

Thallium Poisoning- A Review

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Abstract: Thallium is one of the most toxic of the heavy metals. Its continued use as a rodenticide in many developing countries and its increasing use in an expanding number of new technologies raise concerns about exposure risk to animals and humans. Thallium is a tasteless, odorless, and water-soluble chemical element for which both accidental intoxication and criminal poisoning have been reported. Thallium poisoning is one of the serious toxicities known to man. The symptomatology of its toxicity is usually nonspecific due to the multi-organ involvement.¹ The initial symptoms of thallium poisoning may include fever, gastrointestinal problems, delirium, convulsions and coma. Common symptoms are mild gastrointestinal disturbances, polyneuritis, encephalopathy, tachycardia, skin eruptions, stomatitis, atrophic changes of the skin, nail changes (Mee's lines), and skin hyperesthesia (mainly in the soles of the feet and the tibia).¹ The current therapy for thallium poisoning is the use of prussian blue and potassium chloride. Potassium therapy is probably the single most effective agent in the treatment of thallium poisoning. Treatment with prussian blue (or activated charcoal) will interrupt the enterohepatic cycling of Thallium, thus enhancing fecal elimination of the metal. Forced diuresis with potassium loading will increase the renal clearance but should be used cautiously because neurologic and cardiovascular symptom may be exacerbated.² If recognized and treated early, Thallium poisoning carries a favorable prognosis for full recovery.

Keywords: Thallium, poisoning, symptoms, diagnosis, treatment

Introduction: Thallium was accidentally discovered in 1861 by Sir William Crookes, who noted an unexpected green banding on colorimetric spectroscopy, while researching tellurium ore. Thallium is a metal with a storied history of medicinal and commercial applications as a depilatory, syphilis remedy, rodenticide, ant killer, and in the manufacturing of photocells and semiconductors. Today, medicinal use is limited to trace amounts of radioactive thallium for nuclear imaging. Thallium is a tasteless, odourless, and extremely potent poison and its acute ingestions of as little as one gram of thallium salt may kill an adult. Thallium is a well-known poison cited in numerous works of fictional literature, but is also a popular real-life agent of murder with worldwide homicidal usage documented since the 1800s.

Thallium, a chemical element with the symbol Tl, has an atomic number 81 on the periodic table. Thallium sulfate was once used as an ant and rat poison. The occupational limit for thallium exposure is 0.1 mg/m³ to the skin for eight hours a day. Levels of 15 mg/m³ are considered immediately dangerous to one's health. Thallium is readily absorbed through the skin as well as during inhalation. Due to thallium being tasteless, odourless, and water-soluble, accidental and criminal intoxication has been reported. More current uses of thallium are in the semiconductor and optical industries. Thallium is used in rat poison and ant killer, and because it is both odourless and tasteless, it has become an accidental intoxication as well as a criminal poison in some cases. To this day, thallium is seen in rodenticide and insecticide in other countries. In Africa, thallium has been used as a pesticide, which has led to food contamination. Intoxication occurs by cumulative intake through the skin, respiratory, and gastrointestinal tracts.³ Accidental snorting by cocaine abusers, accidental injection by heroin users, as well as skin absorption through protective gloves has been reported.

Thallium is structurally similar to potassium and is treated as such at the cellular level. The following five major toxicological effects are seen with thallium toxicity:

1. Tissues with high potassium concentrations also accumulate large concentrations of thallium. This causes early stimulation, followed by inhibition of potassium-dependent processes.
2. Riboflavin sequestration due to thallium and inhibition of flavin adenine dinucleotide disrupts the electron transport chain and decreases ATP production.
3. Thallium's high ability for disulphide bonds disrupts cysteine residue cross-linking, causing a reduction in keratin formation.
4. Ribosomes are damaged by thallium's effects on protein synthesis, especially the 60S ribosome.
5. Lastly, thallium causes degeneration of myelin in the central and peripheral nervous systems, though the mechanism remains unknown.

Toxicokinetics

Intravascular Distribution Phase: During the first 4 hours post-exposure, thallium is distributed to organs via the blood.

CNS Distribution Phase: During the next 4 to 48 hours, thallium reaches the central nervous system.

Elimination Phase: This phase begins around 24 hours post-exposure and is mainly achieved through renal excretion and feces. This is a slow phase and may take up to 30 days.

Sign and symptoms:

Acute Exposure: Symptoms include gastrointestinal, neurological, and dermatological.

Chronic Exposure: Results in continuation of the above; however, neurological symptoms persist even as blood thallium levels decrease.

Gastrointestinal Symptoms Abdominal pain, Nausea/Vomiting, Diarrhea or constipation, Rarely vomitus or stool containing blood.

Neurologic Symptoms Ascending peripheral neuropathies, Distal motor weakness, Ataxia, Tremor, Cranial nerve palsies, Headache, Seizures, Insomnia, Coma, Death may occur.

Ocular Symptoms Diplopia, Ptosis, Seventh cranial nerve palsy, Nystagmus, Optic neuropathy, Lens opacities.

Dermatologic Symptoms At first nonspecific findings such as scaling and acneiform/pustular eruptions may occur. After 2 to 3 weeks, alopecia begins due to the cysteine disulfide bond disruption. One month after poisoning, Mees lines appear on the nails. Hypohidrosis, Anhidrosis, Painful glossitis etc.

Physical though the exam should focus on the affected areas, a neurologic, ophthalmologic, and gastrointestinal examination is crucial.

Abdominal/GI: A rectal examination and stool guaiac test should be performed with an abdominal examination.

Neurological: All cranial nerves, nystagmus, and ptosis may be present.³ Lower extremity strength, as well as decreased sensation to pinprick, vibration, and proprioception, may be present.

Ophthalmologic: Slit lamp and fundoscopic exams while evaluating visual acuity and color vision are needed.

Diagnosis: The diagnosis of thallium poisoning may be difficult, because it is often unsuspected. The cardinal features are gastroenteritis, peripheral neuropathy, and then later, alopecia, the last occurring at a stage when treatment is likely to be ineffective. The possibility of thallium poisoning should be borne in mind in obscure neurological illnesses, especially where there is peripheral neuropathy with alopecia; in addition, thallium should be looked for in the urine. A simple screening test for thallium in urine (see

Section 2) may lead to early diagnosis. However, thallium, being slowly excreted by the kidneys, may be present in the urine in significant amounts for some weeks after absorption; a level $>7-10 \mu\text{g/L}$ would be confirmatory evidence of poisoning. A brownish black pigmentation close to the hair root is characteristic of thallium exposure and may appear as early as the third or fourth day (Gerdt, 1974; Mathews and Anzarut, 1968). The diagnosis of thallium poisoning was established 1 week after ingestion by the microscopic examination of hair after the application of 10% sodium hydroxide, which revealed dark bands of pigmented material characteristic of the presence of thallium traces (Uges and Huizinga, 1976). The criteria for the diagnosis of mild thallium poisoning resulting from low-level occupational exposure have been given by Glömme (1983). An occupational history involving the handling of rodenticides; the production or use of thallium or its various salts; and work on lead, zinc, or cadmium production—together with neurological symptoms dominated initially by subjective effects in the form of paresthesia—should alert to the possibility of occupational thallium poisoning. A urinary excretion of thallium in the order of $300 \mu\text{g/L}$ would provide confirmatory evidence.

Treatment: The management of thallium toxicity is by an interprofessional team that includes an emergency provider, poison control, internist, neurologist, nurse practitioners, and intensivist. The triage nurse should follow protocols for patients suspected of poisoning and have them admitted right away. The next step is to notify the emergency provider, who will communicate with the interprofessional team. The initial management of a patient with thallium toxicity follows the trauma ABCDE protocol. The nurses play an active role in resuscitation by ensuring IV access, providing oxygenation, documenting the event, and placing the patient on monitoring devices. Activated charcoal can be used for patients presenting within one hour of ingestion. If the patient had dermal exposure, their skin is to be washed with soap and water.³ For eye exposure, irrigation of the eyes with room temperature water is necessary.

Activated charcoal and Prussian blue may be used for gastrointestinal ingestion. Prussian blue has been shown to be more successful and is approved by the United States Food and Drug Administration. After resuscitation, it should be determined how and why the patient ingested thallium; if it was intentional, then the patient must be seen by a mental health nurse prior to discharge. Finally, the patient must be seen by the neurologist to determine the extent of neurological deficits.

Large doses of potassium chloride may hasten the excretion of thallium but may cause a transient increase in blood levels and a redistribution in tissues that may lead to a temporary exacerbation of symptoms. Chelating agents, including BAL, EDTA, diethyldithiocarbamate (dithiocarb), and dithizone, are contraindicated in the treatment of thallium poisoning. An electroencephalogram should be ordered for any seizure-like activity as well as a nerve conduction study for patients experiencing neurological symptoms.

Initial Care- Much like many exposures, care starts with stabilization, airway, breathing, and circulation, as well as removing contaminated clothing.³ Activated charcoal can be used for patients presenting within one hour of ingestion.

Emergency Department- If the patient had dermal exposure, their skin is to be washed with soap and water. For eye exposure, irrigate the eyes with room temperature water. Activated charcoal and Prussian blue may be used for gastrointestinal ingestion. Prussian blue has been shown to be more successful and is approved by the United States Food and Drug Administration.

Differential Diagnosis: The presentation of thallium toxicity is like other toxicities and also mimics other diseases. Following differentials should be considered in patients with thallium toxicity i.e. Carbon monoxide, Arsenic, Isoniazid, Mercury, Organophosphates, Thiamine deficiency, Diabetic polyneuritis, Botulism, Vasculitis, Poliomyelitis etc.

Patients who are exposed to thallium accidentally should wash their skin with tap water and remove contaminated clothing as soon as possible. Patients who intentionally ingest thallium should have a psychiatric evaluation. Mouth hygiene should be closely monitored. Shaving the patient's head may reduce the stress induced by hair loss and improve the patient's morale. All patients should have close follow-up care. The prognosis for patients with thallium toxicity depends on the dose ingested and the presence of neurological symptoms. Those with minimal symptoms can fully recover with treatment, but patients with severe toxicity may continue to have neuropsychiatric deficits for a long time.

Discussion: Thallium was once commonly used as a household rodent or ant killer, but many countries have banned such use due to unintentional or criminal poisonings of humans. A common initial clinical manifestation of thallium poisoning is gastrointestinal symptoms followed by delayed onset of neurological symptoms and alopecia.

Part of the reason for thallium's high toxicity is that when present in aqueous solution as the univalent thallium(I) ion (Tl^+) it exhibits some similarities with essential alkali metal cations, particularly potassium (owing to similar ionic radii). It can thus enter the body via potassium uptake pathways. Other aspects of thallium's chemistry differ strongly from that of the alkali metals, such as its high affinity for sulfur ligands. Thus this substitution disrupts many cellular processes by interfering with the function of proteins that incorporate cysteine, an amino acid containing sulfur.

Among the distinctive effects of thallium poisoning are peripheral nerve damage (victims may experience a sensation of walking on hot coals) and hair loss. However hair-loss generally occurs only with low doses; with high doses the thallium kills before hair loss can occur. Thallium was an effective murder weapon before its effects became understood and an antidote (Prussian blue) discovered. It has been called the poisoner's poison since it is colorless, odorless and tasteless; its slow-acting, painful and wide-ranging symptoms are often suggestive of a host of other illnesses and conditions.

Thallium poisoning has a distinctive clinical picture comprising skin manifestations, alopecia, neuropathy, and other systemic manifestations. The typical clinical picture unfolds by 2–3 weeks of acute poisoning. By then, precious time for therapeutic intervention is lost. In the early stage, thallium poisoning simulates Guillain-Barré syndrome, porphyria, myocardial infarction, diabetic neuropathy, arsenic poisoning, lead poisoning, systemic lupus erythematosus, carbon monoxide poisoning, and organophosphate poisoning. Peripheral neuropathy is quite characteristic and an early feature of thallium poisoning. It is consistent with distal symmetrical axonopathy with secondary loss of myelin.⁴ In our patient the nerve conduction studies were normal except peroneal motor conduction velocity, which was unrecordable. In these patients, small fibre involvement cannot be excluded and this could account for preservation of sensory conduction velocity at the same time resulting in the severe dysaesthesia. Histopathological findings in thallium neuropathy have revealed axonal degeneration with secondary demyelination. Nerve biopsy in our patient also revealed axonal degenerations. In thallium poisoning cranial neuropathy resulting in ptosis, external ophthalmoplegia, dysautonomia due to vagal nerve involvement, facial weakness due to seventh cranial nerve palsy, and optic neuropathy have been reported. Our patient had severe visual impairment and prolonged P100 latency of visual evoked potential due to retrobulbar neuritis.⁵ In one study up to 25% of patients with severe thallium poisoning have been reported to develop optic neuropathy.

Severe dermatitis, stomatitis, and neuropathy in our patient was consistent with riboflavin deficiency. Skin lesions similar to thallium poisoning have been reported in riboflavin deficiency. Thallium interferes with riboflavin homeostasis, forming an insoluble complex and intravascular sequestration of riboflavin. In our patient hyperkeratotic lesions on palms and soles, ichthyotic lesions on his legs, and acneform lesions on his face were apparent by the end of the second week and alopecia appeared on the 18th day. Interaction between the sulphhydryl group and thallium result in abnormality in form and

function of structural proteins; this accounts for disturbances of hair growth, alopecia, growth of nails, and Mee's lines.

The presence of gastrointestinal, skin, liver, kidney, and peripheral nerve dysfunction in our patient at one stage simulated arsenic poisoning. Alopecia is quite characteristic of thallium poisoning and manifests during the second to third week but can also occur in arsenic poisoning. Mee's lines, keratosis, axonal neuropathy, and a variable degree of encephalopathy can occur in both thallium and arsenic poisoning but the presence of severe constipation, ptosis, nystagmus, and variety of movement disorders such as masking of the face and tremor of head and trunk were suggestive of thallium poisoning in our patient. The involvement of basal ganglia in thallium poisoning can result in tremor, chorea, and extrapyramidal motor disturbances and rigidity. Such central nervous system abnormalities are not reported in arsenic poisoning.

Thallium elimination mainly occurs through large and small bowel, although there is some enteric absorption as well. Renal excretion also mirrors total body thallium and can be enhanced by forced diuresis. Prussian blue is considered as specific antidote and chelates the intestinal thallium. Potassium supplementation, B complex administration, and haemodialysis are also useful measures. We started haemodialysis in the third week. Although some improvement in consciousness occurred after the first dialysis, after seven cycles of haemodialysis there was further clinical improvement in consciousness, skin, neurological manifestations, liver and kidney function parameters. Haemodialysis has been described to be more effective than forced diuresis and has been found to be useful up to 12 days after poisoning. Non-availability of Prussian blue and lack of Food and Drug Administration approval have been problems in certain countries. Haemodialysis in critically ill patients, especially those with renal and cardiac dysfunction, may be effective in the third week even though benefit has been reported in the first 48 hours only.

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