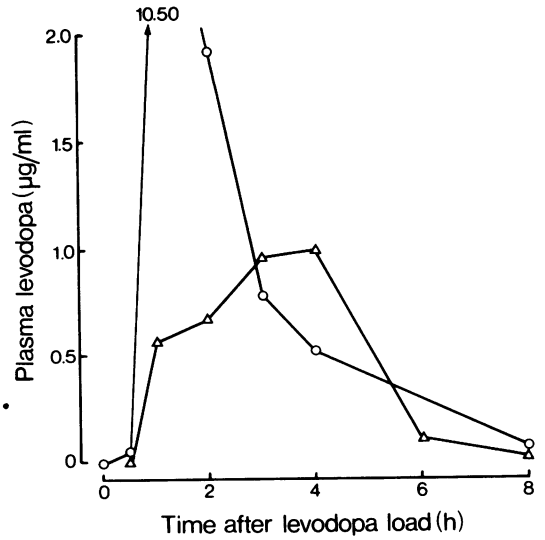

Fig. 2 Plasma levodopa concentrations in two subjects after oral dose of levodopa (1.5 g) to show extreme variability of response.

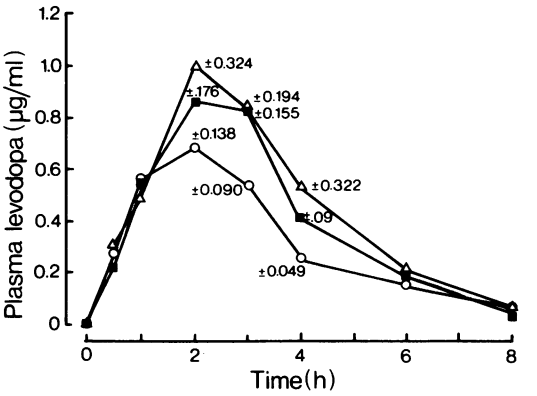

Fig. 3 Plasma levodopa concentrations (mean ± 1 s.d.) after an oral dose of levodopa (1.5 g) to patients separated into groups: (○) No previous levodopa (n = 21); (△) Treatment with levodopa for less than 1 year (n = 10); (■) Treatment with levodopa for more than 1 year (n = 8).

levodopa prior to the test stopped treatment a week beforehand). Figure 3 compares plasma levodopa concentrations in 21 patients who had not received levodopa treatment with those in ten patients on prior therapy for less than 1 year, and 8 patients who had taken the drug for more than a year. No significant differences were noted.

Plasma 3-o-methyldopa. Plasma 3-o-methyldopa concentration rose gradually, consistently reaching a maximum later than the levodopa peak (Figure 4). Mean concentrations rose linearly to a value at 4 h after levodopa administration which was essentially the same as that found 8 h after loading.

Patients who had been on treatment with levodopa prior to the standard dopa load test but in whom levodopa had been withdrawn at least one week previously showed no detectable 3-o-methyldopa in the plasma before the standard oral levodopa load. Concurrent treatment with anticholinergics, amantadine or both did not affect 3-o-methyldopa concentration.

Cerebrospinal fluid homovanillic acid. Lumbar CSF HVA concentration at 8 h after levodopa loading was 147 ± 14 ng/ml (34 subjects). Comparison with a value of 14 ± 9 ng/ml (26 subjects) obtained on a different group of Parkinsonian subjects who had not been given levodopa demonstrated a large increase of CSF HVA following a single levodopa load.

Previous treatment with levodopa (withdrawn a week before the test) had no apparent effect on CSF HVA values. Mean value for 9 patients who

Table 1 Plasma levodopa, plasma 3-o-methyldopa and CSF HVA levels (mean ± s.e. mean) after standard levodopa load (1.5 g) in relation to other drugs taken at time of test

	No other drugs	*Anticholinergics**	*Amantadine*	*Anticholinergics and amantadine*
Number of patients	6	17	9	9
Peak plasma levodopa (μg/ml)	0.87 ± 0.17	2.26 ± 0.75	0.94 ± 0.12	1.25 ± 0.31
Total plasma levodopa (μg/ml)	3.07 ± 0.38	4.61 ± 0.79	3.16 ± 0.47	3.62 ± 1.12
Plasma 3-o-methyldopa (μg/ml)	1.84 ± 0.31	1.56 ± 0.15	1.62 ± 0.22	1.54 ± 0.38
CSF HVA (ng/ml)	111 ± 20	176 ± 28	161 ± 25	131 ± 29

* Nine of these 17 patients were taking benzhexol.
None of the differences reach statistical significance at less than the 5% level.

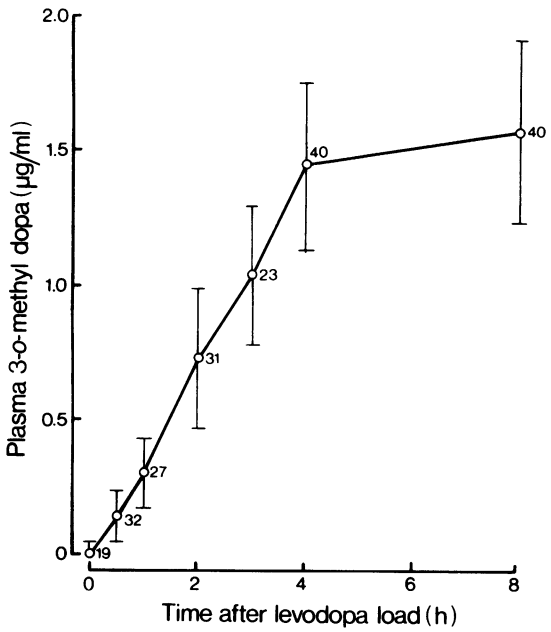

Fig. 4 Plasma 3-*o*-methyldopa concentration after an oral dose of levodopa (1.5 g). Bar lines indicate ±1 s.d. and the number of subjects for each point is given.

had not taken the drug before was 149 ng/ml, while in 11 patients who had, it was 146 ng/ml (in 5 who had taken the drug for more than a year the figure was 146 ng/ml also).

Relation between plasma levodopa, plasma 3-o-methyldopa and CSF homovanillic acid. The total area under the levodopa curve was significantly and positively correlated with the 3-*o*-methyldopa level 8 h after loading ($r = 0.396$, $P = 0.01$, 39 subjects). There was no clear correlation between peak levodopa concentration and 3-*o*-methyldopa concentration ($r = 0.218$, NS, 39 subjects).

The data was also analysed to determine the relation of CSF HVA concentrations after levodopa loading to plasma levodopa concentration. A difficulty here derives from the wide range of times at which plasma levodopa attains its peak value and the likelihood of a considerable time lag between the appearance of a plasma levodopa peak and any subsequent CSF HVA peak. Thus there was no correlation between peak levodopa concentration and CSF HVA in the 33 subjects studied ($r = 0.103$, NS). However, when only those 17 subjects were considered in whom peak levodopa concentration occurred within 1-2 h of loading, a significant positive correlation emerged ($P < 0.01$). For the whole group there was also no correlation between total plasma levodopa and CSF HVA ($r = 0.225$, NS, 33 subjects). However, 3 subjects had extraordinarily high total plasma levodopa levels of 11.50, 11.9 and 13.0, the mean total plasma levodopa for all subjects being 3.79 (± 1 s.d., 2.73) mg/ml. Also 2 other subjects had strikingly high CSF HVA concentrations, 469 and 298 mg/ml, compared with the mean of 147 ± 81 (1 s.d.) for the whole group. When these 5 subjects were excluded, and the relationship of peak levodopa concentration and total levodopa levels to CSF HVA were recalculated for the remaining 28 subjects, significant positive correlations emerged (for peak levodopa concentration *v.* CSF HVA, $r = 0.400$, $P < 0.05$; for total plasma levodopa *v.* CSF HVA, $r = 0.514$, $P < 0.01$). However, the considerable scatter of values implies that though peak levodopa concentration and total levodopa level have predictive value for CSF HVA in a group of subjects, it has little predictive value for individual subjects.

There was no significant correlation between 3-*o*-methyldopa concentration 8 h after the levodopa load and CSF HVA concentration at that time.

Correlations between clinical response and biochemical results

The clinical response of 39 patients after more than 3 months subsequent treatment with levodopa at various dosages was compared with plasma levodopa levels, plasma 3-*o*-methyldopa levels and CSF HVA after the standard oral dose. While the majority of patients were treated with levodopa alone, 11 of the patients from King's College Hospital were treated with levodopa plus α-methyldopahydrazine, the latter in a fixed dose of 200 mg daily. No significant correlation was found between the biochemical parameters and determined response to treatment (Table 2). There was no patient in this series in whom failure to respond to levodopa could be explained by failure to absorb levodopa and the plasma concentrations of levodopa and the CSF HVA levels did not differ significantly between those 9 patients who showed a therapeutic response of less than 20% and the 20 patients with a clinical response greater than 50%.

But the therapeutic dose of levodopa for the patients in this investigation (excluding those on α-methyldopahydrazine as well) varied between 0.5 g daily and 4.5 g daily with a mean daily dose of 2.5 ± 0.8 g. Thus the clinical response to treatment was in most cases assessed at a very different dose of levodopa than that used for the standard levodopa load. In order to correct for this variation in dosage the patient's optimal levodopa dose was divided by the dose given for the

levodopa load test (1.5 g). When the plasma levodopa after the standard oral dose was multiplied by this factor an index of the possible circulating plasma levodopa in each patient while taking their optimal dose was obtained. The implicit assumption of a linear relation between plasma levodopa concentration and dose of levodopa in the therapeutic range seems reasonable (Dunner, Brodie & Goodwin, 1971).

When this correction was used a significant correlation between response to treatment and 'corrected total plasma levodopa' was found in the 28 patients who were subsequently treated with levodopa. This correlation existed both between the patients showing little or no response (< 20% improvement) when compared with those who gained significant benefit (> 20% improvement) ($P < 0.01$) and between those patients with no response and those with moderate response (20-50%) ($P < 0.01$). There was no significant difference between those with no response and those with a considerable response (> 50% improvement). However there was a large scatter of values in the latter group (Table 3).

These findings suggest that there is a relationship between clinical response to levodopa and effective circulating plasma levels of levodopa. There was also a significant correlation between corrected 3-*o*-methyldopa levels and this clinical response (Table 3).

Comparison between CSF HVA after levodopa loading and clinical response after 3 months of levodopa treatment showed no significant relationship. However, when CSF HVA was corrected for levodopa dosage (i.e. multiplied by the patient's optimal levodopa dose divided by 1.5) it was found that clinical benefit was associated with a higher corrected CSF HVA level. Thus mean 'corrected CSF HVA levels' were higher in those patients with moderate improvement (20-50%) and those with considerable improvement (>50%) when compared with patients showing little or no improvement (<20%) ($P = 0.05$ and $P < 0.02$ respectively) (Table 3). These findings suggest that there is a relationship between clinical response to levodopa and CSF HVA levels.

In those taking levodopa alone, there was no relation between final optimal levodopa dose and peak plasma levodopa concentration, total plasma levodopa, 3-*o*-methyldopa, or CSF HVA. Nor was there a significant difference in optimum levodopa dosage between those who gained improvement and those who did not.

Table 2 Relation of plasma levodopa, plasma 3-*o*-methyldopa and CSF HVA levels (mean ± s.e. mean) after standard dopa load (1.5 g) to therapeutic response after 3 months treatment

	<20% Improvement	*20-50% Improvement*	*>50% Improvement*
Number of patients	9	10	20
Peak plasma levodopa (μg/ml)	0.94 ± 0.07	1.41 ± 0.32	1.92 ± 0.65
Total plasma levodopa (μg/ml)	2.77 ± 0.18	4.38 ± 1.03	4.06 ± 0.70
Plasma 3-*o*-methyldopa (μg/ml)	1.56 ± 0.23	1.77 ± 0.36	1.57 ± 0.15
CSF HVA (ng/ml)	108 ± 24	198 ± 39	150 ± 13

None of the differences reach statistical significance at the 5% level.

Table 3 Relation of plasma levodopa, plasma 3-*o*-methyldopa and CSF HVA levels (mean ± s.e. mean) corrected for optimal levodopa dose after 3 months treatment to therapeutic response at that time

	<20% Improvement	*20-50% Improvement*	*>50% Improvement*
Number of patients	7	8	13
Mean levodopa dose (g/day)	2.0 ± 0.5	2.6 ± 0.2	2.7 ± 0.3
Peak plasma levodopa (μg/ml)	1.18 ± 0.30	2.64 ± 0.46*	4.72 ± 1.99
Total plasma levodopa (μg/ml)	3.66 ± 0.94	8.09 ± 0.94**	9.00 ± 2.21
		8.65 ± 1.39**	
Plasma 3-*o*-methyldopa (μg/ml)	1.54 ± 0.34	3.14 ± 0.32	2.94 ± 0.44
CSF HVA (ng/ml)	128 ± 44	396 ± 96*	286 ± 30*

* Differs from mean for those with <20% improvement at 5% level.
** Differs from mean for those with <20% improvement at 1% level.

Four patients were suffering from post-encephalitic Parkinsonism. These patients showed similar HVA levels in the CSF after standard levodopa load (mean 0.16 ± 0.05) to other patients in the series with idiopathic Parkinsonism (HVA mean 0.14 ± 0.08). Likewise there was no significant difference between these two groups in total plasma levodopa or 3-*o*-methyldopa levels.

Correlation between side effects and biochemical results

Twenty-two patients developed abnormal movements as a toxic effect of levodopa. This group was compared with the 16 patients who did not show this complication. No biochemical differences could be demonstrated between these two groups. Even when CSF HVA and total plasma levodopa were corrected for optimal levodopa dose there was no significant difference between those who developed abnormal movements and those who did not (Table 4). Severity of abnormal movements often varied with time after a given dose of levodopa but there did not appear to be any correlation between peak height of plasma levodopa and abnormal movements.

Nine patients showed the variability of response that has been described as 'on/off response' or hypotonic episodes' (Barbeau, 1971). In all these patients, the beneficial effects of levodopa were lost for periods of between 0.05 and 2 hours. During this time the patients were generally akinetic but showed little or no rigidity. Abnormal movements were evident in some. The relationship of this effect to timing of dose appeared to follow a pattern in the individual patient and by adjusting size of dose or the timing of separate doses some mitigation of the side effect could usually be achieved. It therefore seemed likely that a correlation between plasma levodopa kinetics and this 'on/off response' might be demonstrable. No such relationship to the absorption or clearance of levodopa after the single standard oral dose could be shown. However two patients who developed 'on/off' effect had peak plasma levodopa levels among the four highest levels of plasma levodopa in this study. The levels of HVA in the CSF did not differ significantly between the two groups. 'Corrected total plasma levodopa' and 'corrected CSF HVA levels' likewise showed no correlation with 'on/off' response (Table 4).

Patients who complained of nausea and vomiting did not appear to differ in their absorption or metabolism of levodopa when compared with those who did not show these effects. Similarly 'corrected total plasma dopa' and 'corrected CSF HVA levels' did not show any correlation with nausea or vomiting during subsequent treatment (Table 4). Accurate records of the development of nausea or vomiting during the levodopa load test were available for 20 patients, 5 of whom vomited and 7 of whom experienced nausea during the test. Parameters of levodopa absorption and metabolism in these 12 patients were no different from the 8 patients who did not develop this side effect. Five of the 12 patients with nausea or vomiting had peak plasma levodopa levels of less than 1.0 μg/ml whereas 3 of 8 without these symptoms had peak levodopa levels of more than 1.0 μg/ml.

Discussion

Absorption from the gastro-intestinal tract is an obvious requirement for therapeutic effectiveness

Table 4 Relation of plasma levodopa, plasma 3-*o*-methyldopa and CSF HVA levels (mean ± s.e. mean) corrected for optimal levodopa dose after 3 months treatment to side effects

	Abnormal movements		*'On/off' effect*		*Nausea and vomiting*	
	Yes	*No*	*Yes*	*No*	*Yes*	*No*
Number of patients	12	16	5	15	15	13
Mean levodopa dose (g/day)	2.7 ± 0.3	2.3 ± 0.2	2.9 ± 0.2	2.4 ± 0.3	2.7 ± 0.3	2.2 ± 0.2
Peak plasma levodopa (μg/ml)	3.51 ± 1.30	3.05 ± 1.39	5.95 ± 2.95	3.10 ± 1.47	4.47 ± 1.71	1.82 ± 0.41
Total plasma levodopa (μg/ml)	7.69 ± 1.31	7.19 ± 1.77	9.42 ± 2.73	7.62 ± 1.82	8.96 ± 1.91	5.61 ± 0.92
3-*o*-methyldopa (μg/ml)	3.34 ± 0.42	2.16 ± 0.32*	3.60 ± 0.73	2.51 ± 0.38	2.71 ± 0.39	2.47 ± 0.40
CSF HVA (ng/ml)	239 ± 39	312 ± 58	264 ± 25	311 ± 73	276 ± 32	294 ± 74

* Difference significant at 5% level.

of levodopa and treatment failure has been reported in which levodopa was not being adequately absorbed (Rivera-Calimlim, Dujovne, Morgan, Lasagna & Bianchine, 1970). Also, anticholinergic drugs reduce gastric motility and might thereby diminish or delay absorption of levodopa. However, in none of our patients was failure to respond to levodopa treatment correlated with slow or reduced absorption of a standard oral dose of levodopa; nor did concurrent treatment with amantadine or anticholinergic drugs appear to affect absorption.

There was considerable variation between patients in blood levels of levodopa, indicative of wide variability of rates of absorption and clearance. There was a significant correlation between calculated estimates of plasma levodopa concentration at optimal levodopa dose and therapeutic effect. Similarly calculated CSF HVA concentrations also correlated with therapeutic benefit.

Thus a therapeutic response to levodopa appears to be related to plasma levodopa levels and to cerebral dopamine turnover inasmuch as this is indicated by CSF HVA, but no correlation between corrected plasma levodopa and corrected CSF HVA levels and toxic effects could be demonstrated. In particular we were unable to show any consistent difference between plasma levodopa in a group of 9 patients who showed the 'on/off' response, and values found for the other subjects. This finding is in contrast to that of Claveria, Calne & Allen (1973), but it must be emphasized that we were measuring plasma levodopa after a single oral dose. It may well be that repeated plasma levodopa estimations throughout the day may correlate with 'on/off' phenomena occurring during therapy.

Animal experiments indicate that the *o*-methylation of levodopa to 3-*o*-methyldopa might have both positive and negative influences on levodopa action. For example, as 3-*o*-methyldopa has a long half life and can be demethylated to levodopa *in vivo* it was suggested to act as a levodopa reservoir (Bartholini, Pletscher & Kuruma, 1970). Also, the methylation of levodopa could result in the depletion of methionine and as this is also required for the destruction of dopamine in the synaptic cleft increased functional efficiency of dopamine might ensue (Chalmers *et al.*, 1971). Conversely, 3-*o*-methyldopa, being like levodopa an aromatic amino acid, might interfere with transport of the latter to the brain and thus diminish its therapeutic effect. Results obtained in the present study, however, point neither to a positive nor negative role of 3-*o*-methyldopa in the therapeutic action of levodopa. The lack of benefit in Parkinsonian patients given 3-*o*-methyldopa (Calne *et al.*, 1973) is consistent with this finding.

There is an expected correlation between plasma levodopa and CSF HVA but this correlation can only be demonstrated when the results are analysed as a group because considerable inter-patient variation exists. This variability probably reflects differences between patients of extra cerebral metabolism of dopa. However, the observed correlation indicates that the turnover of dopamine in the brain (as reflected in CSF HVA) is dependent on the concentration of levodopa in blood reaching the brain. Thus the higher the plasma levodopa the greater the CSF HVA. Since plasma levodopa is more or less linearly related to levodopa dosage (Dunner *et al.*, 1971), this indicates, albeit indirectly, that the greater the dose of levodopa given the more the brain metabolizes dopamine to form HVA. Clinical experience indicates that the therapeutic benefits of levodopa in the individual patient depend on the dose given, up to the limit imposed by side effects. Taken together these two observations are consistent with the hypothesis that the symptoms of Parkinson's disease are due to striatal dopamine deficiency (Hornykiewicz, 1973) and that levodopa is effective because it replaces this deficiency. This conclusion receives further support from the observed relationship of success of treatment to corrected plasma levodopa levels and corrected CSF HVA concentrations.

The results presented here show that it is not possible to predict the toxic or therapeutic effects of levodopa in the individual by biochemical investigations of plasma levodopa levels or CSF HVA after a standard oral levodopa load. There is great variation in the optimal dose of levodopa tolerated by different patients and this variation does not correlate with differences in rate of absorption or clearance of levodopa. It is likely that differences in optimal therapeutic dosage reflect differences in receptor sensitivity to dopamine. By analogy with animal experiments (Anden, Dahlstrom & Fuxe, 1966; Ungerstedt, 1971), there are good reasons to suspect that the corpus striatum lacking its normal nigro-striatal input in Parkinson's disease may show the phenomenon of denervation supersensitivity to dopamine. The degree of such change in receptor sensitivity may be as important as the amount of levodopa reaching the brain in determining the levodopa dose required to produce the best clinical response to treatment, and also some of its side effects.

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