

3-O-Methyldopa and the Response to Levodopa in Parkinson's Disease

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Plasma 3-O-methyldopa (3OMD) concentrations in parkinsonian patients treated with levodopa on a long-term basis reflect daily levodopa dosage and do not vary markedly during the day. Oral challenges with 3OMD reduce the clinical response to levodopa infusions, but 3OMD is no more potent than phenylalanine in this regard. These observations, plus the fact that 3OMD makes a small contribution to the total concentration of large neutral amino acids competing with levodopa for transport at the blood-brain barrier, support the contention that 3OMD is not an important determinant of clinical response to levodopa.

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3-O-Methyldopa (3OMD), an *O*-methylated metabolite of levodopa, has a 15-hour half-life [5, 18] and therefore accumulates during long-term levodopa therapy so that plasma levels of 3OMD are often several times higher than those of levodopa [9, 16, 17]. 3OMD does not bind to the dopamine receptor [21] and has no recognized direct pharmacological actions. However, 3OMD is a large neutral amino acid and is transported by the same saturable carrier system that transports levodopa and other large neutral amino acids [19]. Thus, 3OMD can compete with these other amino acids for transport at the blood-brain barrier. The coadministration of 3OMD and levodopa reduces brain levodopa and dopamine concentrations [4, 7, 14] and decreases levodopa-induced motor activity [7, 15].

Three clinical observations suggest that 3OMD influences the response to levodopa in patients with Parkinson's disease. First, dyskinesia may be associated with elevated levels of 3OMD [2, 3]. Second, the 3OMD/levodopa ratio is increased in patients with a poor response to the drug [16, 17]. Third, coadministration of 3OMD and levodopa reduced the response to levodopa in parkinsonian patients [8]. We have attempted to evaluate the clinical importance of 3OMD in patients with a fluctuating response to levodopa by investigating (1) the relationship of 3OMD plasma concentrations to single and multiple levodopa doses; (2) the diurnal variation of plasma 3OMD levels; and (3) the ability of 3OMD to antagonize the effects of levodopa.

Methods

Thirty-four patients with idiopathic Parkinson's disease participated in these studies after giving informed consent. Six

patients had not previously received dopaminergics. Six patients who had been treated long-term with levodopa had no clinically apparent fluctuations. Twenty-two long-term-treated patients had fluctuations that consisted of classic "peak-dose" and "wearing off" effects as well as more complex fluctuations ("on-off"). All levodopa-treated patients were also receiving carbidopa. Other medications included anticholinergics (14 patients), dopamine agonists (12 patients), and amantadine (2 patients).

Plasma concentrations of 3OMD were studied under several conditions. To determine the contribution of a single dose of levodopa to the plasma 3OMD level, plasma 3OMD and levodopa concentrations were monitored hourly following a single oral dose of levodopa in 6 previously untreated patients. To determine diurnal variation in plasma 3OMD concentrations, 3OMD levels were measured hourly in 5 patients with fluctuations who were receiving levodopa every 2 to 3 hours throughout the day. The relationship between the plasma 3OMD level and total daily levodopa dose was examined in 28 patients by measuring 3OMD at 9 AM when the patients had been without levodopa overnight.

To examine the effect of 3OMD on the clinical response to levodopa, orally administered 3OMD challenges (100 mg/kg) were given to 4 patients with fluctuations during long, constant levodopa infusions, once steady-state plasma levodopa levels and constant motor responses were achieved [11]. To estimate the relative potency of 3OMD in inhibiting levodopa transport, 3OMD, phenylalanine, and glycine or lysine challenges (100 mg/kg) were given to 6 patients with fluctuations during 2-hour infusions of levodopa. The effects of the amino acid challenges on the duration of the clinical response following discontinuation of the infusion were compared. The order of phenylalanine and the control amino acid (glycine or lysine) was randomized. 3OMD was given last in 5 of the 6 patients because of its long plasma half-life. The patients were unaware of which amino acid was administered; the evaluating nurses were generally, but not always,

blind to the amino acid administered. Two-hour infusions followed overnight levodopa abstinence, but other antiparkinsonian agents were continued. Carbidopa (25 mg orally) was administered 1 hour before the infusions and repeated every 2 hours until completion of each study.

The patients' motor state was monitored by the speed with which a patient could alternately tap two counters, rise from a chair, walk a measured distance, and return to the chair [11]. Plasma levodopa and 3OMD levels were measured by high-performance liquid chromatography using electrochemical detection [12]. Detection limits for 3OMD were 50 pmol/ml.

Results

Plasma 3OMD Levels after a Single Levodopa Dose

Five of 6 untreated parkinsonian patients had no detectable 3OMD in their plasma prior to receiving levodopa. Single oral doses of 1 or 3 mg/kg of levodopa, preceded by 50 mg of carbidopa 1 hour before, produced peak 3OMD levels of 1.9 ± 1.1 nmol/ml (mean \pm standard deviation) (Table 1), occurring 4 hours after levodopa administration. This suggests that each individual dose of levodopa contributes very little to the plasma concentration of 3OMD seen during long-term use of the drug.

Hourly 3OMD Concentrations during Long-term Levodopa Therapy

3OMD levels were monitored hourly in 5 patients receiving levodopa combined with carbidopa every 2 to 3 hours throughout the day. 3OMD levels were relatively constant throughout the day (Fig 1). The standard deviations of the means averaged 9% of the mean concentrations.

Relationship between Plasma 3OMD Level and Daily Levodopa Dose

Plasma 3OMD levels were significantly correlated with the total daily levodopa dose in patients with a stable

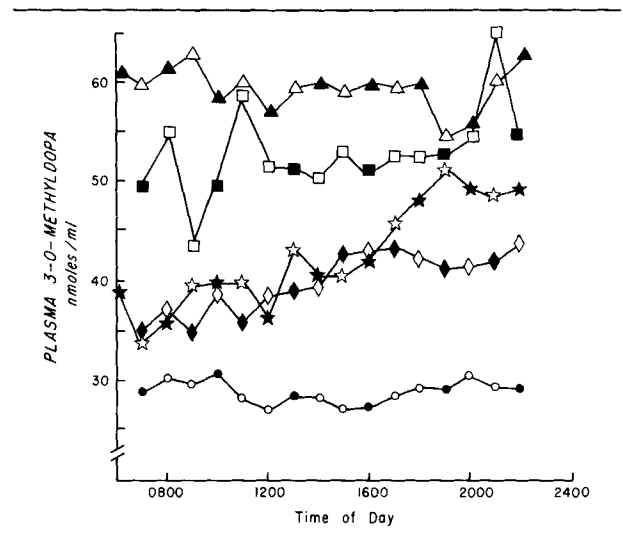


Fig 1. Hourly plasma 3-O-methyldopa concentrations in 5 patients with fluctuations. Darkened symbols represent levodopa administration. (○ = 25/100 {25 mg of carbidopa and 100 mg of levodopa} every 3 hours; △ = 20/200 every 2 hours; □ = 30/300 every 3 hours; ◇ = 10/100 every 2 hours; ☆ = 20/200 every 2 hours.)

response to therapy and in those with a fluctuating response (Fig 2).

Plasma 3OMD Levels after Oral Challenges with 3OMD

Oral 3OMD challenges (100 mg/kg) in 10 patients produced average peak plasma 3OMD levels of 689 ± 188 nmol/ml, occurring 2 ± 1.2 hours after administration. This is comparable to the elevated concentrations of plasma phenylalanine, leucine, or isoleucine observed with 100-mg/kg oral challenges of these amino acids in a previous study [11].

Table 1. Plasma 3OMD Levels after First Dose of Levodopa in Previously Untreated Patients^a

Patient No.	Dose (mg/kg)	Plasma 3OMD (nmol/ml)				
		0 hr	1 hr	2 hr	3 hr	4 hr
1	1	0	0	0.9	1.5	1.7
2	1	0	0.8	1.0	1.2	1.2
3	1	0	0.5	1.6	1.6	1.8
4	1	0	0.5	1.0	1.3	1.2
5	3	0.2	0.1	1.4	4.0	4.0
6	1	0	0.2	0	1.1	1.5
Mean		0	0.4	1.0	1.8	1.9
SD		0.1	0.3	0.6	1.1	1.1

^aCarbidopa (50 mg orally) was given 1 hour before levodopa administration, and 25 mg was given every 2 hours thereafter until completion of blood sampling.

3OMD = 3-O-methyldopa.

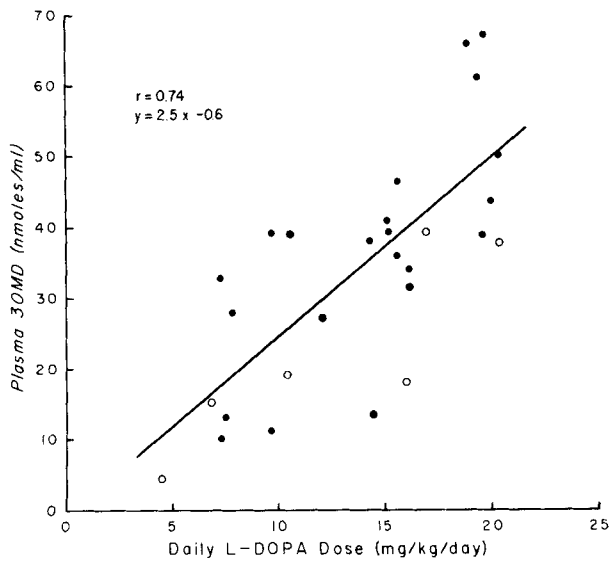


Fig 2. Correlation between fasting plasma 3-O-methylidopa (3OMD) concentration and daily levodopa dosage in patients treated long term with levodopa ($p < 0.001$). Open circles indicate patients with a stable response to levodopa.

3OMD Challenges during Long Levodopa Infusion

3OMD challenges (100 mg/kg orally) were given during four prolonged levodopa infusions. In 1 patient there was a striking reduction in the clinical response following administration of 3OMD (Fig 3), but the effect was mild or equivocal in the other 3. In none of these 4 patients was dyskinesia increased by 3OMD administration.

3OMD Challenges during Short Infusions

The duration of clinical response following a 2-hour levodopa infusion is proportional to the peak plasma concentration achieved during the infusion [10]. This suggests that the effect of an amino acid challenge on response duration might be a sensitive indicator of antagonism of levodopa's clinical effect. The large neutral amino acids, phenylalanine and 3OMD, reduced the duration of the clinical response compared to challenges with glycine or lysine, amino acids that do not use the large neutral amino acid transport system and would not be expected to interfere with levodopa's effect (Fig 4). Phenylalanine was slightly, but not statistically, more potent than 3OMD in antagonizing the effects of levodopa (Table 2).

Discussion

Plasma 3OMD levels are relatively constant in patients receiving levodopa on a long-term basis, as would be predicted from its known plasma half-life of 15 to 17 hours [5, 18]. Furthermore, each dose of levodopa probably makes a small contribution to the overall plasma 3OMD concentration, as indicated by the small

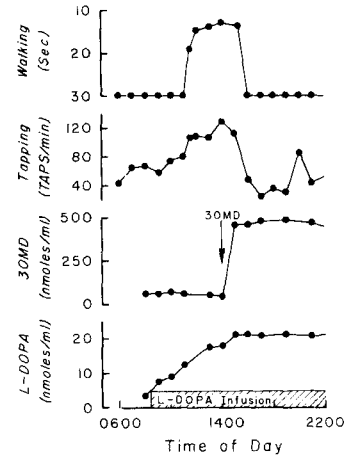


Fig 3. A 3-O-methylidopa (3OMD) challenge (100 mg/kg orally) during constant levodopa infusion abolished the clinical response to levodopa (worsening of tapping, and walking) from 3 PM to 10 PM.

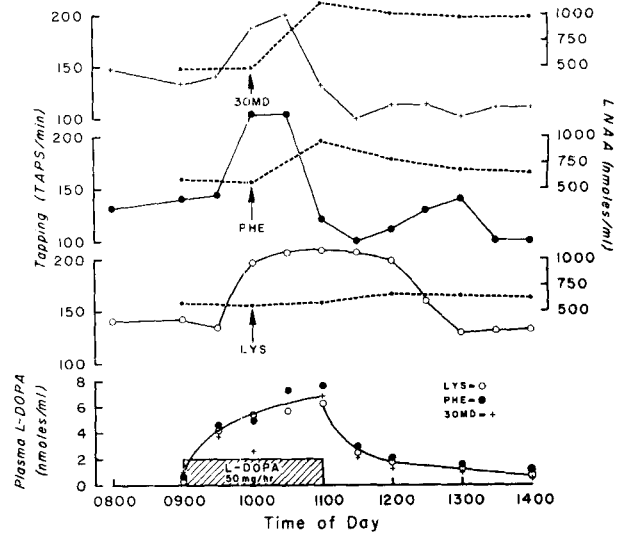


Fig 4. Response of a single patient to challenges with lysine (LYS), phenylalanine (PHE), and 3-O-methylidopa (3OMD) (100 mg/kg orally) during 2-hour infusions on 3 successive days. The lower panel illustrates plasma levodopa concentrations during the infusions (\circ = short infusion when lysine challenge administered; \bullet = infusion with phenylalanine challenge; $+$ = infusion with 3OMD challenge.) The solid lines in the upper panels show the tapping scores on the various days with an increase in tapping representing improvement in motor performance. The dotted line shows the plasma concentration of large neutral amino acids (LNAA) (sum of tyrosine, phenylalanine, leucine, isoleucine, valine, histidine, and 3OMD). Lysine, a basic amino acid, did not alter the concentration of the large neutral amino acids.

Table 2. Effect of Phenylalanine and 3OMD Challenges on Duration of Clinical Effect of 2-Hour Levodopa Infusions

Patient No.	AUC ^a (% control)	
	Phe	3OMD
1	54	85
2	3	0
3	24	73
4	0	19
5	0	22
6	56	34
Mean	23 ^b	39 ^b

^aArea under the time-tapping score curve (Patients 1–3, 6) or time-walking score curve (Patients 4 and 5) for the 3 hours following discontinuation of the infusion. Values are the percentage of area under the curve (AUC) relative to the AUC for challenges with lysine or glycine (control).

^bSignificantly different from control ($p < 0.05$) by one-way analysis of variance with repeated measures and difference between individual means judged by least-significant-difference test.

Phe = phenylalanine; 3OMD = 3-O-methyldopa.

rise in the plasma 3OMD level in the untreated patients after their first dose of levodopa [1, 18; present data]. The diurnal fluctuations in the plasma 3OMD level that do occur may represent a redistribution of 3OMD within body tissues rather than additional 3OMD formed from each dose of levodopa. The plasma levels of 3OMD achieved during prolonged dosing appear to reflect largely the total levodopa dosage, as has been suggested previously [2, 13, 16, 18], despite the fact that the red blood cell concentration of catechol-O-methyltransferase may differ fourfold [20]. Similarly, a correlation between daily levodopa dose and brain 3OMD concentrations has been noted in autopsy material [6].

The plasma 3OMD/levodopa ratio has been suggested to be a predictor of clinical response [16, 17]. The preceding observations indicate that interpatient variations in the 3OMD/levodopa ratio will largely reflect differences in the temporal pattern of plasma levodopa concentrations because the 3OMD levels are predictable from the daily dose and do not vary markedly during the day. Plasma levodopa concentrations are proportional to infusion rate [10], and therefore the fluctuations in plasma levodopa concentrations after oral administration primarily represent variations in levodopa absorption. Plasma levodopa levels fluctuate very rapidly because of rapid redistribution and metabolism of the drug and variable absorption influences timing and number of peaks. Thus, the 3OMD/levodopa ratio would appear to be a rather capricious indicator unless plasma levodopa levels are monitored very frequently to accurately determine peak plasma levodopa levels or area under the plasma concentration curve. We would interpret the reports of high 3OMD/

levodopa ratios as indicating large daily doses of levodopa and/or slow absorption of levodopa and not necessarily evidence for a difference in levodopa metabolism. However, we cannot exclude that a subpopulation of patients have a quantitatively different peripheral metabolism of levodopa, as we did not specifically study "nonresponders."

By the same reasoning, the correlation between elevated plasma 3OMD and dyskinesia [3] could in reality be an association between daily dose of levodopa and dyskinesia. Certainly, an argument against 3OMD directly causing dyskinesia is the observation that the large oral doses of 3OMD did not produce or increase dyskinesia in our patients, but instead produced akinesia and tremor.

3OMD challenges can block the clinical effects of levodopa as demonstrated in our patients receiving levodopa infusions. This is consistent with findings in animal studies in which coadministration of levodopa and 3OMD reduced brain levels of levodopa and dopamine [4, 14] and decreased the pharmacological effects of levodopa [7, 15]. The question then becomes: Are the plasma levels of 3OMD present during long-term dosing sufficient to alter the flux of levodopa into the brain? As the total concentration of large neutral amino acids in plasma ranges from 450 to 700 nmol/ml and plasma 3OMD levels vary from 15 to 70 nmol/ml, 3OMD is a relatively small contributor to the total large neutral amino acid pool competing with levodopa for entry into the brain. However, if 3OMD had a particularly high affinity for the transport system, its influence might be out of proportion to its plasma concentration. Comparison of the effect of 3OMD and phenylalanine on levodopa response during the short infusions suggests that 3OMD is no more potent than phenylalanine in antagonizing the effects of levodopa. Thus, 3OMD does not appear to have an unusually high affinity for the transport system, an observation that is consistent with estimates for transport equilibrium constants in animals [19].

In conclusion, although 3OMD is capable of blocking the clinical effects of levodopa, it is unlikely to play a major role in the response to levodopa during normal dosing because: (1) the plasma levels of 3OMD do not fluctuate widely; (2) 3OMD represents a small proportion of the total large neutral amino acids competing with levodopa for transport across the blood-brain barrier; and (3) 3OMD does not have a higher affinity for the transport system than do other large neutral amino acids.

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References

1. Curzon G, Kantamaneni BD, Trigwell J: A method for determination of DOPA and 3-*O*-methyldopa in the plasma of parkinsonian patients. *Clin Chim Acta* 37:335-341, 1972
2. Durso R, Feldman RG, Szabo G: Plasma and CSF 3-*O*-methyldopa levels in Parkinson's disease. *Neurology* 35(Suppl 1):223, 1985
3. Feuerstein C, Tanche M, Serre F, et al: Does *O*-methyldopa play a role in levodopa-induced dyskinesias? *Acta Neurol Scand* 56:79-82, 1977
4. Gervas JJ, Muradas V, Bazan E, et al: Effects of 3-*OM*-dopa on monoamine metabolism in rat brain. *Neurology* 33:278-282, 1983
5. Kuruma I, Bartholini G, Tissot R, Pletscher A: The metabolism of L-3-*O*-methyldopa, a precursor of dopa in man. *Clin Pharmacol Ther* 12:678-682, 1971
6. Lloyd KG, Davidson L, Hornykiewicz O: The neurochemistry of Parkinson's disease: effect of L-DOPA therapy. *J Pharmacol Exp Ther* 195:453-464, 1975
7. McLean JR, Ensor CR, McCarthy DA, et al: Effects of L-DOPA and L-3-methoxytyrosine on D-methamphetamine-induced motor activity and seizures induced by electroshock. *Proc Soc Exp Biol Med* 143:1083-1087, 1973
8. Muentner MD, Dinapoli RP, Sharpless NS, Tyce GM: 3-*O*-methyldopa, L-DOPA, and trihexyphenidyl in the treatment of Parkinson's disease. *Mayo Clin Proc* 48:173-183, 1973
9. Muentner MD, Sharpless NS, Tyce GM: Plasma 3-*O*-methyldopa in L-DOPA therapy of Parkinson's disease. *Mayo Clin Proc* 47:389-395, 1972
10. Nutt JG, Woodward WR: Levodopa pharmacokinetics and pharmacodynamics in fluctuating parkinsonian patients. *Neurology* 36:739-744, 1986
11. Nutt JG, Woodward WR, Hammerstad JP, et al: The "on-off" phenomenon in Parkinson's disease: relation to levodopa absorption and transport. *N Engl J Med* 310:483-488, 1984
12. Nutt JG, Woodward WR, Carter JH: Clinical and biochemical studies with controlled-release Sinemet. *Neurology* 36:1206-1211, 1986
13. Prasad ALN, Fahn S: A semiautomated method for the rapid determination of DOPA: comparison of plasma and erythrocyte-DOPA concentration in levodopa-treated patients. *Biochem Med* 27:297-304, 1982
14. Reches A, Fahn S: 3-*O*-methyldopa blocks dopa metabolism in rat corpus striatum. *Ann Neurol* 12:267-271, 1982
15. Reches A, Mielke LR, Fahn S: 3-*O*-methyldopa inhibits rotations induced by levodopa in rats after unilateral destruction of the nigrostriatal pathway. *Neurology* 32:887-888, 1982
16. Reilly DK, Rivera-Calimlim L, Van Dyke D: Catechol-*O*-methyltransferase activity: a determinant of levodopa response. *Clin Pharmacol Ther* 28:278-286, 1980
17. Rivera-Calimlim L, Tandon D, Anderson F, Joynt R: The clinical picture and plasma levodopa metabolite profile of parkinsonian nonresponders. *Arch Neurol* 34:228-232, 1977
18. Sharpless NS, Muentner MD, Tyce GM, Owen CA: 3-methoxy-4-hydroxyphenylalanine (3-*O*-methyldopa) in plasma during oral L-DOPA therapy of patients with Parkinson's disease. *Clin Chim Acta* 37:359-369, 1972
19. Wade LA, Katzman R: 3-*O*-methyldopa uptake and inhibition of L-DOPA at the blood-brain barrier. *Life Sci* 17:131-136, 1975
20. Weinshilbaum RM, Raymond FA, Elveback LR, Weidman WH: Correlation of erythrocyte catechol-*O*-methyltransferase activity between siblings. *Nature* 252:490-491, 1974
21. Wooten GF, Ferrari MB: Competition for the striatal dopamine receptor by metabolites of L-Dopa (abstract). *Ann Neurol* 14:136, 1983