

## Mini Review

# Time-Lag between Establishing Clinical Pharmacology Principles and Advances in Practice: The Case of Tolerance to Levodopa

R John Dobbs<sup>1</sup>, Sylvia M. Dobbs<sup>1\*</sup>, Clive Weller<sup>1</sup>, André Charlett<sup>2</sup>, and David Taylor<sup>1</sup>

<sup>1</sup>Pharmaceutical Sciences Clinical Academic Group, King's Health Partners, London

<sup>2</sup>Statistics Unit, Health Protection Agency, London

**\*Corresponding author**

Sylvia M. Dobbs, Pharmaceutical Sciences Clinical Academic Group, King's College London, London, Tel: 44(0)1442873571; Email: sylvia.dobbs@kcl.ac.uk

Submitted: 29 May 2017

Accepted: 22 June 2017

Published: 24 June 2017

ISSN: 2333-7079

**Copyright**

© 2017 Dobbs et al.

**OPEN ACCESS****Keywords**

- Levodopa
- Tolerance
- Parkinson's disease
- Dyskinesia

**Abstract**

Levodopa is widely used, but rarely is the topic of tolerance raised. Escalating requirement and 'on/off' fluctuations are often ascribed to disease progression, rather than admitted to be iatrogenic. The risk should be discussed before introduction, since 'weaning off' levodopa is difficult and usually unsuccessful. Dependence on the mood elevation and relief of anxiety might add to the difficulty. Tolerance develops rapidly, especially after infusion or oral sustained release formulation. It is, in part, pharmacokinetic, being associated with the accumulation of the long  $t_{1/2}$  metabolite, 3-O-methyldopa. Therefore, effective use of catechol-O-methyl transferase inhibition should reduce tolerance.

**INTRODUCTION**

With an ageing population, it is likely that Parkinson's disease (PD) will increasingly pervade general practice, general and geriatric medicine and neurology. Falls and fractures make it no stranger to orthopaedics. It may present with dyspepsia and slow transit to gastroenterology. Parkinsonism is rarely far away from adult psychiatric practice:-(i) PD, dementia and depression are overlap conditions; (ii) Panic attacks, obsessive/compulsive behaviour and 'bradyphrenia' are well-known in untreated PD; (iii) Mood swings, hallucinations, delusions and psychosis are well-recognised adverse effects of dopaminergic therapy; (iv) Anti-psychotic drugs may exacerbate PD, a disease that had not passed the diagnostic threshold overt, or cause secondary parkinsonism; (v) Selective serotonin re-uptake inhibitors can exacerbate or cause movement disorders, tremor and dyskinesias. Tricyclic antidepressants can exacerbate or cause tremor and dysarthria. Here we draw attention to the most important adverse effect of the most commonly used antiparkinsonian agent, levodopa. It is an effect which is commonly not acknowledged for what it is.

Advances in practice are often lag behind the science. This is so for tolerance to levodopa. Tolerance is defined by the need to increase the dose of a drug to obtain an effect previously seen at a lower dose. Acquired tolerance is well known, especially with opiates. It can be due to reduced sensitivity of receptor sites or increased metabolism as a result of enzyme induction. Disease

progression is a potential confounder, but here the same effect may not be regained by raising a dose which had been maximally efficacious. Pharmacological tolerance is frequently conflated/confused with tolerability to the patient (i.e. the propensity to continue a treatment without or despite adverse effects).

**SOME RELEVANT ARCHIVAL LITERATURE**

In three studies [1-3], we demonstrated tolerance to levodopa and described a model to explain the pharmacokinetic aspect. Relevant background is that levodopa is routinely prescribed with a peripheral decarboxylase inhibitor. This reduces adverse effects outside the blood brain barrier, increases availability to the brain two to threefold, and allows decarboxylation to dopamine in the brain [4]. However, 90% of oral levodopa is metabolised by catechol-O-methyl transferase (COMT) to 3-O-methyldopa (3OMD), which has a relatively long elimination  $t_{1/2}$  ( $\approx 15$ h) [5], compared with levodopa.

In 1992, we evaluated tolerance in a randomised, double-blind, placebo-controlled, within-subject cross-over comparison of the response to different oral levodopa challenges [3]. No routine doses of levodopa were given from 22.00 h on the day before a challenge until after the assessment. Gait analysis and clinical ratings were carried out immediately before a challenge and hourly for 6 hours after, a concentration/time profile of plasma levodopa and 3OMD being obtained over the same period. Eight PD sufferers, all exhibiting "end of dose"

effect within 4 h of a dose of their maintenance therapy with levodopa (100 mg)/carbidopa (25 mg) in a conventional-release formulation (Sinemet Plus, MSD), were studied. They received single dose, placebo-balanced challenges, with one and two tablets of controlled-release levodopa (200mg)/carbidopa (50 mg) (Sinemet CR, MSD) and placebo alone, each challenge being separated by 3 to 6 days. After just 21 weeks on an individually optimised Sinemet CR maintenance regimen, these single dose challenges were repeated, again in random order. In the initial challenges, the mean increment in the primary outcome, mean stride length at free walking speed, achieved by active treatment as compared with placebo, did not differ significantly between the one (210 mm) and two (235 mm) tablet Sinemet CR doses. Moreover, following two active tablets, the increment over placebo values did not differ significantly between initial and subsequent (192 mm) challenges. However, the increment produced by one active tablet in the subsequent challenge (79 mm) was not only significantly less than that produced by two, but also than that produced by one tablet in the initial. Findings for free walking speed mirrored those for stride length. Similarly, a rightward shift of dose-response curves to boluses of levodopa has been shown after 7 to 12 days of continuous intravenous levodopa infusion in advanced Parkinson's disease [6], and the duration of response after discontinuing a 21 h infusion found to be shorter than that after a 2h infusion in patients with levodopa-associated motor fluctuation and dyskinesia [7].

It is difficult to ascribe reduction in effect over hours or a few months to disease progression rather than tolerance. Indeed, in our study [3], baseline performance had improved following introduction/optimisation of the maintenance CR regimen. There was no evidence that a ceiling had been reached: absolute stride length ranked higher on the subsequent than on the initial challenge.

Tolerance appeared to be, in part, pharmacokinetic. Although the mean plasma levodopa concentration did not differ significantly between initial and subsequent occasions for either the one or the two tablet challenge [3], the mean 3OMD concentration was approximately doubled on the subsequent occasion. Response of stride length was positively associated with levodopa concentration, negatively with 3OMD. Plasma levodopa made a significant contribution to explaining the difference in response between placebo, one CR tablet and two. Incorporation of the 3OMD concentration in the model, as a covariate, partially explained the residual variance. Moreover, the difference between initial and subsequent challenges in response to one tablet of Sinemet CR was no longer significant after incorporating 3OMD. Previously [1], we had shown the 3OMD concentration to be positively associated with abnormality of foot strike (i.e. toe first or flat footed), as measured by pedobarography. Increased wastage of levodopa by O-methylation, plus/minus a dose-related adverse effect of 3OMD, appeared to contribute to development of tolerance over 5 months. Indeed, competition between levodopa and 3OMD for transport into the brain by the large, neutral amino acid carrier system has been demonstrated [8]. We were not the first to point the finger at 3OMD accumulation having a deleterious effect on the efficacy of levodopa [9,10]. Moreover, clearance of 3OMD had been proposed as the explanation of the temporary increase in responsiveness following a drug holiday

[11,12]. Duration of response in walking speed to a 2 h levodopa intravenous infusion increased significantly after a 2 to 4 day interruption in long-term levodopa therapy [13]. This gap is compatible with virtual clearance of 3OMD.

With a longer duration (mean 4½ (range ½, 15) years) of maintenance levodopa therapy (Sinemet Plus) [2], we showed a significant negative regression between duration and area under the plasma levodopa concentration/time curve attributed to a single dose challenge (AUC<sub>0-1</sub>). The association was not explained by age or disease severity. This would fit with the common clinical experience of shorter duration of levodopa/decarboxylase inhibitor action with prolonged use.

## MAKING TOLERANCE A DEFINING THERAPEUTIC ISSUE

On/off fluctuations and/or dyskinesia, associated with levodopa dose escalation, add greatly to the burden of PD. Why, then, is levodopa tolerance not a defining therapeutic issue? First, the ubiquitous global scores are a blunt instrument for its definition. Demonstration of tolerance is facilitated by objective assessment of Parkinsonism. Interestingly, of our secondary outcome measures [3], tremor was the most sensitive of the subjective clinical ratings to the tolerance effect. However, had this been the primary outcome, nearly five times as many patients would have been required to achieve the same power. Second, focus on the pharmacokinetic determinants of tolerance is needed. How critical the 24 h levodopa concentration/time profile during maintenance therapy is to the development of tolerance should be a prime consideration in choice of formulation (e.g. controlled release) and delivery (e.g. as intestinal gel via enteral tube). Third, the emphasis is on evidenced based prescribing rather than applying pharmacological principles. The UK National clinical guideline [4] does not consider catechol-O-methyl transferase inhibitors (COMTI) in the context of "early pharmacological therapy". Comparative study of the response to different levodopa dose challenges before and after a few months' maintenance therapy, with levodopa/decarboxylase inhibitor alone and in combination with a COMTI, might pave the way to extending levodopa/decarboxylase/COMTI combination usage.

Similarly, dependency on levodopa dosage for mood elevation and anxiety reduction [14], in fluctuating Parkinson's disease, would promote dose escalation and tend to thwart effects at dose reduction.

## 5 KEY POINTS

1. Topic of tolerance to and dependency on levodopa should be raised before its prescription
2. Formulation/delivery should be discussed in terms of escalation of tolerance
3. Tolerance is, in part, explained by accumulation of the long t½ metabolite, 3-O-methyldopa
4. Experimental work is needed to confirm that effective catechol-O-methyl transferase inhibition can reduce tolerance
5. Increased requirements for levodopa should not

automatically be ascribed to disease progression

## REFERENCES

1. Hughes JR, Bowes SG, Leeman AL, O'Neill CJA, Deshmukh AA, Nicholson PW, et al. Parkinsonian abnormality in foot strike: a phenomenon of ageing and/or one responsive to levodopa therapy? *Brit J Clin Pharmacol.* 1990; 29: 179-186.
2. Bowes SG, O'Neill CJA, Nicholson PW, Leeman AL, Deshmukh AA, Dobbs RJ, et al. Effect of duration of levodopa/decarboxylase inhibitor therapy on the pharmacokinetic handling of levodopa in elderly patients with idiopathic Parkinson's disease. *Eur J Clin Pharmacol.* 1991; 41: 459-462.
3. Bowes SG, Dobbs RJ, Henley M, Charlett A, O'Neill CJA, Nicholson PW, et al. Objective evidence for tolerance, against a background of improvement, during maintenance therapy with controlled release levodopa/carbidopa. *Eur J Clin Pharmacol.* 1992; 43: 483-489.
4. Parkinson's disease. National clinical guideline for diagnosis and management in primary and secondary care. London: Royal College of Physicians. 2006.
5. Kuruma I, Bartholin, G, Tissot R, Pletscher A. Metabolism of L-3-O-methyldopa, a precursor of dopa in man. *Clin Pharmacol Ther.* 1971; 12: 678-682.
6. Mouradian MM, Heuser IJE, Baronti F, Chase TN. Modification of central dopaminergic mechanisms by continuous levodopa therapy for advanced Parkinson's disease. *Ann Neurol.* 1990; 27: 18-23.
7. Nutt JG, Carter JH, Woodward W, Hammerstad JP, Gancher ST. Does tolerance develop to levodopa? Comparison of 2- and 21-H levodopa infusions. *Movement Disorders.* 1993; 8: 139-143.
8. Wade DN, Katzman R. Synthetic amino acids and the nature of L-dopa transport at the blood-brain barrier. *J Neurochem.* 1975; 25: 837-842.
9. Meunter MD, Sharpless NS, Tyce GM. Plasma 3-O-methyldopa in L-dopa therapy of Parkinson's disease. *Mayo Clinic Proc.* 1972; 47: 389-395.
10. Rivera-Calimlim L, Tandon D, Anderson F, Joynt R. The clinical picture and plasma levodopa metabolite profile of Parkinsonian non-responders. Treatment with levodopa and decarboxylase inhibitor. *Arch Neurol.* 1977; 34: 228-232.
11. Direnfeld L, Spero L, Marotha J. The L-dopa 'on-off' effect in Parkinson's disease: treatment by transient drug withdrawal and dopamine receptor resensitization. *Ann Neurol.* 1978; 4: 573-575.
12. Lee T, Seeman P, Rajput A, Farley IJ, Hornykiewicz O. Receptor basis of dopaminergic supersensitivity in parkinson's disease. *Nature.* 1978; 273: 59-61.
13. Nutt JG, Carter JH, Woodward WR. Effect of brief levodopa holiday holidays on the short-duration response to levodopa: evidence for tolerance to the antiparkinsonian effects. *Neurol.* 1994; 44: 1617-1620.
14. Maricle RA, Nutt JG, Valentine RJ, Carter JH. Dose-response relationship of levodopa with mood and anxiety in fluctuating Parkinson's disease: a double-blind, placebo-controlled study. *Neurol.* 1995; 45: 1757-1760.

### Cite this article

Dobbs RJ, Dobbs SM, Weller C, Charlett A, Taylor D (2017) Time-Lag between Establishing Clinical Pharmacology Principles and Advances in Practice: The Case of Tolerance to Levodopa. *J Pharmacol Clin Toxicol* 5(5):1084.