Case Report
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Acute high dose toxicity of 1,4-Dioxane following occupational exposure – A clinical and an autopsy perspective

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Abstract

1,4-Dioxane is a cyclic ether with a molecular formula of C4H8O2. It is used as a solvent and degreasing agent in industries like textile, paints, varnishes, oil, dyes etc. Occupational exposure can occur in the industrial workers. Absorption of 1,4-Dioxane usually occurs by inhalation, oral or dermal routes. Exposure to high doses is associated with severe kidney and liver damage. We report a fatal case of acute high dose toxicity of 1,4-Dioxane following occupational exposure. The deceased was exposed to the chemical while washing large industrial tanks containing 1,4-Dioxane. Autopsy examination revealed extensive renal cortical necrosis, centrilobular hepatic necrosis, pulmonary oedema and intra-alveolar haemorrhages. This case had medico-legal implications and a lawsuit was filed by the family of the deceased to get compensation for death due to occupational exposure.

Keywords: 1,4-Dioxane, renal cortical necrosis, centrilobular hepatic necrosis

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1. Introduction

1,4-Dioxane is a cyclic ether with a molecular formula of $C_4H_8O_2$. It is also known as diethylene dioxide, p-dioxane and glycoethylene ether. It is used as a solvent and degreasing agent in industries like textile, paints, varnishes, oil, waxes, dyes etc.

Exposure and absorption of 1,4-Dioxane usually occurs by inhalation, oral or dermal routes. Occupational exposure may occur by any of these sources. Occupational Safety and Health Administration (USA) has set a legal limit of 100 ppm 1,4-dioxane in air, averaged over an 8-hour work day. Exposure to high concentrations of 1,4-Dioxane causes vertigo, irritation of eyes and nose, headache, abdominal pain, nausea, vomiting, coma and death.[1] In fatal cases, renal damage, hepatic lesions, oedema and demyelination of the brain have been observed.[2] Chronic exposure to low doses have not been well studied in humans, but dermatitis, eczema, central nervous depression, nausea, abdominal tenderness, liver and kidney damage have been described.[3]

We report a fatal case of acute high dose toxicity of 1,4-Dioxane following occupational exposure and an autopsy examination done thereafter.

2. Case report

A 30 year old male patient, an industrial worker by occupation, presented to emergency services of a tertiary care hospital with abdominal pain, 28-30 episodes of vomiting and 15-20 episodes of loose motions since 3 days. History of anuria was present since 1 day. A provisional diagnosis of acute gastroenteritis with acute renal failure was made and he was started on conservative treatment. The patient was dialyzed twice but his condition worsened. A meticulous enquiry revealed a history of washing large industrial tanks containing 1,4-Dioxane, a few hours before the development of symptoms. On examination, the patient was afebrile, blood pressure was 140/80 mm Hg and respiratory rate was 14/min. No pallor, icterus, clubbing, cyanosis, lymphadenopathy or organomegaly was seen.

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Haematological investigations revealed a haemoglobin level of 11.9 g/dl, total leucocyte count of 15,300/mm^3 and a platelet count of 57,000/mm^3. Peripheral smear showed neutrophilic leukocytosis which rapidly increased from 80% to 92%. Blood gas analysis revealed a pH of 7.25 (7.35-7.45), PCO_2 of 32.3 mm Hg (38-42 mm Hg), PO_2 of 50 mm Hg (75-100 mm Hg) and bicarbonate levels of 17 mmol/L (22-29 mmol/L). Blood urea nitrogen increased from 35 mg/dl to 50 mg/dl (7-18 mg/dl), serum creatinine was 6.4 mg/dl at the time of admission and increased to 8.5 mg/dl (0.7-1.3 mg/dl) and serum uric acid was 63 mg/dl (4-8.6 mg/dl). Na^+ was decreased and K^+ was raised. ECG showed normal axis with tall tented T wave suggestive of hyperkalemia. Patient was treated for metabolic acidosis and hyperkalemia.

USG revealed right kidney of 10.2x4.8 cm and left kidney of 10.5x4.5 cm size. There was increased echogenicity with bilateral accentuation of corticomedullary differentiation, suggestive of a medical renal disease. The patient's condition deteriorated rapidly and he died on the fourth day of admission.



Figure 1. Parts of both kidneys showing extensive haemorrhages amidst which are seen creamy white areas of cortical necrosis.

A complete autopsy study was done. External examination was unremarkable. On internal examination, both lungs were markedly congested. The stomach showed 100 ml of semi-solid material. Kidneys were bilaterally enlarged, reddish brown, oedematous and extremely haemorrhagic (Figure 1). The cut surface showed multiple creamy white areas of cortical infarcts occupying almost the entire cortex. Liver was enlarged in size and the cut surface was unremarkable. Microscopic examination of kidneys showed renal cortical necrosis i.e. areas of coagulative necrosis of renal parenchyma where cellular outlines were preserved but cellular details were lost. Large areas of haemorrhage were seen. Multiple thrombi were seen in the arterioles and the small arteries. The fibrin stain was positive (Figure 2). The liver showed severe centrilobular necrosis (Figure 3). The lungs showed features of pulmonary oedema, focal intra-alveolar haemorrhages and bronchopneumonia.

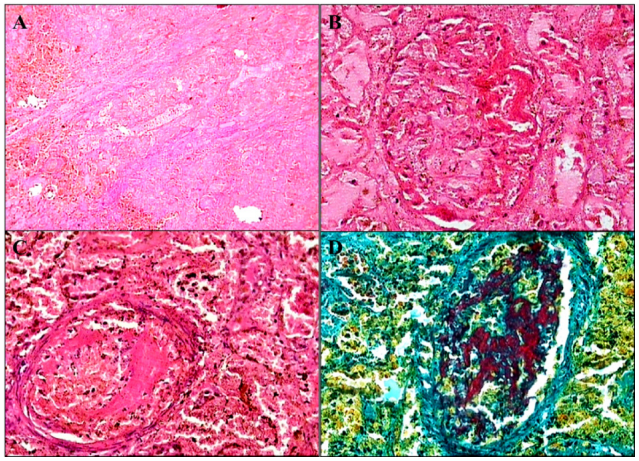


Figure 2. (A) Light microscopic image of kidney showing extensive areas of renal cortical necrosis [H&E, 100X]. (B) A glomerulus and surrounding tubules showing coagulative necrosis [H&E, 400X]. (C) An arteriole showing thrombus [H&E, 400X]. (D) Fibrin in the thrombus stained with a bright orange color [Putz fibrin stain, 400X].

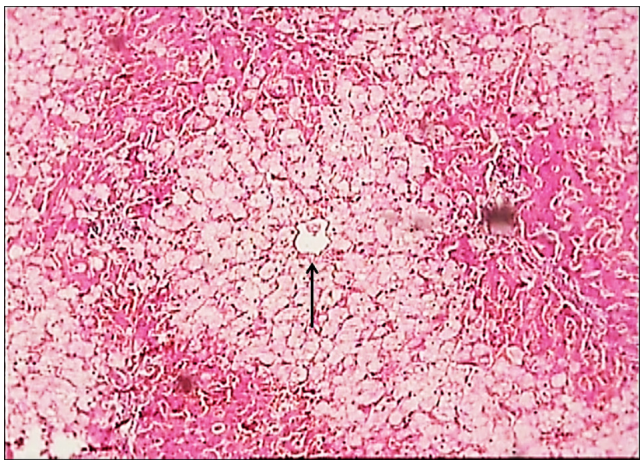


Figure 3. Light microscopy of liver showing centrilobular necrosis. The arrow points to the central vein [H&E, 400X].

Final autopsy diagnosis was acute renal failure following renal cortical necrosis with centrilobular necrosis of the liver with pulmonary oedema, intra-alveolar haemorrhages and bronchopneumonia.

3. Discussion

Acute high dose exposure to 1,4-Dioxane is an occupational hazard. The common route of absorption is inhalational and dermal contact as was seen in our case. The chemical is metabolized to 2-hydroxyethoxyacetic acid (HEAA) which is mainly excreted in urine.[4] Liver and kidney are the target organs of 1,4-Dioxane toxicity.

Our patient was initially diagnosed as acute gastroenteritis with acute renal failure based on the clinical manifestations. Detailed history taking revealed an occupational exposure to 1,4-Dioxane while cleaning industrial tanks containing this chemical which led to catastrophic course of events culminating in death. Autopsy revealed extensive bilateral renal cortical necrosis, centrilobular hepatic necrosis, pulmonary oedema, intra-alveolar haemorrhages and bronchopneumonia. Renal cortical necrosis is a rare cause of acute renal failure characterized by ischemic necrosis of renal cortex resulting from vascular spasm or microvascular injury. Centrilobular hepatic necrosis is the ischemic coagulative necrosis of hepatocytes in the central region of lobules, caused by variety of toxins as well as medical causes.

A couple of studies were conducted abroad on occupational workers exposed to high concentration of 1,4-Dioxane. The clinical manifestations were abdominal pain, vomiting, oliguria and/or anuria, haematuria and death. Autopsy studies showed centrilobular necrosis of liver and necrosis of the kidneys which was similar to our case.[5]

This case had medico-legal implications and a lawsuit was filed by the family of the deceased to get compensation for death due to occupational exposure. One of the authors was summoned to the court twice as expert witness to certify that the autopsy findings and death was due to acute toxicity of 1,4-Dioxane.

4. Conclusion

Acute toxicity of 1,4-Dioxane, which is a common solvent in many industries has not been reported in Indian literature. These cases may be readily missed as the toxicity may closely mimic medical emergencies like acute gastroenteritis or acute renal failure. Eliciting careful occupational history and a suspicion for toxins is essential. As short term exposure to high levels of this chemical has catastrophic effects, extreme caution and measures for occupational safety are warranted.

5. Conflict of Interest

None Declared

6. References

1. U.S. Department of Health and Human Services. Hazardous Substances Data Bank. National Toxicology Information Program, National Library of Medicine, Bethesda, MD. 1993.
2. U.S. Environmental Protection Agency. p-Dioxane Health Advisory. Office of Drinking Water, Washington, DC. 1987.
3. Agency for Toxic Substances and DiseaseRegistry (ATSDR). 2012. "Toxicological Profile for 1,4-Dioxane."
4. Young JD, Braun WH, Gehring PJ, et al. 1976. Short Communication. 1,4-dioxane and betahydroxyoxyacetic acid excretion in urine of humans exposed to dioxane vapors. Toxicol Appl Pharmacol 38:643-646.
5. Barber H. 1934. Hemorrhagic nephritis and necrosis of the liver from dioxane poisoning. Guys Hosp Rep 84:267-280.