

## Dose-dependent L-dopa/carbidopa-induced hyponatremia presenting with hiccups

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### ABSTRACT

Levodopa (L-dopa) is the most effective antiparkinsonian agent and is well tolerated at all stages of the disease. However, both motor and nonmotor adverse events are reported with the use of L-dopa. Electrolyte imbalances such as hyponatremia and hiccups with L-dopa/carbidopa are very rare. For the first time, we are reporting a case of L-dopa/carbidopa-induced hyponatremia and hiccup cooccurring in a 75-year-old male. He symptomatically improved after reducing the dose of levodopa/carbidopa, indicating a dose-dependent nature of these adverse events. Clinicians who prescribe L-dopa/carbidopa should be mindful of the potential for precipitating SIADH and hiccups, especially in elderly patients.

**Keywords:** Adverse events, hyponatremia, hiccups, L-dopa/carbidopa

### Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder with distal resting tremor, rigidity, bradykinesia, and asymmetric onset as the cardinal physical signs.<sup>[1]</sup> Levodopa (L-dopa) is the most effective antiparkinsonian agent and is well tolerated at all stages of the disease.<sup>[2]</sup> However, both motor and nonmotor adverse events are reported with the use of L-dopa. The commonly reported adverse events include motor fluctuations, dyskinesia, chorea, dystonia, myoclonus, ocular dyskinesia, respiratory dyskinesia, neuropsychiatric symptoms including psychosis, sweating, facial flushing, hyperthermia, urinary disturbances, bloating, abdominal discomfort, dysphagia, drooling of saliva, dry mouth, dyspnea, pain, numbness, paresthesia, restlessness, and akathisia.<sup>[3]</sup> Electrolyte imbalances such as hyponatremia and hiccups with L-dopa/carbidopa are very rare. A Medline search till October 2017 revealed only one report of L-dopa/carbidopa-induced hyponatremia and

no report of L-dopa/carbidopa associated hiccups.<sup>[4,5]</sup> For the first time, we are reporting a case of L-dopa carbidopa-induced hyponatremia and hiccup cooccurring in a single patient.

### Case Report

A 75-year-old male presented to our hospital with recurrent hiccups and high colored urine. His past medical history revealed that he was on regular treatment from a neurologist for ischemic stroke, Parkinson's disease, seizure disorder, diabetic mellitus, and hypertension. He was on oral syncapone [levodopa (150 mg), carbidopa (37.5 mg), entacapone (200 mg)] 4 times a day, oral sodium valproate 600 mg/day, oral telmisartan 20 mg/day, and gliclazide/metformin. There was a history of admission to a tertiary care hospital 2 weeks prior to the onset of current symptoms, with probable acute coronary syndrome and paroxysmal atrial fibrillation. He was started on double antiplatelets, nitrates, beta-blocker (Tab. metoprolol 100 mg/day), and due to worsening of parkinsonian symptoms, levodopa/carbidopa dose was hiked to 500 mg/day along with syncapone 150 mg QID.

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On evaluation, he was found to have features of acute cystitis and profound hyponatraemia (120 mEq/L). Hyponatremia was euvolemic in nature (urine sodium: 43 mmol/L, serum uric acid: 2.9 mg/dl, urine specific gravity: 1.010). Possible causes of hyponatremia and hiccups such as myocardial infarction, cerebrovascular accidents, and uraemia were excluded by appropriate clinical and laboratory examinations. His antiplatelets were stopped due to hematuria and he was started on broad-spectrum antibiotics (cefoperazone + sulbactam) and sodium was corrected with concentrated saline. His serum sodium increased to 132 mEq/L within 48 h, but hiccups persisted. His serum sodium started coming down again when the concentrated saline was stopped. He was started on Tab. Tolvaptan 15 mg/day, but with no response. He was given Tab. Baclofen for symptomatic relief of hiccups, but was ineffective. Considering the rare possibility of levodopa-induced hyponatremia and hiccups, we stopped recently hiked dose of L-dopa/carbidopa 500 mg and continued Tab. syncapone [levodopa (150 mg), carbidopa (37.5 mg), entacapone (200 mg)] 4 times a day, which resulted in a marked improvement in hiccups, serum sodium started increasing and reached normal levels within 48 h. The patient was discharged the next day. During follow-up after 2 weeks, patient was found to have no hiccups and sodium level was normal.

## Discussion

In this case, the patient developed hyponatremia and hiccups after hiking L-dopa/carbidopa dose, and there was no recent change in any other regular medications. The resolution of both the symptoms after reducing the dose of L-dopa/carbidopa indicates a probable causal relationship.

We could find two past case reports of L-dopa/carbidopa associated hyponatremia. The first case was reported in a 68-year-old male who developed hyponatremia on the next day of starting L-dopa/carbidopa.<sup>[4]</sup> The second case was reported in a 73-year-old woman who developed hyponatremia 4 days after starting L-dopa/carbidopa (100 mg/10 mg three times a day).<sup>[5]</sup> Our case is different from the past reports in the delayed and dose-dependent onset of hyponatremia.

In all the reported cases including ours, the laboratory findings are suggestive of euvolemic hyponatremia, indicating the probable pathophysiological mechanism being an inappropriate secretion of antidiuretic hormone (ADH). Both animal and human studies indicate that dopamine agonists can stimulate ADH secretion and can cause hyponatremia probably through this mechanism.<sup>[5]</sup> The risk of hyponatremia with psychotropic medications is usually greatest during the first 2 weeks of treatment and is unrelated to drug dose.<sup>[6]</sup> But, in our case hyponatremia occurred late and found to be dose dependent.

Hiccups are the product of the simultaneous involuntary spasmodic contraction of the diaphragm, intercostal muscles, and glottic closure resulting in blockade of the air entry into

the trachea, mediated by sensory branches of phrenic, dorsal sympathetic, and vagus nerves.<sup>[7]</sup> The neurotransmitters such as dopamine, serotonin, and gamma-aminobutyric acid (GABA) have been documented to play a significant role in the generation of hiccups.<sup>[7]</sup> Hiccups are reported more frequently in Parkinson's disease patients than healthy controls.<sup>[8]</sup> Furthermore, persistent hiccups are a frequent manifestation of hyponatremia. A case-control study found a strong and independent association between hyponatremia and hiccups, with a dose-response relationship. The study showed that for every 10 mEq/L reduction in serum sodium, the patients were 17 times at risk of developing hiccups.<sup>[9]</sup> But in our case, hiccups persisted even after a significant correction in serum sodium level, indicating the possibility of drug-induced hiccup rather than a symptom of hyponatremia.

While dopaminergic therapies are implicated in the development of hiccups in pharmacovigilance surveys, we could not find a previous report of hiccups associated with L-dopa/carbidopa in the English language literature (PubMed), probably due to underreporting.<sup>[10]</sup> A past study reported two cases of hiccups associated with dopaminergic therapies (pramipexole and pergolide), but both of them later maintained well on L-dopa/carbidopa with no recurrence of hiccups.<sup>[11]</sup> There are also reports of treatment of intractable hiccups by dopaminergic agents like pramipexole and amantadine.<sup>[12]</sup>

## Conclusion

To the best of our knowledge, this is the first case report of dose-dependent L-dopa/carbidopa-induced hyponatremia and hiccups cooccurring in a single patient. Primary care and family physician who prescribe L-dopa/carbidopa should be mindful of the potential for precipitating SIADH and hiccups, especially in elderly patients.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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