Excretion of a Toxic Dose of Thallium

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We report a successfully treated case of severe thallium intoxication that required 95 days of assisted ventilation and 224 days of hospitalization. Monitoring of the patient for 500 days by measuring thallium in whole blood, serum, and urine is documented, and the role of the laboratory and utility of the measurements are considered.

Since its discovery, thallium has been associated with toxicity. Sir William Crookes, its discoverer, and his assistant Lamy both suffered from its toxic effects and the latter did some toxicological studies on dogs, ducks, and hens (1). After the turn of the century, the simple salts of thallium were used in various therapeutic roles but this was stopped by 1912 because of the toxic side effects (2). Notwithstanding this, the use of thallium salts, especially thallium(I) acetate, was restarted as a treatment for Trichophyton infection (3) until again withdrawn around 1940.

The general lack of smell, color, and taste of the simple salts, and the insidious onset and protean nature of the symptoms of toxicity, make thallium salts an excellent choice for the poisoner (4).

The literature contains many conflicting accounts of the pharmacokinetics of thallium (5–8), particularly with regard to tissue distribution and rates of elimination. These inconsistencies may result from differences in dose, species, and individual variation; it also may reflect the fact that analytical methods and equipment have only recently been able to measure thallium reliably at toxic and physiological concentrations (9–11) with an acceptable degree of accuracy and precision.

The aim of this paper is to present some reliable data from a successfully treated case of thallium poisoning.

Clinical Study

A 39-year-old bar manager, with a past history of heavy alcohol intake, became ill about one week after returning from a holiday in Spain. The illness began acutely, with generalized pain and tingling all over his body and head. On admission to a district general hospital he was found to be greatly distressed, with shooting pains in his legs and back and some leg weakness. He was initially regarded as having an alcoholic syndrome but because of continued deterioration, despite treatment with multivitamins, he was transferred to the regional neurology unit and thence to the intensive care unit of the Royal Victoria Hospital, Belfast, 20 days after first becoming ill.

Initial neurological examination showed an ill man with evidence of respiratory distress. There was also evidence of early scalp hair loss. He had gaze-evoked nystagmus in all directions; there was bilateral lower motor neuron, facial, and bulbar weakness; his arms were minimally weak with preserved reflexes, but his legs showed a flaccid paralysis with absent reflexes. Results of initial biochemical investigations were within age- and sex-appropriate reference intervals for electrolytes (sodium, potassium, chloride, and bicarbonate), urea, and creatinine, as were liver-function tests (bilirubin, alkaline phosphatase, γ-glutamyltransferase, and alanine and aspartate aminotransferases). The electrophoresis pattern of serum proteins was normal. A nonspecific autoimmune profile did not detect any autoantibodies. Screening tests for abnormal urinary porphyrins gave negative results. A complete blood count was within the reference intervals, except for a slightly increased mean corpuscular volume (97 fl). Cerebrospinal fluid was acellular with a protein content of 1.5 g/L. Nerve conduction studies showed absent sensory and motor responses for the legs but normal values for the arms.

On the basis of the clinical picture on admission to the Intensive Therapy Unit, particularly the hair loss, samples of serum and urine were sent for thallium assay, which was found to be present in toxic concentrations. The patient further deteriorated and developed visual failure, complete external ophthalmoplegia, and total arreflexic paralysis of all limb and neck muscles. At this time he was given two treatments of plasma exchange. Treatment with potassium ferrihexacyanate (5 g every 6 h by nasogastric tube) was commenced some 35 days into the illness and continued for two months; at the same time, intravenous potassium supplements (100–400 mmol/day) were given. He made a slow recovery, complicated by septicemia, recurrent supraventricular tachycardias, and psychosis. He required nearly 96 days of assisted ventilation and a total of 224 days in the hospital before being fit for discharge. Some 500 days after the initial insult he still had a significant visual handicap, no fine finger function, and only walked a few steps with aid. The source of his thallium poisoning remains unknown.

Materials and Methods

Instrumentation. Determinations were made with a Model 5000 atomic absorption spectrophotometer, equipped with an HGA 500 graphite furnace, an AS 40 autosampler (Perkin-Elmer, Bucks., U.K.), and a Vitaron PA800 programmable analyzer (Fisons Ltd., Crawley, U.K.).

Reagents. Appropriate thallium standards were prepared from 1 g/L aqueous thallium(I) sulfate (Aldrich Chemical Co. Ltd., Gillingham, Dorset, U.K.). All other reagents were of ANALAR-grade except for toluene and nitric acid, which were of "Aristar"-grade (B.D.H. Ltd., Poole, Dorset, U.K.). All water used was de-ionized, doubly dis-
tilled in all-glass apparatus; all appropriate apparatus had been soaked for at least a week in dilute nitric acid. External quality-control samples used during this study were "Seronorm Trace Elements Urine" (Nycomed AS Diagnostics, 0401 Oslo 4, Norway) and "Lanonorm Metals 2 and 3" (Behring Diagnostics, Hounslow, U.K.).

Procedures. The methods used to determine thallium in urine were all modifications of the electrothermal atomic absorption spectrophotometry (EAAS) method of Chandler and Scott (12). This assay system, which is used routinely in this laboratory, has a detection limit of 0.29 nmol/L (0.06 µg/L), as defined by Caulcutt and Boddy (13). We use it in preference to methods involving Zeeman atomic absorption spectrophotometry (14). Some modifications to the basic technique were required to accommodate the changes in the concentrations of thallium, which covered five orders of magnitude during the course of the patient's recovery. Flame atomic absorption spectrophotometry was used for the early (high-concentration) samples. 4-Methylpentan-2-one was used as the extracting solvent; sprayed directly, it causes little analytical noise. This method was sensitive enough to determine as little as 0.98 µmol/L (0.2 mg/L) of thallium. All subsequent work was done by the standard EAAS method except that, to vary the sensitivity, we changed the preconcentration step, changed the volume of sample injected into the furnace, and adjusted the internal gas flow at atomization. Samples and standards from the previous runs were included with each subsequent run to try to ensure consistent analytical accuracy and precision and to minimize the "step" functions often seen in longitudinal toxicological studies when changes to methodology are necessary.

Creatinine, used as an indicator of urine concentration, was determined by the Jaffé method without deproteinization (15).

Samples of whole blood and plasma or serum were analyzed for thallium by chelation with sodium diethyldithiocarbamate and gentle extraction into 4-methylpentan-2-one. The emulsion that formed was broken down by refrigerated centrifugation, after which thallium was measured in the organic extract by EAAS.

Standard curves were prepared from time-expired transfusion blood or plasma, as appropriate, with added thallium(I) sulfate to give concentrations in the range 9.8–98 nmol/L (2–20 µg/L). Urine standards were prepared as in the method of Chandler and Scott (12). Detection limits for blood and plasma were 4.9 nmol/L (1.0 µg/L) and 3.4 nmol/L (0.7 µg/L), respectively, about 100-fold more sensitive than the method of Amore (16) used by Hologgias et al. in 1980 (6).

Laboratory quality assurance for thallium assays, established over a continuous five-year period, makes use of the esum technique with a truncated V-mask to demarcate the control limits (17); aliquots of a pooled urine, with added thallium(I) sulfate to give analyte values within the range of values most frequently found, are stored at −20 °C until analysis. The analytical parameters for two of the laboratory quality-assurance samples, in nmol/L, are shown with 95% confidence intervals (see above right).

At the time of the study, no known external quality-assurance source was available at the concentrations usually encountered or expected in this laboratory, but samples of a synthetic urine with toxic thallium concentrations, as detailed above, were assayed with the higher thallium concentration urine samples.

Results

Specimens of the patient's urine, whole blood, and serum were available for analysis for thallium primarily during the 20 to 80 days after admission to hospital and then at less frequent intervals up to 15 months after admission. Owing to the isomorphic behavior of thallium and potassium (one of the proposed mechanisms of thallium toxicity), we analyzed several paired samples of whole blood and serum but found no difference between them, despite the suspicion that, as with potassium, the whole-blood values should have been higher. In the Figures and the Tables, day zero relates to the date of admission to hospital: the exact date of the insult or insults is unknown, and in attempts to fit curves containing one or more exponential terms, an arbitrary assignment of a time as day zero is satisfactory.

Figure 1 shows the changes in thallium concentrations in urine, serum, and whole blood after the patient's admission and treatment; Figure 2 shows the ratio of urine thallium to creatinine. We used a logarithmic scale for the concentrations of thallium to accommodate the large range of values. All estimates show random fluctuations on the declining trend.

We attempted to fit mixtures of exponential models to the available data, using a Gauss–Newton optimization method with various different weighting functions. None of the curves could be expressed in terms of a combination of exponential models. Only two relatively short periods of data conformed to any simple model; these covered part of the early collection period of both serum and blood, a single exponential function providing an approximate fit (Table 1). The half-lifetime for both the serum and blood values between days 8 and 40 was about four days; after this, the rate of decrease slowed considerably and data could no longer be approximated. For no period could the urine thallium or ratio of urine thallium to creatinine excretion curve be fitted to a descriptive pharmacokinetics curve.

Discussion

Thallium(I) salts are among the most toxic of all simple inorganic compounds, weight for weight. Thallium is used in relatively small quantities today, mainly in the optical, costume jewelry, photographic, and electronics industries. Its largest use is now in the production of batteries in which seawater is the electrolyte. Thallium(I) salts were used as a pesticide and rodenticide before 1940 but its toxicity, described by Munch (18, 19), caused its withdrawal for those purposes in most countries. It also has been used as a criminal poison, and a famous case of this was described by Holden (4).

In a study of 70 cases of thallium poisoning (20), many signs emerged as being important in the diagnosis, including polyneuritis and hair loss. The only pathognomonic feature of thallium poisoning is the demonstration of excess thallium in the body fluids. The best fluid to analyze is urine because of the requirement for large volumes that can be preconcentrated before measurement.
In this study, the dose of thallium, the salt used, and the pattern of dosage remains unknown. The successful therapy of a severely ill patient masked the patterns of change of concentration of thallium in blood, serum, and urine; furthermore, the toxicity of this agent can mask its own pharmacokinetics by altering the mechanisms of its absorption and excretion. Thallium has a considerable disruptive effect on basic cell function because it can be exchanged for potassium in many reactions. In the control of cell membrane ion flux, for example, thallium(I) substi-
stitutes for potassium in sodium–potassium-stimulated ATPase, altering the pK adversely, and showing 10 times greater affinity for the enzyme than does the potassium ion (21). The slowing of absorption after the initial toxicity was a feature of a case in which reportedly sufficient thallium salts remained in the gut to be seen by plain abdominal radiography (8).

Thallium and potassium are partly interchangeable, owing to the similarity of their ionic radii. Loading the body with potassium and diuretics that enhance potassium excretion both cause thallium excretion, the former by mass action. Although both methods have been used to increase thallium excretion, in this case only potassium loading was used. The patient also received enteric administration of potassium ferrihexacyanate (Prussian Blue) to hold the thallium(I) ion in the gut; this slows absorption and will combine with any thallium secreted into the lumen in place of potassium.

The therapeutic interventions and the toxic effects of thallium that interfere with both absorptive and excretory mechanisms mean that the observed variations in the excretion of thallium are not surprising and prevent its satisfactory modelling, even by powerful and apparently appropriate computerized curve-fitting techniques. The little modelling that was successful agreed to some extent with other estimates of the half-life of the substance in blood, i.e., about four days.

References