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Article *in* Clinical Toxicology · January 2008

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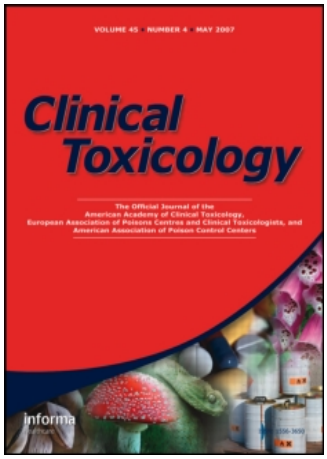

Clinical Toxicology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597279

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First Published on: 15 August 2007
To cite this Article: Cheraghali, A. Majid, Haghqoo, Soheila, Shalviri, Gloria, Shariati, Yaghoub R., Ghassemi, Maleehe and Khosravi, Shahram (2007) 'Fatalities following skin exposure to arsenic', Clinical Toxicology, 45:8, 965 - 967
To link to this article: DOI: 10.1080/15563650701437682
URL: http://dx.doi.org/10.1080/15563650701437682

Clinical Toxicology (2007) **45**, 965–967

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650701437682

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CASE SERIES

Fatalities following skin exposure to arsenic

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Arsenic is a toxic metal that can cause death following exposure. In an unusual event, seven patients unintentionally applied a 30% arsenic solution to their entire body instead of a benzyl benzoate solution to treat their scabies. Hours later they developed severe skin reactions, including bullae, and were admitted to the hospital with gastrointestinal and cardiovascular disorders. Despite therapeutic interventions, three patients died and the rest were discharged from hospital with neurological sequelae. Toxicological analysis confirmed the presence of arsenic in the solution used by patients.

Keywords Arsenic; Topical; Fatality; Benzyl benzoate

Introduction

Arsenic is a toxic metal that has been used in cosmetics, medicines, pigments, and in agriculture to protect crops from pests. Human arsenic toxicity results from the ingestion of contaminated water (1), food, and unintentional use of arsenic salts. Most cases of acute arsenic poisoning occur from unintentional ingestion of insecticides or pesticides containing arsenic, and less commonly from attempted suicide (2). Although the gastrointestinal tract is the main site of arsenic absorption, arsenic may also be absorbed through the skin or by inhalation (3,4). Literature reports of acute arsenic poisoning following skin exposure are rare. This article reports seven cases of acute arsenic toxicity following the unintentional topical use of an arsenic solution.

Case series

A dermatologist in Behbahan, Iran wrote prescriptions for benzyl benzoate 25% in isopropyl alcohol to treat scabies in three separate cases over two consecutive days for a family of five, a pregnant woman, and a five-year-old girl. The patients took their prescriptions to the same pharmacy and the pharmacist prepared the benzyl benzoate 25% solution in isopropyl alcohol from the stock he claimed had already been used several time before. The pharmacist directed all the patients to apply the solution to their skin from neck to toe.

Family of five

As soon as they applied the solution to their skin, all five family members felt their skin itching and burning but thought this was an expected effect of the medicine. One hour later, their conditions became worse and blisters appeared on their skin. The mother contacted the pharmacist for advice and he recommended that they take a shower and wash the medicine off their skin. The father was not able to take a shower as the others did. Their clinical conditions continued to worsen and all five family members were referred to the hospital. The father, a 49-year-old, presented to the hospital 3.5 hours after applying the solution with severe burns, blisters and bullae on his skin, respiratory distress, hypotension (BP=100/70 mmHg), anuria, elevated BUN (27 mg/dl), creatinine (2.4 mg/dl), nausea, vomiting, and dizziness. He was admitted to the Intensive Care Unit 13 hours post-application in coma and died 24 hours after applying the solution. In ICU, he received dobutamine, aminophyline, and in a later stage, atropine, adrenaline, and electrical shock. The 16-year-old son was admitted to the hospital with nausea, vomiting, pallor, generalized erythema, blisters and bullae on skin, tachycardia (pulse rate = 160 bpm), oliguria, and respiratory distress. His blood pressure was 90/60 mmHg and in first stage of the treatment he received hydrocortisone (100 mg IV), prometazine (25 mg IM), and aminophyline. However, following developing respiratory distress (RR = 30 bpm) he was referred to the ICU. On admission to the ICU, he had BUN=23 mg/dl, creatinine = 0.9 mg/dl, and WBC = 8900. He died 72 hours after applying the solution. In the ICU he

Received 30 November 2005; accepted 2 March 2006.
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mainly received dopamine, adrenaline, and electrical shock. The 45-year-old mother and a 23-year-old son were admitted to the hospital with similar symptoms including itching, bullae, dizziness, and vomiting. However, treatment including IV fluid therapy (normal saline), hydrocortisone, promethazine, repeated skin washing with saline and care of blisters, was effective. They both survived and were discharged from the hospital on day five with keratosis, scaling and pigmented skin, and numbness in all four extremities. They were referred to the neurology department for further treatment of their polyneuropathy. The 5-year-old son presented with severe erythema, itching, blisters, vomiting, fever (37.6°C), and seizures. His manifestations were controlled with hydrocortisone (100 mg IV) and phenobarbital (85 mg IM) along with supportive care. He was discharged from hospital four days later.

Pregnant woman

The pregnant woman (38 weeks gestation) was admitted to the hospital 11 hours post-application of the solution with severe rash and bullae, nausea, vomiting, fever (37.9°C), hypotension (80/40 mmHg), respiratory rate = 97 bpm, WBC = 32000, diarrhea, fatigue, and peripheral cyanosis. She and her fetus died in the ICU eight hours after admission due to multi-organ failure.

Five-year-old girl

This patient also developed clinical findings similar to those of the family including itching, bullae, spots on skin, and vomiting. The laboratory values were BUN=37 mg/dl, creatinine=0.8 mg/dl, and WBC=5600. She was treated symptomatically and was discharged from hospital four days later with numbness in all four extremities.

Although all patients received symptomatic and supportive treatment in the hospital, none received specific treatment for arsenic poisoning and no chelator was used. No bodily fluids were obtained for determination of arsenic concentrations. Relatives of the patients did not agree to post-mortem investigations.

Discussion

Due to these unprecedented events, the remaining solution that was used by the patients and the main stock solution in the pharmacy were confiscated by the Medical Forensic Office and samples were sent to the Ministry of Health central Food and Drug Control Labs (FDCL) for analysis. The FDCL tested samples used by the patients first for presence of benzyl benzoate using TLC, GC, and HPLC and only trace amounts of benzyl benzoate were found. However, examining isopropyl alcohol and the main stock of benzyl benzoate confirmed their conformity with those of standards. The clinical picture of the patients and the fact that one laboratory technician became severely nauseated following unintended inhalation of the test solutions generated the hypothesis that a toxic substance might be present in the solution. The solution had a pH of about 2 so it was tested for some organic and inorganic acids and compounds such as phenol, formaldehyde, cyanide, and arsenic. Test results for arsenic were positive. Quantitative tests of the solution used by patients using a colorimetric Merck Arsenic Kit and an atomic absorption analysis revealed a 30% arsenic solution. The tests were repeated using authentic standards of arsenic trioxide and the results were confirmed. In a separate experiment, samples of the solution used by the patients were applied to the whole bodies of three Balb-C mice. All mice died in less than half an hour post-application of the solution. The mice skins were filled with red and black spots. Mice that were treated with benzyl benzoate 25% solution did not show any clinical complications. The chemistry laboratory of the Iran Atomic Energy Agency also confirmed the presence of 30% arsenic in the solution used by the patients.

Despite the abundance of arsenic poisoning cases following ingestion of arsenic, even in entire families (5), there are no published reports of acute poisoning and fatality following skin exposure to arsenic. Chronic arsenic poisoning may occur from absorption through skin, and skin lesions are common in patients with acute arsenic poisoning (6). Chronic exposure to arsenic causes cancer, keratosis, hypopigmentation, and hyperpigmentation (7,8). Incidence of palmar-plantar lesions was reported to be over 50% in a group of patients received doses of up to 3 g of arsenic in a topical solution (Fowler's solution) (9). It was previously reported that in experimental animals, dissolving arsenic in organic solvents such as chloroform and toluene significantly enhances dermal penetration of arsenic (10). Therefore, it is possible that the absorption of arsenic through the skin of the patients was enhanced by several mechanisms. First, the isopropyl alcohol in the solution may have enhanced the dermal penetration of arsenic; second, the scabies might have resulted in excoriated skin patches; third, the low pH of the solution (pH=2) may have contributed to the rapid development of skin lesions (itching, redness, burning sensation, small blisters); and fourth, the patients did not wash their skin for hours after the application.

Blood and urine arsenic concentrations were not determined because arsenic was not considered in the initial differential diagnoses. The systemic clinical picture, including the polyneuropathy, supports the clinical diagnosis of arsenic toxicity. Retrospectively, this diagnosis was corroborated by laboratory analysis of the solutions dispensed by the pharmacist.

Conclusion

Three adults and four children unintentionally applied an isopropyl alcohol solution containing 30% arsenic to their skin instead of 25% benzyl benzoate for the treatment of scabies. All patients followed the doctor's and pharmacist's directions to apply the solution to their skin from neck to toe. This

application resulted in substantial dermatotoxicity, multi-organ failure, the death of three patients in hospital, and neurologic sequellae in the four surviving patients.

The presence of arsenic in the solution was confirmed analytically. The questions of how and why such a solution was dispensed remain unanswered. At present, the case is under criminal investigation.

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