Cardiotoxicity after Massive Amantadine Overdose

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ABSTRACT

Introduction: Amantadine hydrochloride is an antiviral medication used as therapy for parkinsonism and as a cognitive enhancer. We report 2 cases of massive, acute ingestion of amantadine hydrochloride confirmed with serial serum levels.

Case Reports: A 47-year-old woman presented to the emergency department (ED) 30 minutes after ingesting 10 g of amantadine (150 mg/kg) by her report. Initial ECG revealed a sinus rhythm with rate of 93 bpm, and a QRS of 84 msec. While in the ED, the patient sustained a pulseless cardiac arrest and the monitor revealed ventricular tachycardia. She was successfully defibrillated. Postdefibrillation ECG showed a sinus rhythm (rate = 82 bpm), QRS of 236 msec, and QTc of 567 msec. The serum potassium was 1.0 mEq/L (1.0 mmol/L). The patient was given 300 ml (300 cc) 3% sodium chloride IV over 10 minutes. Ten minutes after completion of the hypertonic saline infusion, the patient's ECG abnormalities resolved and the QRS was 88 msec. Her potassium was repleted over the next 11 hours postpresentation, and she also received an IV bolus of 4 g of magnesium sulfate immediately after the cardiac arrest. No further hypotension, dysrhythmia, conduction delay, or ectopy was noted during the patient's hospital stay. The second case involved a 33-year-old female patient who presented 1 hour after ingesting 100 tablets of amantadine hydrochloride (100 mg/tab). Initial ECG revealed sinus tachycardia with a QRS of 113 msec, an R wave in lead aVR of 4–5 mm and a QTc of 526 msec. Her serum potassium was 3.0 mEq/L (3.0 mmol/L), her serum calcium was 9.4 mg/dl (2.35 mmol/L), and serum magnesium was 2.1 mg/dl (0.86 mmol/L) on labs drawn at initial presentation. The patient was intubated for airway protection, and her potassium was repleted and corrected over the next 9 hours. Her ECG abnormalities improved 8 hours after initial presentation and normalized at approximately 14 hours postingestion. The patient was discharged home 11 days after her ingestion.

Conclusion: Acute amantadine toxicity manifests with life-threatening cardiotoxicity. Concurrent, often profound, hypokalemia may complicate the administration of sodium bicarbonate in the management of cardiac dysrhythmias.

INTRODUCTION

Amantadine hydrochloride is an infrequently encountered pharmaceutical agent in acute poisoning cases. Case reports in the literature suggest that amantadine's toxicity is twofold, with chronic overdosage—either by intentional ingestion of a small amount, by therapeutic misadventure, or by unintentional accumulation of the drug due to pharmacokinetic alterations—manifesting as neurotoxicity (hallucinations, disorientation, confusion, and acute toxic psychosis). In large overdoses, amantadine causes significant

cardiotoxicity, manifested primarily by widening of the QRS complex, QT prolongation, ventricular ectopy, and unstable ventricular dysrhythmias which, in many of the literature cases we reviewed, have proven fatal.

CASE REPORTS

Patient 1: A 47-year-old woman with schizophrenia presented to the emergency department (ED) 30 minutes after an intentional ingestion of 10 g amantadine hydrochloride (150 mg/kg)

Keywords: amantadine, overdose, torsades, hypokalemia

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Figure 1: Arrival ECG (Patient 1).

and 250 mg of diphenhydramine. The amounts were admitted by the patient.

In addition to these 2 medications, she received depot haloperidol intramuscularly every month (last dose 3 weeks previously) and reported using ephedra (Metabolife) sporadically. The patient smoked cigarettes, but did not use illicit drugs or alcohol. Per her mother, with whom she lived, the patient did not have access to any other medications.

Initial vital signs were blood pressure 120/80 mm/Hg, heart rate 70 bpm, respirations 16 breaths/minute, and temperature 36.1°C. The patient was placed on oxygen via nasal cannula and an IV line was initiated. An electrocardiogram (Figure 1) on arrival to the ED revealed sinus rhythm at a rate of 93 bpm, with QRS duration of 84 msec. The QTc was 403 msec.

The patient was alert and oriented to person, place, time, and situation. Her pupils were 4 mm, equal, and reactive to light; mucous membranes were moist and bowel sounds were normal. Her neurological examination was unremarkable. There was no jugular venous distension; lung sounds were clear to auscultation and heart sounds were normal.

As the ED physician completed the physical examination, the patient suffered a pulseless cardiac arrest. The monitor revealed ventricular tachycardia and the patient was immediately defibrillated once at 200 joules, with subsequent return of spontaneous

circulation. Postdefibrillation vital signs revealed a pulse of 60 bpm, a blood pressure 70/50 mmHg, and agonal respirations. A dopamine infusion was started at 20 µg/kg/min. Endotracheal intubation was accomplished without the use of adjunctive medication. A central venous catheter and an arterial line were placed. Fifty grams of activated charcoal was administered via nasogastric tube.

Repeat ECG (Figure 2) showed sinus rhythm with a QRS of 200 msec and a QTc of 534 msec. Results of the postintubation arterial blood gas were pH 7.51, pCO₂ 20 mmHg, the pO₂ 356 mmHg, bicarbonate 15 mEq/L (15 mmol/L), sodium 138 mEq/L (138 mmol/L), and potassium 1.0 mEq/L (1.0 mmol/L). Rapid repletion of potassium through the central line (40 mEq over 4 hours), NG tube (40 mEq), and 2 peripheral intravenous lines was initiated. Based on the widened QRS complex and the profound hypokalemia, 300 ml (300 cc) of a 3% sodium chloride solution were rapidly administered over 10 minutes in an effort to treat the presumed sodium channel effects. Administration of sodium bicarbonate was withheld because of the concern that the patient's profound hypokalemia could be worsened by the rapid administration of sodium bicarbonate. Figure 3 was recorded after the first 2 minutes of the 3% saline infusion, and Figure 4 was recorded at approximately 5 minutes after the end of the infusion but prior to narrowing of the patient's QRS complex. The

Figure 2: Post-defibrillation ECG (Patient 1).

Figure 3: Hypertonic saline infusion initiated (Patient 1).

Figure 4: Five minutes post-hypertonic saline infusion (Patient 1).

patient's QRS narrowed 10 minutes after the completion of the hypertonic saline infusion, but an ECG was not obtained immediately after the narrowing was observed. Four hours after completion of the hypertonic saline infusion and 6 hours after initial presentation to the ED, the patient did have a repeat ECG (Figure 5), which showed sinus bradycardia with a QRS duration of 88 msec and a QTc of 444 msec.

The patient also received 4 g magnesium sulfate IV 2 hours after presentation to the ED. Dopamine was replaced with norepinephrine (8 μ g/min) with a corresponding increase in the heart rate to 80 bpm and a rise in the blood pressure to 130/70 mmHg. Subsequently, the norepinephrine infusion was reduced to 4 μ g/min and weaned off over the next 6 hours after her cardiac arrest.

Figure 5: Four hours post-hypertonic saline infusion (Patient 1).

Other laboratory results obtained 2 hours after presentation to the ED were: sodium, 140 mEq/L (140 mmol/L); potassium, 1.3 mEq/L (1.3 mmol/L); chloride, 105 mEq/L (105 mmol/L); bicarbonate, 18 mEq/L (18 mmol/L); and glucose, 178 mg/dl (9.88 mmol/L). The calcium was 10.0 mg/dl (2.50 mmol/L) and the magnesium was 2.3 mg/dl (0.95 mmol/L). The blood urea nitrogen was 12 mg/dl (4.28 mmol/L) and the creatinine was 1.2 mg/dl (106.08 μ mol/L). The creatine phosphokinase was 96 U/L, the MB fraction was 0.4 U/L, and the troponin I was <0.01 ng/ml (<0.01 μ g/L). The complete blood count, AST, ALT, alkaline phosphatase, bilirubin, and albumin were normal.

The urine toxicology screen was negative for opiates, benzodiazepines, cocaine metabolites, amphetamines, cannabinoids, barbiturates, and phencyclidine. Serum levels of acetaminophen, salicylates, and ethanol were undetectable. The beta human chorionic gonadotropin assay was negative.

The patient's potassium concentration at approximately 5 hours after presentation to the ED had risen to 1.8 mEq/L (1.8 mmol/L). Eleven hours after initial presentation to the ED and 6 hours after admission to the intensive care unit the potassium level had increased to 4.6 mEq/L (4.6 mmol/L), and repletion was stopped. The magnesium levels during the initial 11 hours after presentation ranged from 2.6 to 3.2 mg/dl (1.07 to 1.31 mmol/L).

After treatment with hypertonic saline, no further hypotension, dysrhythmia, conduction delay, or ectopy was noted. Twenty-six hours after presentation, the ECG remained normal and the patient had normal vital signs without any vasopressor support. Serial measurements of the amantadine and diphenhydramine concentrations in the patient's serum were made at 2.5, 24, and 51 hours postingestion (Table 1). Comprehensive screening with GC/MS detected only diphenhydramine and ephedrine in addition to amantadine. No haloperidol was detected.

Patient 2: A 33-year-old woman with hypertension and pseudotumor cerebri presented to the ED 60 minutes after an intentional ingestion of approximately 10 g of amantadine hydrochloride (166 mg/kg) and 4 tablets of alprazolam of unknown strength. The patient had access to olmesartan, cyclobenzaprine

Table 1: Analytical Results for Case Patients

	Time Postingestion (h)	Amantadine Concentration (μ g/ml)	Diphenhydramine Concentration (μ g/ml)
Patient 1	2.5	29.0	5.2
	40	7.0	1.2
	51	0.92	0.90
Patient 2	3.5	13.0	
	16	5.3

Figure 6: Post-intubation (Patient 2).

and loperamide but denied ingesting those in our initial as well as follow-up interviews. The patient suffered from major depressive disorder and did not use illicit drugs or alcohol.

Initial vital signs were blood pressure 95/65 mm/Hg, heart rate 83 bpm, respirations 16 breaths/minute, and temperature 36°C. The patient was placed on oxygen via nasal cannula and an IV line was initiated. The patient was alert and oriented to person, place, time, and situation. Her pupils were 6 mm, equal, and reactive to light; mucous membranes were moist and bowel sounds were normal. Her neurological examination was unremarkable. There was no jugular venous distension; lung sounds were clear to auscultation and heart sounds were normal. The patient was given 50 g of activated charcoal.

Shortly after her arrival, her mental status deteriorated and she was intubated for airway protection. Her ECG (Figure 6) revealed sinus tachycardia with a QRS of 113 msec, an R wave in lead aVR of 4–5 mm, and a QTc of 526 msec. Her serum potassium was 3.0 mEq/L (3.0 mmol/L), her serum calcium was 9.4 mg/dl (2.35 mmol/L), and serum magnesium was 2.1 mg/dl (0.86 mmol/L). The urine toxicology screen was positive for opiates and benzodiazepines, but negative for cocaine metabolites, amphetamines, cannabinoids, barbiturates, and phencyclidine. Serum levels of acetaminophen, salicylates, and ethanol were undetectable. The beta human chorionic gonadotropin assay was negative. The patient was started on polyethylene glycol by nasogastric tube at a rate of 1 L/hr, and she received 40 mEq IV potassium chloride

repletion and 2 g magnesium sulfate IV. Her serum potassium corrected over the next 9 hours from the time of initial presentation (10 hours after ingestion). Her ECG abnormalities improved 8 hours and normalized 14 hours postingestion. The patient was admitted to the medical intensive care unit and was extubated on the second day of her admission. The rest of her hospital stay was uneventful. She was transferred to the psychiatry service 5 days later and was finally discharged to her home 11 days after her initial admission. Serial measurements of her serum amantadine levels obtained on samples drawn 3.5 and 16 hours postingestion (2.5 and 15 hours postpresentation) are demonstrated in *Table 1*. Her cyclobenzaprine quantitative level was 20 ng/ml measured on the sample obtained 3.5 hours after ingestion. No comprehensive GC/MS analysis was performed due to insufficient sample; however, in light of the admission by the patient that she took 4 alprazolam tablets, we believe that alprazolam was responsible for the finding of benzodiazepines on the urinary screen.

DISCUSSION

Amantadine hydrochloride is a dopamine agonist with antiparkinsonian activity. Amantadine also inhibits the M2 potassium channel activity of influenza A virus, hence its indication for the prevention and symptomatic treatment of influenza. The therapeutic serum level for the treatment of influenza A infection is 0.03–1.0 µg/ml. The central nervous system is the primary site of toxicity from chronic overdose with amantadine or small intentional ingestions [1,2,3]. In large, acute overdoses, however, amantadine toxicity primarily results in cardiovascular toxicity manifested as QRS widening, QT prolongation, and ventricular dysrhythmias [4,5,6,7,8,9,10]. Neurotoxicity from amantadine has been reported at serum levels >1 µg/ml [3]. Amantadine-induced neurotoxicity may occur due to accumulation of the drug as a result of excessive dosing or decreased renal clearance, with

subsequent increase of serum concentration to toxic levels in the range of 1–5 µg/ml. Neurotoxicity may present with subtle signs and symptoms such as behavioral changes, aggression, disorientation, and confusion, eventually progressing to acute toxic psychosis. Macchio et al. described a patient with a therapeutic misadventure (100 mg bid instead of 100 mg weekly)—in the context of hemodialysis-dependent ESRD—who developed anxiety, confusion, and mental status changes, ultimately progressing to coma; the serum amantadine level was 1.6 µg/ml [3]. Fahn et al. described a patient who ingested 2.8 g of amantadine in a suicide attempt. Their patient developed an acute toxic psychosis, and they describe urinary retention requiring catheterization, and mydriasis. In addition to the dopaminergic action of amantadine, the authors postulate that amantadine may have anticholinergic properties. The anticholinergic mechanism of action may contribute to the neurotoxicity seen at elevated serum levels in mild to moderate overdose [11]. Recent evidence suggests that amantadine acts as a noncompetitive NMDA antagonist [12].

Amantadine-induced cardiotoxicity manifests after large acute ingestions. The onset of ECG changes, ventricular dysrhythmias, and hemodynamic instability (including cardiac arrest) may occur suddenly and often present a challenge to manage clinically. We conducted a Medline search of the literature from 1965 to the present using these keywords: amantadine PLUS overdose, ingestion, poisoning, toxicity, death, dysrhythmia, and cardiac. *Table 2* summarizes the observed cardiac effects, treatment, and outcomes of acute amantadine poisoning cases reported in the literature. Several cases of amantadine overdose that resulted in neurotoxic effects but no cardiotoxicity are referenced here but not included in the table [1,2,3,11].

Animal-experiment evidence and case reports of human poisoning suggest that in acute overdose amantadine blocks the outward-rectifying potassium current and poisons 2 fast sodium

Table 2: Cardiac Dysrhythmias, Treatment, and Outcome of Acute Amantadine Overdose Reports in the Literature

Citation	Sex* (Age)	Dysrhythmia†	Therapy	Outcome	Ingestion (Plasma concentration)
Berkowitz, 1979 [4]	F (2)	ST	Physostigmine	Recovered	600 mg (ND§)
Sartori et al, 1984 [5]	F (37)	TdP, RBBB	Atropine, isoproterenol, lidocaine, dopamine	Died	2.5 g (ND)
Cook et al, 1986 [6]	M (23)	Found dead	None	Died	3.0 g (4.8 mg%, postmortem)
Simpson et al, 1988 [7]	M (34)	Not reported	ACLS‡	Died	2.0 g (ND)
Brown et al, 1987 [8]	F (37)	SB, Vtach	Not reported	Died	12 g (serum 23.4 µg/ml)
Pimentel et al, 1991 [9]	F (17)	PVCs, SB	Lidocaine	Recovered	1.4 g (ND)

*F, female; M, male
†ST, sinus tachycardia; TdP, Torsades de Pointes; RBBB, right bundle branch block; SB, sinus bradycardia; Vtach, ventricular tachycardia; PVCs, premature ventricular complexes
‡ACLS, advance cardiac life support
§ND, not done

channels in the heart. Amantadine induces afterpotentials and automaticity through 2 different mechanisms [13]. Electrophysiological studies in frog, rabbit, dog, and calf have demonstrated that repolarization is prolonged with increasing concentrations of amantadine, resulting in 2 different types of afterdepolarizations [13]. One type of afterdepolarization observed was tetrodotoxin (TTX) sensitive and is believed to be due to incomplete fast sodium-channel repolarization. Experimentally, this type of afterdepolarization was abolished when TTX was added to the test system [14]. The tricyclic structure of amantadine may be responsible for this activation of tetrodotoxin (TTX)-sensitive fast sodium channels, which leads to the incomplete repolarization and decreased action potential amplitude [14]. Hiraoka et al. demonstrated in isolated guinea pig ventricular cells that amantadine induces afterpotentials by activating tetrodotoxin-sensitive sodium channels at a point at which inward Na current is noninactivating [14]. This fast sodium channel activation might explain the QRS interval widening observed in fatal overdose cases and the left bundle branch block (LBBB) pattern in our Case Patient 1.

However, amantadine also activated an inward current that was TTX resistant and occurred despite a low sodium concentration in the test system. The activation of this second inward current caused depolarization of the diastolic potential [14]. Hiraoka et al. concluded that amantadine activates 2 different inward currents, resulting in 2 distinct types of afterpotentials: one due to incomplete repolarization resulting from activation of a TTX-sensitive fast sodium channel, and a second delayed afterdepolarization (DAD) resulting from activation of the TTX-insensitive inward current identified in their experimental model [14].

Amantadine has also been shown to block the outward-rectifying potassium current in guinea pig ventricular myocytes [14]. The delayed outward potassium current (I_K) was depressed by amantadine in a dose-dependent manner. This second type of afterdepolarization observed in these experiments was a classic DAD resulting from depression of the delayed potassium tail current during repolarization [13]. In distinction to the DAD associated with activation of the TTX-resistant inward current described by Hiraoka et al., the amplitude of triggered activity associated with DADs resulting from block of I_K decreases with heart rate. It has been observed that overdrive pacing may suppress amantadine induced depolarizations; basic science studies on DADs support this hypothesis [13,14]. However, the catecholamine-sensitive nature of DADs may explain the worsening of amantadine cardiotoxicity upon institution of dopamine therapy in 1 reported case [5]. Amantadine-induced dopamine release and/or the administration of exogenous catecholamines may actually exacerbate ventricular myocardial irritability and increase the risk of dysrhythmias. In our Case Patient 1, after the initial episode of ventricular tachycardia, dopamine was initiated but subsequently replaced with norepinephrine, after which our patient did not suffer any further dysrhythmias.

Lastly, in the guinea pig model described by Hiraoka, amantadine also depressed the calcium current (I_{Ca}) without an appreciable change to its voltage dependence.

Clinically, acute amantadine overdose can be manifest by the rapid and dramatic development of cardiotoxicity consisting primarily of malignant ventricular dysrhythmias: monomorphic ventricular tachycardia and Torsades de Pointes (TdP). However, in some cases, cardiotoxicity has not developed for many hours: Sartori et al. report a case in which the patient developed TdP 40 hours after an acute ingestion of 2.5 g amantadine [5]. It is unclear in their case whether TdP or some other ventricular dysrhythmia was responsible for their patient's initial cardiac arrest. The development of cardiotoxicity can be variable in moderate overdoses: in the case reported by Fahn et al., no cardiac toxicity was reported despite 2.8-g ingestion [11].

In our 2 case patients, each with very large ingestions, the QRS widening was most likely due to fast sodium channel activation. Based on the described mechanism of sodium channel poisoning, this raises an important question regarding management with sodium bicarbonate or hypertonic saline. While cardiac toxicity due to sodium channel effects (activation: amantadine, aconite; or blockade: TCAs) may be difficult to distinguish when addressing the critically-ill patient acutely, there is at least a theoretical risk of sodium loading if there is an augmented inward sodium current. In our case patients, bicarbonate therapy was relatively contraindicated in light of the profound hypokalemia and the risk of sodium bicarbonate shifting more potassium intracellularly. Hypertonic saline was used instead of bicarbonate, with a rapid normalization of the QRS widening.

The ECGs of Case Patient 1 demonstrated QT interval widening, probably as a result of slowing of the outward rectifying potassium channel in cardiac myocytes from the direct effects of amantadine [14], and possibly exacerbated by the patient's profound hypokalemia. The etiology of the hypokalemia from amantadine poisoning is unclear. Although it is possible that hypokalemia was a preexisting condition (i.e., prior to the overdose), the rapid correction of her serum potassium over 11 hours suggests that hypokalemia was a result of intracellular shift and not total body depletion. Given amantadine's toxic effects at the sodium and potassium channels in the myocyte, we suspect that amantadine toxicity was responsible for the hypokalemia seen in our patients. The lack of hypokalemia or prolonged QT in the patient reported on by Sartori et al. is interesting: it suggests that the finding of QT prolongation and hypokalemia may not always be present despite significant cardiotoxicity. It also suggests that, despite their patient's late development of TdP, the initial cardiac arrest was more likely due to a ventricular dysrhythmia other than TdP. Although anecdotally it has been absent in amantadine overdose cases, clinicians should suspect hypokalemia in amantadine poisoning for two reasons: an extremely low potassium level may be a contraindication to sodium bicarbonate if it is being considered as therapy; and IV repletion of potassium in the acute setting may be indicated, especially if profound QT prolongation is present. In addition, dysrhythmias in the setting of amantadine poisoning may provoke the clinician to consider the use of amiodarone, a common antiarrhythmic for the treatment of ventricular dysrhythmias. However, theoretically, amiodarone

could worsen the potassium channel blockade. Lidocaine might be an alternative pharmacological agent for the treatment of amantadine-induced ventricular dysrhythmias or ectopy if clinical indicators such as hypokalemia or prolonged QT cause concern for the use of amiodarone.

At therapeutic doses amantadine hydrochloride has a bioavailability of between 55 and 90% [15]. This bioavailability appears to be independent of ingested dose, leading to dose-dependent increases in absorbed drug in the acute overdose setting. At plasma concentrations between 0.1 and 2.0 $\mu\text{g/ml}$, amantadine was 67% protein bound [16]. Amantadine had an apparent V_d of 4.4 L/kg in healthy controls [15].

Our Case Patient 1 ingested 10 g amantadine and experienced cardiac arrest approximately 2 hours after ingestion. The serum concentrations obtained from the case patients at 2.5, 24 and 51 hours (Patient 1), and at 3.5 and 16 hours (Patient 2), after ingestion are shown in *Table 1*. The serum concentration of Patient 1 at 2.5 hours approximates the likely peak as determined by pharmacokinetic data, and best identifies the concentration at the point of maximum cardiotoxicity. Patient 1 did not have significant enough concentrations of diphenhydramine to explain the cardiotoxicity, and comprehensive toxicology testing by GC/MS identified only traces of ephedra and no other cardiotoxic drugs in the samples. Patient 2 had a therapeutic level of cyclobenzaprine (20 ng/ml; range following 10 mg tid dosing 3–36 ng/ml) detected on quantitative testing, which was not felt to be sufficient to cause cardiotoxicity.

CONCLUSION

We describe 2 cases of massive amantadine ingestion resulting in significant cardiotoxicity with similar management and clinical courses. In contrast to amantadine-induced neurotoxicity following chronic overdose, acute amantadine overdose frequently manifests as a spectrum of cardiotoxicity from ectopy and interval changes to lethal ventricular dysrhythmias. The cardiac electrophysiological changes caused by the underlying poisoning of multiple myocyte ion channels can be varied and pose a significant challenge for acute clinical management by the toxicologist. Because of the possibility of coexisting hypokalemia, hypertonic saline may be a better choice than sodium bicarbonate for the initial treatment of wide-complex dysrhythmias in the setting of amantadine overdose, if in fact sodium loading is being considered. Magnesium replenishment was useful in our case patients, and prior case reports have described TdP in the setting of amantadine overdose [5]. Cardiac dysrhythmias may be responsive to overdrive pacing, but there is the theoretical risk of exogenous catecholamine administration worsening DADs. The complex

nature of amantadine-induced cardiotoxicity makes it one of the more difficult toxidromes to manage clinically.

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