New Onset Neuropsychiatric Symptoms in a TBI Patient with Renal Dysfunction: A Case of Amantadine Toxicity

Nikhil Potpally, BA[1], Nicole Diaz-Segarra, MD[1,2], Neil Jasey, MD[1,2]

[1] Rutgers New Jersey Medical School, Department of Physical Medicine and Rehabilitation, Newark, NJ

[2] Kessler Institute for Rehabilitation, West Orange, NJ

Introduction

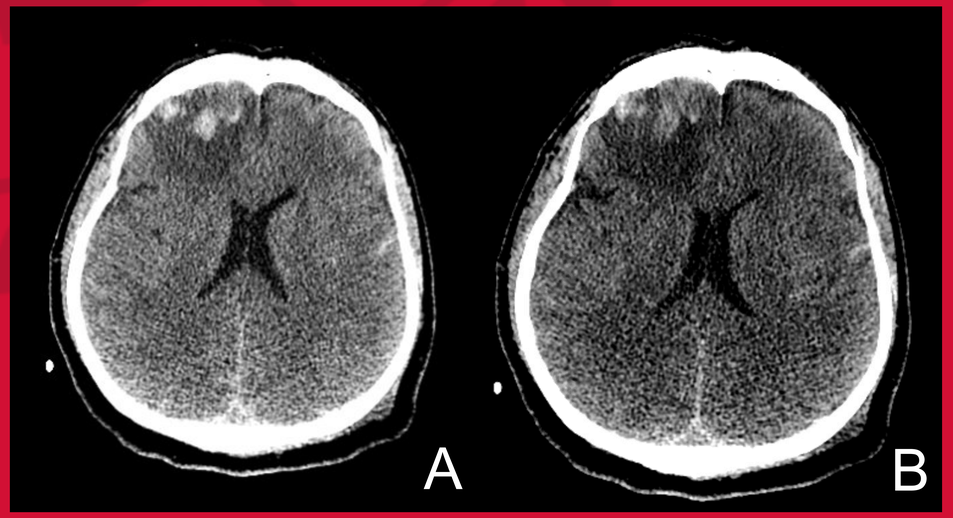
- Amantadine hydrochloride is a medication commonly prescribed for patients with post-traumatic disorders of consciousness (DOC) undergoing inpatient neurorehabilitation.
- Studies have suggested that amantadine may accelerate functional recovery in these patients.
- Accumulation of amantadine can lead to new neuropsychiatric manifestations, which may gradually resolve after cessation of the medication.

Case Report

- A 72-year-old male with a past medical history of coronary artery disease and hypertension presented with acute encephalopathy after falling.
- Physical examination was consistent with a state of unresponsive wakefulness. Computed tomography (CT) showed diffuse subarachnoid hemorrhages, subdural hemorrhage, and hemorrhagic contusions with surrounding edema (**Figure 1a-b**).
- On hospital day four, he was started on 100 mg of amantadine. This dose was later increased to 150 mg twice daily.
- He emerged from his DOC on Day 15 and was discharged to acute rehabilitation on Day 20.
- During this time, his renal function declined, and serum creatinine increased from 0.96 to 1.33 mg/dL.
- At the rehabilitation center, he developed worsening confusion, agitation, restlessness, impulsivity, and new-onset visual hallucinations.
- Subsequent laboratory testing, infectious work-up, and repeat imaging to evaluate for causes of his decline did not reveal any new abnormalities.
- Amantadine was discontinued and intravenous fluids were administered, and his neuropsychiatric symptoms and renal dysfunction significantly improved within two days.

Discussion

- Neuropharmacologic therapies are commonly used off-label to increase arousal and behavioral responsiveness in neurorehabilitation.
- Amantadine, a dopamine modulator and N-Methyl-D-Aspartate receptor antagonist, has been shown to aid functional recovery following severe traumatic brain injury (TBI) through an unclear mechanism.
- Amantadine is renally excreted and may accumulate in elderly patients with renal dysfunction.
- There is currently minimal evidence to support a relationship between plasma amantadine levels and toxic manifestations, and elevated levels are not required for a diagnosis of toxicity.
- Toxicity can occur in settings of mild to severe renal impairment, with varying daily therapeutic doses between 150 mg and 400 mg.
  - This can present clinically as neuropsychiatric symptoms including confusion, auditory or visual hallucinations, agitation, aggression, ataxia, and coma.
- When amantadine toxicity is suspected, prompt discontinuation is essential for management, enabling gradual resolution of symptoms.



Conclusions

- ✓ This case demonstrates resolution of toxic neurologic manifestations following cessation of amantadine in the setting of mild renal impairment.
- ✓ Patients given amantadine after TBI should be monitored carefully for new-onset neuropsychiatric symptoms, with high index of suspicion for toxicity in the setting of renal dysfunction, especially in the elderly.
- ✓ If toxicity is suspected, amantadine should be discontinued, with good prognosis for symptom resolution as seen in this case

REFERENCES

1.Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med*. 2012;366(9):819-826.

2.Meythaler JM, Brunner RC, Johnson A, Novack TA. Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: a pilot double-blind randomized trial. *J Head Trauma Rehabil*. 2002;17(4):300-313.

3.Michalski LS, Hantsch Bardsley C, Holt DR, Milner JE, Hou SH. Altered mental status in a transplant patient. Amantadine toxicity. Kidney International. 2009 Jan;75(2):243-244.

4.Nakata M, Ito S, Shirai W, Hattori T. Severe reversible neurological complications following amantadine treatment in three elderly patients with renal insufficiency. *Eur Neurol*. 2006;56(1):59-61.

5.Spritzer SD, Kinney CL, Condie J, et al. Amantadine for patients with severe traumatic brain injury: a critically appraised topic. *Neurologist*. 2015;19(2):61-64.

Figure 1a-b: Axial CT imaging of the head without contrast showing subarachnoid hemorrhages in the bilateral frontal and parietal lobes, subdural hemorrhage along the right frontal and temporal lobes, and hemorrhagic contusions in the bilateral frontal and temporal lobes with surrounding edema