A Fatal Case of Thallium Toxicity: Challenges in Management

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Abstract

Background Thallium is a highly toxic compound and is occasionally involved in intentional overdoses or criminal poisonings. Accidental poisonings also occur, but are increasingly rare owing to restricted use and availability of thallium. We report a fatal suicidal ingestion of thallium sulfate rodenticide in which multi-dose activated charcoal (MDAC) and Prussian Blue (PB) were both used without changing the outcome.

Case report A 36 year old man ingested an unknown amount of thallium sulfate grains from an old rodenticide bottle. He presented to an emergency department (ED) 45 minutes later with abdominal pain and vomiting. On examination he was agitated with a blood pressure of 141/60 mmHg and a heart rate of 146 beats per minute (bpm). He received MDAC during his initial ED management and was started on PB 18 hours post arrival; he was intubated on the following day for airway protection. The patient continued to be tachycardic and hypertensive and subsequently developed renal failure. On hospital day three, the patient developed hypotension that did not respond to fluids. The patient required vasopressors and was transferred to a tertiary care center to undergo continuous renal replacement therapy (CRRT). The patient died shortly after his transfer. His last blood thallium concentration was 5369 mcg/L, a

spot urine thallium >2000 mcg/L, and a 24- hour urine thallium was >2000 mcg/L.

Conclusion Though extremely rare, thallium intoxication can be lethal despite early administration of MDAC and use of Prussian blue therapy. Rapid initiation of hemodialysis can be considered in cases of severe thallium poisoning, to remove additional thallium, to correct acid-base disturbance, or to improve renal function.

Keywords Thallium · Prussian blue · Multi-Dose activated charcoal · Hemodialysis

Introduction

Thallium is an odorless, tasteless, and colorless heavy metal discovered in the 1860s during the use of flame spectroscopy to experimentally determine the composition of minerals [1]. Thallium salts were first used as pesticides in Germany in the 1920s and because of their severe toxicity eventually became used as rodenticides [2]. However, after several poisonings, thallium use as rodenticide was banned in the United States in 1965. Thallium is still considered one of the more toxic compounds known to man with a lethal dose reported to be 10–15 mg/kg and with deaths in adults being reported from doses as low as 8 mg/kg [3, 4]. From 1995 to 2005, the American Association of Poison Control Centers reported 830 human exposures to thallium including one death from 1995 to 2009 [5]. Several treatment modalities have been used for thallium toxicity, but no single antidote has been shown to be effective in severe toxicity. However, combinations of different treatments have been proven to be beneficial in a number of cases [6]. This case report will describe our experience with a patient who received multi-dose activated charcoal and Prussian blue but died even as Continuous Renal Replacement Therapy (CRRT) was being

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considered. We will also discuss the importance of considering early hemodialysis in severe thallium toxicity

Case Report

A 36-year-old, 70-kg male patient ingested an unknown amount of thallium sulfate granules from an unlabeled bottle of a rodenticide. He presented without the container via Emergency Services to the emergency department (ED) of a local community hospital 45 min after ingestion. On arrival, he was complaining of severe abdominal cramps and was vomiting. His medical history was significant for depression and alcoholism, but he was not taking any medication. On physical examination, his blood pressure was 141/60 mmHg, and his pulse was 146 beats per minute. He was agitated and confused and had a diffusely tender abdomen. Initial routine laboratory values were unremarkable except for a serum ethanol of 300 mg/dL. Abdominal radiographs did not show any evidence of radiopaque material. A medical toxicology consultation was requested through the regional poison center and resulted in a recommendation to administer multi-dose activated charcoal with airway protection pending the acquisition of Prussian blue. The patient received multi-dose activated charcoal, intravenous fluids, and an intravenous lorazepam infusion for sedation in the ED. His clinical course was further complicated by aspiration which required endotracheal intubation, and he was admitted to the intensive care unit (ICU). Severe abdominal pain and a concern for mechanical intestinal obstruction warranted consultation with the surgical team followed-up with repeated abdominal radiograph and physical examinations that remained unable to detect any obstructive cause. Because of Prussian blue unavailability, it was not administered until 18 h after the toxic ingestion. The manufacturer was notified of the emergent need for the antidote and shipped it by overnight courier. Prussian blue was administered by orogastric tube at a dose of 4 g every 6 h (200 mg/kg/day) along with sorbitol (200 mg/kg/day), and the multi-dose activated charcoal was discontinued. Tachycardia and hypertension persisted over the subsequent 48 h with a maximal blood pressure of 167/90 mm Hg and a pulse of 155 bpm. On the third hospital day, the patient developed worsening renal function with a BUN of 36 mg/dL, a creatinine of 4.51 mg/dL, and decreasing urinary output. Conservative management with fluid boluses initially improved the renal function and increased the urinary output, but oliguria supervened. On the fifth day, he developed circulatory shock with a systolic blood pressure of 90 mmHg and was unresponsive to fluid boluses and the addition of vasopressors. At this time, he had a metabolic acidosis with serum bicarbonate of 15 mmol/L. Enhanced elimination techniques such as hemodialysis had not been

considered earlier and because of refractory hypotension could no longer be performed. As a result, he was transferred to a tertiary-care university hospital for further management. After arrival at the university hospital through EMS, he was immediately placed on CRRT. Approximately 2 h later, he developed unstable ventricular tachycardia leading to ventricular fibrillation that required ultimately unsuccessful cardiopulmonary resuscitation. At the time of death, the patient had already received nine doses of Prussian blue. Initial blood and urine thallium levels were extremely elevated and are presented in Table 1. His serial complete blood counts, complete metabolic panel, and liver biochemical tests appear in Tables 2, 3, and 4, respectively. At autopsy, the cause of death was concluded to be multi-organ system failure, with microscopic findings that were significant for acute and chronic congestion in the lungs, erosive gastritis, renal autolysis with mild glomerular sclerosis, and mild left ventricular hypertrophy. Neuropathology failed to demonstrate any significant histopathological abnormalities.

Discussion

The pathophysiology of thallium toxicity is not well understood, but the structural similarity of this compound to potassium is thought to play a key role in the handling of thallium ions by the body in overdose situations [7]. As a mitochondrial poison, thallium appears to bind sulfhydryl groups on the mitochondrial membrane to interrupt the activity of sodium–potassium ATPase. Thallium is thought to have a tenfold higher affinity for this enzyme compared with potassium [8]. Thallium toxicokinetics follows a three-compartment model. The first rapid exchange compartment consists of the intravascular system and highly perfused organs. The second slow-exchange compartment involves the central nervous system, and the third compartment consists of the large and small intestine. This last compartment is responsible for extensive entero-enteric circulation between all parts of the intestines [9] and contributes to the

Table 1 Blood and urine thallium levels

Day	Blood thallium, mcg/L	Spot urine thallium, mcg/L	24-h urine thallium, mcg/L
1	>1000*	>2000*	
3			>2000*
4	5369		>2000*

Lab normal values of spot urine, <0.4 mcg/L; 24 h urine, <2 mcg/L; random blood, <5 mcg/L. *Actual Thallium level was far above from the lab reporting limit for Blood >1000 mcg/L and Urine >2000 mcg/L

Table 2 Complete blood count

	Day 1	Day 2	Day 3	Day 4	Day 4
WBC, k/ μ L	10.6	11.6	13.9	15.8	6.7
RBC, m/ μ L	6.5	6.1	5.7	6	4.8
HGB, g/dL	18.4	17.7	16.1	17.7	13.8
HCT, %	54.5	52.0	48.9	51.7	41.10
Platelet, k/ μ L	341	299	237	219	156

thallium's prolonged half-life, which can be up to 15 days in patients with massive ingestions [9, 10]. Elimination of thallium occurs via feces (66 %) and urine (33 %) [9]. Treatment options in cases of acute thallium toxicity include, in addition to supportive care and multi-dose activated charcoal, the use of Prussian blue and extracorporeal drug removal including hemodialysis and hemoperfusion [6].

The United States Food and Drug Administration has approved Prussian blue [potassium ferric hexacyanoferrate (II)] for the treatment of thallium toxicity of internal contamination with radioactive cesium. Prussian blue exchanges a potassium ion with thallium and other monovalent cations [11]. It is available in both soluble and insoluble forms; however, the currently available commercial product Radiogardase® by McGuff compounding pharmacy is in the insoluble form. While there are some structural differences between these two forms, it is not clear whether these differences result in substantially different clinical outcomes. Only one animal model suggested that soluble Prussian blue contains more potassium ions than the insoluble product could on that basis be superior in experimental thallium intoxication [12]. Binding of thallium to Prussian blue limits the absorption of thallium in the gastric mucosa, interrupts entero-enteric circulation, and enhances fecal excretion. This effect has been shown in animal studies to decrease the neurotoxicity of thallium [13].

No controlled human trials have evaluated the efficacy of Prussian blue in thallium poisoning. Most of the existing evidence relies on animal studies and case reports. In one case report, a patient was treated with Prussian blue for 46 days as well as with forced diuresis using furosemide, and with hemodialysis, and the three methods were somewhat efficacious in removing thallium with Prussian blue removing the largest amount [14]. In another case report, a patient with severe acute poisoning resulting in serum thallium levels of 5,249 mcg/L received Prussian blue and hemodialysis promptly and had a favorable outcome [15]. The literature suggests the hemodialysis should be considered early in massive toxicities; our patient did not receive CRRT until the fifth day. Despite its large volume of distribution (V_d of 2–3 L/kg), thallium is thought to be dialyzable because of its small size and its lack of protein binding [16]. Additionally, the constipation resulting from the gastrointestinal toxic effects of thallium decreases fecal clearance and increases the availability of thallium in circulation for removal by dialysis [10]. This is particularly true for large ingestions in which hemodialysis instituted within 48 h [17].

Several case reports advocate the use of enhanced elimination techniques such as hemodialysis, forced diuresis, and hemoperfusion. For example, one case report showed hemodialysis eliminated 21 % of an ingested 2 g of thallium [18]. A case series of three cases concluded that hemodialysis may enhance elimination of thallium in greater quantities than forced diuresis [19]. Another case report revealed that hemodialysis eliminated approximately 10 mg of thallium in 1 h, twice the dose that kidney could over the same time period [20]. Finally, one case report of thallium toxicity stated that forced diuresis and hemodialysis were similarly effective in removing thallium (128 mg in 54 h and 276 mg in 120 h, respectively) [21]. A recent case series of ten patients who became critically ill after ingesting a cake contaminated with thallium showed that amount ingested is critical factor in thallium toxicity. Most of these patients required ICU-level care, and three of them died despite receiving four sessions of

Table 3 Biochemistry

	Day 1	Day 2	Day 2	Day 3	Day 4	Day 4
Glucose, mg/dL	150	141	154	193	171	400
BUN, mg/dL	10	12	15	19	36	37
Creatinine, mg/dL	0.99	1.33	1.29	2.47	4.51	5.88
Calcium, mg/dL	9.9	10.2	10.2	10.2	9.3	7.1
Sodium, mmol/L	139	146	147	145	143	128
Potassium, mEq/L	4.0	4.7	4.8	4.6	5.3	4.8
Chloride, mmol/L	102	109	115	111	105	99
Creatine kinase, U/L	64	1,176			530	
CO ₂ , mmol/L	18	20	22	22	24	15
Anion gap	19.0	17.0	10.0	12.0	14.0	14

Table 4 Liver biochemistry test

	Day 1	Day 2	Day 2	Day 4	Day 4
Albumin, g/dL	4.8	4.3	4.1	3.1	1.8
Bilirubin total, g/dL	0.2	0.3	0.4	0.4	0.4
AKP, U/L	135	108	112	131	66
Protein, g/dL	8.8	8.0	7.7	7.2	4.0
ALT (SGPT), U/L	87	93	91	79	268
AST (SGOT), U/L	37	58	62	31	403

hemodialysis and Prussian blue [22]. If hemodialysis is to make a difference, then logic would dictate that it be started as early as possible. In the cases where it was felt to be beneficial, it was started early in the course of therapy. Our patient's course was maybe potentially affected by the delay in starting the extracorporeal removal. The additional efficacy of hemodialysis in removal of thallium could make a difference in outcome when added to Prussian blue administration. In our case, there was also delay in obtaining and starting Prussian blue; the contribution of this delay to our patient's ultimate demise is unclear. In 2009, an expert panel developed evidence-based guidelines for the management of thallium toxicity. This panel recommended the use of Prussian blue without recommending stocking it in acute-care hospitals [23]. It is important for healthcare providers including toxicologists to be familiar with local and regional resources that can provide a supply of this antidote in the event of an emergency.

Conclusion

Though extremely rare, thallium intoxication can be lethal despite early administration of multi-dose activated charcoal and the use of Prussian blue therapy. In cases of severe thallium poisoning, hemodialysis may be considered either alone or in combination with MDAC and Prussian blue, to remove additional thallium, to correct acid–base disturbance, or to improve renal function. However, further studies are needed to validate the role of hemodialysis in the morbidity and mortality from thallium poisoning.

Conflict of Interest None.

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