LETTER TO THE EDITOR

To the Editor

Improvement in Severe Orthostatic Hypotension Following Carbidopa Dose Reduction

Keywords: Amino acid decarboxylase inhibitor, Carbidopa, Levodopa, Orthostatic hypotension, Parkinson's disease

Levodopa/carbidopa is a mainstay of Parkinson's disease (PD) pharmacotherapy. As PD progresses, there is a decrease in intrasynaptic dopamine concentrations and patients require exogenous dopamine to relieve symptoms.[1] Dopamine cannot cross the blood brain barrier (BBB) because it is a polar molecule.[1] Levodopa enters the CNS where it is converted into dopamine by the aromatic amino acid decarboxylase enzyme (AADC). If levodopa is administered without carbidopa, only 1% of the dose reaches the CNS. Carbidopa decreases the peripheral metabolism of levodopa by inhibiting AADC, allowing up to 10% of the levodopa dose to reach the CNS.[1,2]

Approximately three-quarters of patients on levodopa experience orthostatic hypotension (OH).[3,4] Carbidopa can result in OH by inhibiting L-amino acid decarboxylase, the enzyme that decarboxylates dihydroxyphenylserine to norepinephrine (NE). This results in impaired NE formation which can produce a vasodilatory effect. Levodopa and carbidopa also cause OH through the activation of dopamine receptors which results in vasodilation.

Animal studies have shown that carbidopa doses exceeding those recommended can cross the BBB. Jonkers et al. found that two AADC inhibitors administered at low-dose (carbidopa and benserazide) had no effect on the conversion of levodopa to dopamine within the CNS. However, high-dose carbidopa and benserazide significantly decreased the AADC activity and dopamine concentrations in the striate nucleus of rats.[5] Similarly, Shen et al.[6] found that AADC inhibitors have central activity and at higher doses, central effects are greater than peripheral effects. Tayarani-Binazir et al.[7] postulated that AADC inhibitors are used in doses that are higher than those needed to provide maximum benefit from levodopa in marmosets.

Inhibition of AADC activity in the CNS would decrease the conversion of levodopa to dopamine. This can lead to decreased efficacy of levodopa and potentially increase the risk of adverse effects from higher levodopa doses required to achieve the same effect.

This effect was illustrated in a 70-year-old male with a 9-year history of PD who was admitted to hospital following a suicide attempt. His chief complaint was that of severe, persistent OH which resulted in significant dizziness and debilitating headaches. His mobility was limited by dizziness, so he required a one person assist and a walker. The patient presented with minimal bradykinesia, muscle rigidity, and cogwheeling. He experienced intermittent confusion, delirium, and hallucinations throughout the course of his disease, but no hypophonia and micrographia. He had multiple falls before admission, whereby he slid onto the floor due to dizziness. No radiological features of atypical Parkinsonian syndrome were present. He was receiving a total daily dose of levodopa 1,200 mg and carbidopa 300 mg. Orthostatic drops in systolic blood pressure (BP) ranged from 34 to 95 mmHg throughout his hospital stay. Thirteen days into the patient's hospital admission, fludrocortisone was initiated at 0.2 mg daily along with midodrine 10 mg three times a day. These medications were continued for 2 weeks without improvement in OH, dizziness or headache. Both fludrocortisone and midodrine were discontinued ~11 days before the patient's observed improvement in OH.

This patient presented on high-dose carbidopa (300 mg/day) relative to the maximum recommended dose of carbidopa 200 mg/day. In an attempt to minimize the OH, dizziness, and headaches and to apply principles from the above animal studies, the patient's daily carbidopa dose was reduced by 57% from 300 to 130 mg/day. The carbidopa dose reduction was achieved by changing the levodopa/carbidopa 100/25 to 100/10 mg tablet, although carbidopa is also available as a single entity 25 mg tablet through Health Canada's Special Access Program. The levodopa was maintained at 1,200 mg/day. Over the next few days, the patient noted a decrease in the frequency and severity of his headaches and dizziness. Seven days after the initial carbidopa dose reduction, the dose of levodopa was reduced by ~17% to 1,000 mg/day. On follow-up, 7 days after levodopa dose reduction, the patient denied having dizziness and headaches and was able to mobilize independently without issues. Although his OH was still present, the patient became asymptomatic and his orthostatic BP drops became less severe. The patient was discharged home following a 44 day length of stay. At 4 month follow-up, his motor and non-motor signs of PD did not change significantly with the dose reductions compared with the time of discharge and there was no dyskinesias. At this time, his BP was measured to be 90/70 mmHg when lying down and 87/60 mmHg when standing.

Throughout the course of his disease, the patient experienced multiple potential adverse effects of high-dose carbidopa. As confirmed with the patient during the hospital stay, his insomnia, anxiety, hallucinations, suicidal tendencies and constipation were no longer present following the carbidopa dose reduction. According to Neurologist consultation notes 2 years before hospital admission, the patient's overall levodopa and carbidopa doses were reduced by two-thirds in order to mitigate significant hallucinations, confusion, and delirium. The large decrease in levodopa dose resulted in poor motor control. However, during this admission, similar adverse effects were alleviated by only a 17% reduction in levodopa and a 57% reduction in carbidopa. By down-titrating the carbidopa component, the levodopa component was maintained at almost the original dose. This allowed minimization of adverse effects while preserving motor control.

Midodrine and fludrocortisone are not considered confounding factors in this case as the 11-day period between the discontinuation of these medications and the improvement in dizziness and headache would have allowed for a sufficient washout period. Therefore, improvement in dizziness and headache in this case may be more likely attributed to the dose reductions outlined above. According to the Naranjo Algorithm Scale, this adverse reaction was considered "probable".[8]

Excessive carbidopa doses can have a profound impact on PD patients' quality of life. It is important to understand the mechanism of AADC inhibitors, including their propensity to cross the BBB at higher doses according to animal studies. By understanding this effect, PD pharmacotherapy can be optimized on levodopa and carbidopa doses that achieve the best efficacy while minimizing adverse effects.

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Anthony C.W. Lau, BScPharm
Pharmacist
Department of Pharmacy
Surrey Memorial Hospital
Fraser Health Authority
Surrey, BC, Canada

John L. Diggle, BSc, MD, FRCPC, CSCN(ENG), CSCN(EEG)
Neurologist and Regional Medical Director and Head
Regional Department of Medicine
Fraser Health Authority
Surrey, BC, Canada

Clinical Assitant Professor
Faculty of Medicine
University of British Columbia
Vancouver, BC, Canada

Penny P. Bring, BScPharm, ACPR, PharmD
Clinical Pharmacy Specialist Neurology
Department of Pharmacy
Surrey Memorial Hospital
Fraser Health Authority
Surrey, BC, Canada

Clinical Instructor
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC, Canada

Correspondence to: A.C.W. Lau, BSc (Pharm), Pharmacist, Surrey Memorial Hospital Pharmacy Department, Fraser Health Authority, 13750 96 Avenue, Surrey, BC, Canada V3V 1Z2.
Email: Anthony.Lau@fraserhealth.ca

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