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High dose amantadine therapy may cause increased falling in patients with Parkinson's disease: A case report

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Amantadine toxicity presents with hallucinations, confusion and, rarely, myoclonus in patients with Parkinson's disease (PD) [1,2]. To our knowledge there have been no reports on amantadine toxicity in relation to increased fall risk. We report a PD patient with a long-standing history of high dose amantadine therapy, who presented with acute onset of confusion, hallucinations, paranoid delusions and generalized myoclonus. For several years prior, he had been experiencing frequent falls, but no psychotic features or confusion. Following discontinuation of amantadine, he has not had a recurrence of falls for over 2 years.

The patient is a 55-year-old man with a 13-year history of tremor predominant PD. Because of levodopa intolerance, he received deep brain stimulation 5 years prior and was started on amantadine. He was taking 300 mg/day of amantadine for many years and 400 mg/day for the last 2 years. He tolerated this without any psychiatric symptoms and was doing well except requiring a cane to ambulate due to gait impairment with daily falls for the last 5 years. With the increase in amantadine dosage, the number of falls increased from 1 to 2 times/day to 3–4 times/day. He acutely developed confusion, hallucinations, paranoid delusions and myoclonus leading to emergency hospitalization.

Upon admission, amantadine was discontinued while a work-up to rule out other potential causes was initiated. The patient had a normal CBC with diff, CSF and UA. Urine toxicology was negative. BUN/Creatine was elevated at 40/1.96. He followed only simple commands, was disoriented, agitated and had non-sensical speech. Generalized myoclonus was present [see Video 1]. He became increasingly encephalopathic and non-communicative. After 3 days he began speaking again, but nonsensically and expressing delusional thoughts. He did not recognize his wife and could not say his name. Agitation required four-point restraints and lorazepam. One week after discontinuation of amantadine the myoclonus resolved, but confusion and paranoid ideation continued. Speech consisted of actual words strung together in an incoherent fashion, and insight, judgement and memory remained impaired. After 8 days off amantadine he was tremulous, perspiring and still nonsensical. It was proposed that his persistent encephalopathy could represent amantadine withdrawal [3]. Since the myoclonus had resolved, and creatinine had normalized, 100 mg/day of amantadine was restarted on Day 10. When on Day 13 the encephalopathy did not resolve, amantadine was again discontinued, and an amantadine level was sent off (which 1 week later came back at 420 ng/ml, low-normal). On Day 14 he answered and asked appropriate questions, but some confusion, hallucinations and nonsensical statements persisted. Finally, over the next 3 days he rapidly recovered, returned to baseline, and was discharged on Day 17.

At a 2-month follow-up visit he reported his gait was better than it had been in years. He did not consistently grab onto walls for support, no longer needed a cane, and was able to ambulate for prolonged periods of time. Up to the current time, 2 years after discharge, he reports no falls.

This patient went from falling several times a day for years, to not falling at all after stopping amantadine. No other medications were changed to explain the improvement in balance. There is conflicting evidence on the effects of amantadine on gait with some studies reporting improvement in gait and balance while others report worsening [4]. In the GOCOVRI clinical trial for levodopa induced dyskinesia there was a higher incidence of falls with amantadine compared to the placebo, especially in patients over 65 years old [5]. However, in the ADS-5102 trial for MS some aspects of walking ability were improved with amantadine [6]. While psychosis is a typical presentation of amantadine toxicity, this patient had been on amantadine with no problems of hallucinations or confusion for several years. In the absence of hallucinations or confusion, the frequent falls were not considered to be due to amantadine but rather to disease progression, allowing the falling to continue for years. There are no reports of persistent falling in patients taking amantadine long-term in the absence of psychotic features. Clearance of amantadine primarily takes place via glomerular filtration and tubular secretion [1].

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Due to the method of clearance, amantadine toxicity has mainly been reported in geriatric patients with renal failure [7]. On admission, the patient had an elevated BUN/Creatinine which likely triggered the acute psychosis and encephalopathy. A urinary tract infection was ruled out, but he did have a history of kidney stones which may have contributed to renal impairment.

We can only speculate as to why amantadine toxicity would be associated with increased falling.

There is evidence that degeneration in the pedunculopontine cholinergic nucleus is involved in postural instability and orthostatic hypotension experienced by PD patients [8,9]. Amantadine can cause anticholinergic effects [1], perhaps contributing to the increased falling described here.

Clinicians should be aware that falling in PD patients may be a side effect of high dose amantadine therapy even in the absence of hallucinations. We recommend checking renal function/clearance and potentially reducing amantadine dose when an unexplained increase in falling occurs in PD patients who are on amantadine therapy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2020.100045.

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Authorship

All authors had substantial contributions to all the following: (1) the conception and design of the study, or acquisition of data (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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