LETTER TO THE EDITOR

To The Editor

Differences in Drug Pharmacokinetics and Motor Fluctuation in DYT-*GCH1*

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A 49-year-old lady, who is part of a previously reported[1] large *GCH1* mutation-positive family, complained of motor fluctuation. For 27 years, she was maintained on low-dose L-dopa/carbidopa (Sinemet®) 100 mg twice daily and had been completely asymptomatic, without any reported treatment-related complications (Figure 1A). In 2019, Sinemet® was no longer available in Canada. Consequently, she resorted to taking a generic brand of L-dopa/carbidopa, with sub-optimal symptom relief, often complaining of pain, leg cramping, and fatigue. She tried another generic brand of L-dopa/carbidopa, but still with a sub-optimal response and a shortened duration of benefit; dose failures were also occasionally experienced. There was no benefit with taking higher individual doses of the generic L-dopa/carbidopa. Since then, she had to take the medication every 4 hours round-the-clock as well as baclofen and zopiclone but still with poor symptom control and wearing-off throughout the day (Figure 1B). Coincidentally, she had a few tablets of Sinemet® kept in a different container; taking her previous low dose afforded complete symptom relief. On examination, she had right foot eversion despite being in a self-reported "on" state, 1 hour after taking a generic brand of L-dopa/carbidopa. There were no signs of bradykinesia. L-dopa/benserazide (Prolopa®) was then prescribed. At 100 mg thrice daily, she claimed to have complete symptom resolution (without additional baclofen and zopiclone), similar to the response she obtained with low dose Sinemet® (Figure 1C). The benefit has been sustained over the past 6 months, without any recurrence of the motor fluctuation. Foot eversion was no longer observed in the subsequent visits. Moreover, unaware of our patient's experience, her son and one of her cousins had a similar experience with generic L-dopa/carbidopa, but they improved with an increased dose of the drug and the addition of long-acting L-dopa/carbidopa at night in the latter.

Dopa-responsive dystonia (DRD, DYT-*GCH1*) is a rare, genetic, highly treatable form of dystonia with an excellent, long-lasting response to low dose L-dopa.[1,2] Motor fluctuation, a known complication of L-dopa therapy in advanced Parkinson's disease (PD), is typically not a feature of DRD.[2] Inadequate response to L-dopa is considered a diagnosis of exclusion, and the development of wearing-off and L-dopa-induced dyskinesia are deemed atypical of DRD.[3] Subjective wearing-off has been reported in patients with DRD who missed taking a dose of L-dopa/carbidopa; however, on objective evaluation through an L-dopa withdrawal challenge, the dystonic symptoms recurred only after 29 hours.[4] The wearing-off in these patients, which was considered non-motor in nature, was attributed to the effect of L-dopa on mood elevation.[4] To date, all other reported cases of motor fluctuation in DRD have been attributed to the

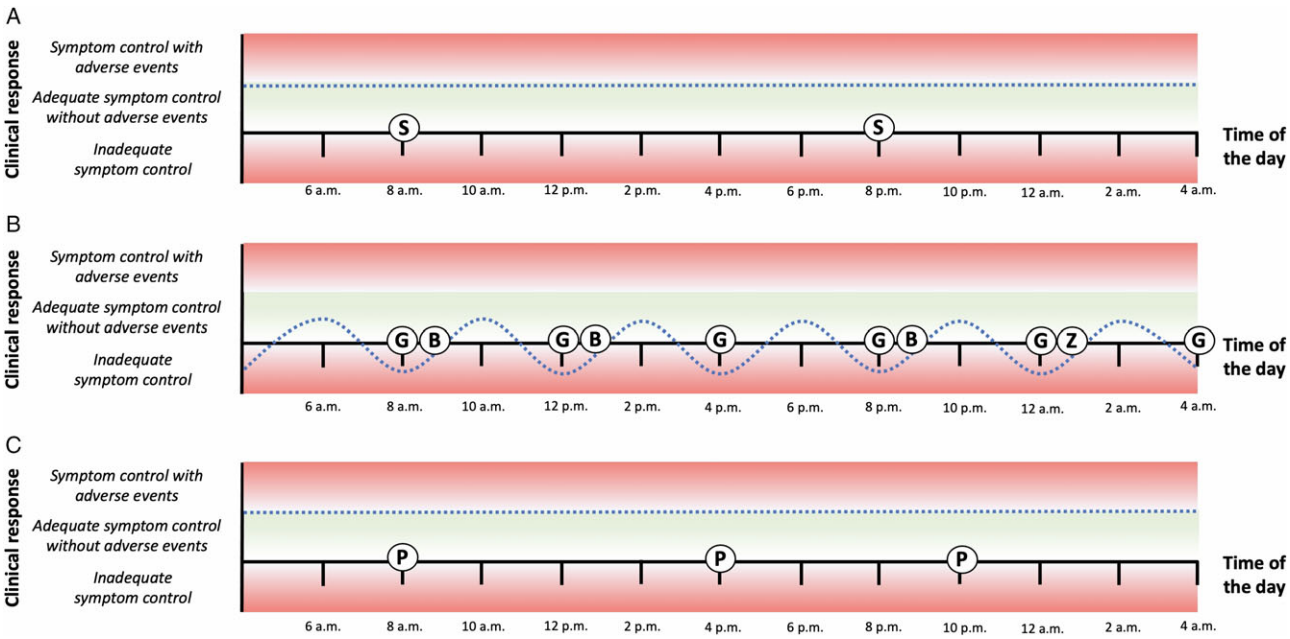

Figure 1: *Patient's clinical response to different formulations of L-dopa. Intake of low-dose Sinemet® (**A**) or Prolopa® (**C**) afforded complete symptom relief. She had poor symptom control and wearing-off every 4 hours with the intake of generic brands of L-dopa/carbidopa (**B**). There was no benefit with taking higher individual and more frequent doses of the generic brand of L-dopa/carbidopa. B = baclofen; G = generic brand of L-dopa/carbidopa; P = Prolopa®; S = Sinemet®; Z = zopiclone.*

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development of neurodegenerative parkinsonism;[1,3,5,6] it has recently been reported that *GCH1* mutations increase the risk of developing PD by as much as 7.5 times expected.[6] Our patient was compliant with her L-dopa schedule, and on examination in the "on" state while taking generic L-dopa/carbidopa, she had mild dystonia. The absence of parkinsonism and the improvement with re-introduction of low doses of Sinemet® or Prolopa® further support our hypothesis that the pharmacokinetic properties of the generic medications caused our patient's motor fluctuation. It is not clear whether this problem related to the lower bioavailability of carbidopa, L-dopa, or both in the two generic forms of L-dopa/carbidopa compared to the innovator brands.

Despite the supposedly rigorous regulations to ensure drug bioequivalence, generic substitution is a known health economic issue. Different brands generally have varying efficacy and tolerability caused by differences in drug additives and other factors such as pressing force.[7] In our experience, some patients with PD (and now DRD) complain of sub-optimal response, dose failures, shortened duration of benefit, and that the generic drugs can "melt" in the vial (a major problem in very humid climates) or spontaneously crumble. For a drug to be deemed bioequivalent, it only has to demonstrate that the area under the drug concentration versus time curves (AUC ratio) and the maximum plasma concentrations (Cmax ratio) fall within 90% and 80%–125% confidence intervals, respectively.[7] This implies that two generic drugs and even different stocks of the same generic brand might differ by as much as 10%–25% of the innovator brand. Moreover, bioequivalence studies are only performed in healthy subjects; other factors that affect drug absorption, efficacy, and safety in patients with the disease (e.g., drug–drug interaction, impaired gastric motility in PD, etc.) are not accounted for.[7] In a study of patients with PD, those who had advanced disease complained of more "off" time, dose failures, and orthostatic hypotension upon switching to generic L-dopa/carbidopa.[8]

Patients with DRD are particularly sensitive to L-dopa, as evidenced by its marked response even with low doses of the drug. However, to our knowledge, there are no published reports on the responses of DRD patients with generic forms of L-dopa/carbidopa. There may only be a subset of patients who are remarkably sensitive to generic drugs; this could explain why our patient was the only one so severely affected by the generic drug substitution and not her son or her cousin. Similarly, DRD is well known to have considerable intrafamilial phenotypic variability.[1]

In summary, motor fluctuation in DYT-*GCH1* is rare, but the development of neurodegenerative parkinsonism is not the only cause. This report describes a case of DYT-*GCH1* with motor fluctuation that is probably secondary to the lower bioavailability of generic forms of L-dopa/carbidopa. Switching to a branded form of L-dopa/benserazide is a reasonable treatment option in this instance.

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Disclosure

Dr. Saranza has nothing to disclose.

Dr. Lang reports personal fees from AbbVie, personal fees from AFFiRis, personal fees from Janssen, personal fees from Biogen, personal fees from Merck, personal fees from Sun Pharma, personal fees from Corticobasal Solutions, personal fees from Sunovion, personal fees from Paladin, personal fees from Lilly, personal fees from Medtronic, personal fees from Theravance, personal fees from Lundbeck, personal fees from Retrophin, personal fees from Roche, personal fees from Photo-Pharmics, outside the submitted work.

Statement of Authorship

Gerard Saranza wrote the paper and managed the patient. Anthony Lang revised the manuscript and managed the patient throughout her entire life.

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