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Acute respiratory distress syndrome: A rare presentation of amantadine toxicity

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDE Juan Cattoni
ABDEF Ravish Parekh

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, U.S.A.

Corresponding Author: Ravish Parekh, e-mail: rparekh1@hfhs.org

Patient: Male, 64
Final Diagnosis: Acute Respiratory Distress Syndrome (ARDS)
Symptoms: Generalized myoclonic jerks • impaired concentration • memory decline • visual hallucinations
Medication: Amantadine HCl
Clinical Procedure: —
Specialty: Toxicology

Objective: Adverse events of drug therapy

Background: Amantadine is indicated for treatment of influenza A infection, Parkinson disease and extrapyramidal reactions. Amantadine overdose affects mainly cardiovascular and central nervous systems. Amantadine-induced respiratory failure has not been described in previous case reports but it is a potential known side effect.

Case Report: We describe the case of a 64-year-old African American male with end stage renal disease who was prescribed amantadine at a dose for normal kidney function (300 milligrams per day) for no clear reasons. Patient's serum level of amantadine drawn on admission was found to be 6200 nanogram per deciliter (ng/dl) with normal range being 700–1000 ng/dl.

Amantadine hydrochloride is not actively metabolized in humans; is mainly excreted unchanged in urine by glomerular filtration and tubular secretion (90% of the ingested dose). It tends to accumulate in patients with impaired renal function; poorly excreted in patients on hemodialysis and has a large volume of distribution.

Conclusions: Our patient with impaired renal function was prescribed a much higher dose and eventually presented with high serum concentration of amantadine and neurological manifestations suggestive of amantadine toxicity. He developed sudden onset respiratory failure and pulmonary edema which is described as a potential lethal complication of amantadine toxicity. Since there is no specific etiology for his respiratory failure, this could represent the first reported case of Amantadine-induced Adult Respiratory Distress Syndrome (ARDS).

Key words: ARDS • toxicity • Amantadine

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Background

Amantadine is a cyclic primary amine that has antiviral and anti-Parkinsonian activities, which interferes with viral replication and the release of dopamine in the substantia nigra. It is indicated for treatment of influenza A infection, Parkinson disease and extrapyramidal reactions. Amantadine overdose affects mainly cardiovascular and central nervous systems [1–3]. Amantadine-induced respiratory failure has not been described in previous case reports but it is a potential known side effect. We described the case of a patient with respiratory failure and adult respiratory distress syndrome (ARDS) induced by Amantadine.

Case Report

A 64-years-old African American male presented with visual hallucinations, gait disturbances, impaired concentration, memory decline and generalized myoclonic jerks for three days. His medical history is pertinent for Type II diabetes mellitus complicated by diabetic nephropathy leading to end stage renal disease (ESRD), seizure disorder, hepatitis C and respiratory failure secondary to previous intracranial hemorrhage, requiring tracheostomy placement. He was started on Amantadine 300 milligrams (mg) orally daily 2 weeks ago without clear indication. On examination, he was found to have myoclonic jerks in his limbs and trunk at rest, exaggerated during voluntary movement. Laboratory testing, chest radiograph and electrocardiogram did not show acute abnormalities.

One day after admission, he became more confused, hypoxemic, with worsening jerky movements. Arterial Blood gas (ABG) showed hypoxemia with ratio of the partial pressure of oxygen in the arterial blood to the fraction of oxygen in the inspired air (PaO2/FiO2) of 69 (Table 1) while chest radiograph showed new bilateral patchy infiltrates. Patient was transferred to the Medical Intensive Care Unit where suspicion of pulmonary congestion due to volume overload arose. Patient was started on mechanical ventilation and emergent hemodialysis was performed over 4 hours with net removal of 3 liters by ultrafiltration. Few hours later, patient became hypotensive (BP=80/60 mmHg), requiring fluid boluses and vasopressors. Repeat ABG showed hypoxemia and anion gap metabolic acidosis due to elevated lactate; while new chest radiograph demonstrated increased pulmonary patchy infiltrates bilaterally. His ventilator requirements increased with elevated peak and plateau pressures suggesting non cardiogenic pulmonary edema. Shortly after, patient went into cardiac arrest with pulseless electrical activity, expiring after 30 minutes of unsuccessful advanced cardiopulmonary resuscitation.

Autopsy showed diffuse alveolar damage with markedly congested alveolar capillaries and hyaline membranes lining alveolar spaces. Both the lungs had patchy bronchopneumonia with edema and infiltration of airspaces by neutrophils. The stains for bacteria and fungus were negative. It also showed pancreas with fat necrosis and vascular congestion with hemorrhage in the surrounding adipose tissue (Table 2). Serum amantadine concentration on admission was reported later at 6200 ng/dL (normal range: 700–1000).

Table 1. Arterial blood gas parameters in the patient on day 2.

Arterial blood gas parameter	Hospital day 2 in the morning	Hospital day 2 after hemodialysis
pH	7.37	7.17
PaCO2	44	45
PaO2	48	62
FiO2	0.7	1
CO2	24	16
SaO2	76	79
Lactate	2.5	9.8
PaO2/FiO2	69	62

pH – power of hydrogen; PaCO2 – partial pressure of carbon dioxide in arterial blood; PaO2 – partial pressure of oxygen in arterial blood; FiO2 – fractional of oxygen in inspired air; CO2 – bicarbonate in arterial blood; SaO2 – oxygen saturation in arterial blood.

Table 2. Important histological findings on autopsy.

Lungs: The lungs have diffuse alveolar damage with markedly congested alveolar capillaries and hyaline membranes lining alveolar spaces. Both the lungs have patchy bronchopneumonia with edema and infiltration of airspaces by neutrophils. Gram stain is negative for bacteria. Grocott stain is negative for fungus
Pancreas: Markedly autolyzed pancreas with fat necrosis and vascular congestion with hemorrhage in the surrounding adipose tissue
Liver: The architecture of the liver is disrupted by portal to portal and portal to central fibrosis with regenerative nodule consistent with cirrhosis. The portal tracts show fibrosis, chronic lymphocytic infiltrate with bile duct proliferation

Discussion

Amantadine hydrochloride is not actively metabolized in humans; is mainly excreted unchanged in urine by glomerular filtration and tubular secretion (90% of the ingested dose). It tends to accumulate in patients with impaired renal function [4].

It is poorly excreted in patients on hemodialysis and has a large volume of distribution. The average half-life of amantadine in patients on maintenance hemodialysis has been previously report to be approximately 13 days [5]. The recommended dosing in patients on hemodialysis is 200mg every 7 days [6]; however our patient was prescribed a much higher dose causing accumulation of the drug.

Serious side effects were reported in previous cases reports and included cardiac dysfunction (arrhythmias, tachycardia and hypertension), central nervous system toxicity (hallucinations, psychosis, delusions, acute mental status changes, myoclonus, aggressive behavior, hyperkinesia, tremor, confusion, lethargy, somnolence, coma, peripheral neuropathy), metabolic disorders, anticholinergic syndrome, neuroleptic malignant syndrome and serotonin syndrome [1–3,7]. To our best knowledge, no previous cases have reported amantadine-induced pulmonary edema or respiratory failure. However, it is described in pharmaceutical books and post-marketing surveillance [8].

Our patient had the visual hallucinations and the myoclonic jerks on presentation which worsened during the hospitalization. He became more confused by the next day of admission. His pulmonary edema was initially considered to be secondary to volume overload due to ESRD since his initial chest radiograph on admission was normal. However, following his hemodialysis and fluid removal, he became hemodynamically unstable and the repeat chest radiograph showed worsening pulmonary infiltrates. It was unlikely at this point that the patient was having pulmonary edema due to volume overload. The cause for developing adult respiratory distress syndrome was unlikely secondary to infectious pneumonia or pancreatitis as the patient didn't have any clinical signs or symptoms on presentation suggesting it and histology did not support the diagnosis. Also this would not explain the neurological symptoms in this patient.

Acute toxicity may be attributable to the anticholinergic effects of amantadine resulting in cardiac, respiratory, renal or central nervous system effects. There is no specific antidote for amantadine over dosage. Gastric lavage can be attempted in acute intoxications. However our patient had toxicity over the course of 2 weeks due to accumulation of the drug. The usual treatment is general supportive measures (establishment of an adequate respiratory exchange, maintenance of an airway and oxygen administration) while cardiovascular status, temperature, serum electrolytes and urinary output are monitored. Electrocardiographic monitoring may be necessary. If required, sedatives and anticonvulsant therapy should be administered. Although the drug is minimally cleared by dialysis [5], daily hemodialysis can be attempted to increase the clearance of the drug. Physostigmine has also been reported for the management of CNS toxicity caused by amantadine [9].

Conclusions

Our patient with impaired renal function was prescribed a much higher dose and eventually presented with high serum concentration of amantadine and neurological manifestations suggestive of amantadine toxicity. He developed sudden respiratory failure and non-cardiogenic pulmonary edema with PaO2/FiO2 ratio less than 200. Since there was no other explanation for the respiratory failure this could represent the first reported case of Amantadine-induced ARDS.

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