



ACUTE NAPHTHALENE TOXICITY PRESENTING WITH STATUS EPILEPTICUS: A RARE COMPLICATION

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Abstract: The neurologic symptoms such as seizures or status epilepticus rarely constitute the initial mode of presentation of poisoning by ingestion of naphthene, usually patients present with acute onset of dark brown urine, watery diarrhea, and non-bloody bilious vomiting 48-96 hours after exposure. Seizures are due to cerebral edema which is probably secondary to acute hemolysis. Vital sign abnormalities include fever, tachycardia, hypotension, and persistent pulse oximetry readings less than 84%-85% despite oxygen supplementation. Laboratory workup demonstrates hyperbilirubinemia with indirect predominance, hemolytic anemia, methemoglobinemia, and renal dysfunction. Treatment options include symptomatic treatment such as anti-convulsant, treatment of cerebral edema supportive care, red cell transfusion, ascorbic acid, methylene blue, and N-acetylcysteine. We present a case of naphthalene toxicity in a 32-year-old schizophrenic male manifesting with status epilepticus, as a rare complication who improved with supportive care, mechanical ventilation, osmotic therapy, anticonvulsant, red blood cell transfusion, and ascorbic acid.

Keywords: naphthalene, status epilepticus, hemolysis, kidney injury, methemoglobinemia, ascorbic acid, toxicity, moth balls

I. INTRODUCTION

Naphthalene is commonly found in moth repellent products such as mothballs in developing countries. We present a case of voluntary intoxication for suicidal purposes moth balls ingestion in A 32-year-old schizophrenic male who presented with a rare manifestation of repetitive seizures, hemolysis, methemoglobinemia and severe metabolic, and review the management. Naphthalene, an ingredient in mothballs, is well absorbed following ingestion, dermal contact, or inhalation. Exposure often causes headache, altered mental status, vomiting, diarrhea, abdominal pain, and fever. [1] Ingestion of naphthalene mothballs also commonly causes hemolytic anemia and methemoglobinemia. [2] The Neurologic symptomatology results from cerebral edema which is probably secondary to acute hemolysis. Rapid progression to coma, convulsions, and status epilepticus (SE) indicated poor prognosis. [3,4] Although naphthalene has no hemolytic properties, its oxidative metabolite alpha-naphthol possesses potent hemolytic activity. [5]

The mean lethal dose in nonsensitive adults may lie between 5 and 15g [6], The toxic dose of naphthalene poisoning is not known. [1] Naphthalene is toxic in normal individuals without recognized red cell defects, primarily G6PD deficiency. Although, ingestion of 12 mothballs has been reported, with resolution of hemolysis and methemoglobinemia after five days of aggressive treatment including adjunct continuous venovenous hemofiltration. [7]

II. CASE PRESENTATION

A 32-year-old schizophrenic male patient presented 2 days after oral ingestion of 12 naphthalene mothballs for the purpose of autolysis, he was transferred to our facility from a local hospital, after presenting with sudden onset of dark brown urine, non-bloody bilious vomiting, and painless watery diarrhea two days earlier, altered sensorium, and 5 episodes of generalized seizures. History was obtained from the patient's brother. His brother reported subjected fevers, and shortness of breath, before the onset of seizures but denied chest pain, recent travels, overdose of his own antipsychotic medications or sick contacts. On presentation to the local hospital, the patient was afebrile, pale, icteric and cyanotic. He was lethargic with GSC 12/15, there was no focal neurological deficit, tachycardic (heart rate 130 and regular), and had a low blood pressure (80/50), the vesical catheterism revealed dark brown urine in color. Oxygen saturation (SpO₂) was 70% on pulseoximeter reading, became 92% on 100% non-rebreather mask. Gastric aspirate was normal. Arterial blood gas at that time showed pH 7.10, partial pressure of carbon dioxide (pCO₂) 32 mmHg, and partial pressure of oxygen (pO₂) of 55 mmHg, HCO₃ de 3.3 mmol/L et un BE à -24 mmol/L, the patient was orthopneic and polypneic with a respiratory rate of 22. The other measurements were as follows: hemoglobin 4,4 g/dL, blood urea nitrogen 2,20 mg/L, creatinine 48 mg/L, total bilirubin 53 mg/L, amylase 90 U/L, lipase 45 U/L, and lactic acid 3.4 mmol/L.

The patient was transferred to our hospital for admission to the critical care unit. On physical examination, the patient was unconscious with GSC 12/15 having repetitive seizures reported as status epilepticus (SE), his sclera was icteric, hands were pale and jaundiced, low blood pressure (82/55), Pulse oximetry was 85%-90% on 100% non-rebreather mask, respiratory rate of 23, his heart sounds were regular, his breath sounds revealed few crackles at the base consecutive to probable acute pulmonary edema, abdomen was soft, non-tender and non-distended to palpation, with normoactive bowel sounds and no rebound, guarding or hepatosplenomegaly. Arterial blood gas was consistent with severe metabolic acidosis: pH of 7.17, pO₂ of 70 mmHg on 100% non-rebreather mask, pCO₂ of 34 mmHg, bicarbonate of 7.3 mmol/L, and a base excess of -20 mmol/L. Methemoglobin level was 11,5%. His labs included hemoglobin 4.3 g/dL and hematocrit 11.5. The patient had leukocytosis (60 000/μL with 80% neutrophils), a platelet count of 350 000/μL, blood urea nitrogen 2,30 mg/L, creatinine level of 50 mg/L, and creatinine clearance (COCKROFT) estimated in 19,8 ml/min suggestive of acute kidney injury. Alkaline phosphatase 50 U/L and alanine aminotransferase (ALT) 34 U/L were within normal limits. His total bilirubin was elevated at 56 mg/L (normal range 0.2-1 mg/dL) with indirect hyperbilirubinemia (43 mg/dL), AST 117 U/L (normal range 5-40 U/L), haptoglobin 10 mg/dL, Lactate dehydrogenase 589 unit/L, and reticulocyte count elevated 6.1% were suggestive to Intravascular hemolysis. His hepatitis panel was negative, prothrombin time was 16.6 seconds, international normalized ratio was 1.3, and partial prothrombin time was 33.0 seconds. Urine analysis showed brown urine with +3 blood, +3 protein, +1 ketones, and a microscopic examination showed only 2-6 red blood cells. because of the epileptic condition, the disorder of consciousness and respiratory distress the patient was intubated, ventilated and deeply sedated, was initially treated with Valium intravenous 10 mg Renewable, phenobarbital in load dose 900 mg and maintenance dose 300 a day, Osmotic therapy with Mannitol 20% that was given 50g then 50g every 3 hours, loop diuretics (Furosemide) 0,7 mg/kg, hyperventilation, supportive care, and intravenous normal saline. He was transfused five units of packed red blood cells with appropriate response to 9.4 g/dL, respiratory support was provided with 5 liters nasal cannula with response oxygen saturation to 97%. The hemodynamic support by Noradrenaline had to be started in order to maintain a MAP 65 mm Hg. The patient was hemodialyzed seen he is anuric and had a severe metabolic acidosis. Gastric washing and administration of activated charcoal were not done for the patient's late presentation. Cerebral scan showed diffuse cerebral edema. Subsequently, his acidosis improved after dialysis session, the arterial blood gas became with pH 7.32, pO₂ Hg 150 mm, PaCO₂ to 30 mmHg, HCO₃ to 19.3, BE of -4 mmol/L, its methemoglobin levels were down with the first day reading of 11.5%, which decreased to 2.6% on the second day. His hemoglobin increased to 11.5g/dL after transfusion of five packed red blood. An intravenous injection of methylene blue at 80 mg (1.5mg/kg) was prescribed on day 2 of admission after verification for Glucose-6-phosphate-dehydrogenase (G6PD) status that was 12.5 U/gHb (normal range 5.5-20 U/gHb), followed by intravenous administration of ascorbic acid 300mg and N-Acetylcystein (NAC) 1.2 g. The electroencephalogram showed no subclinical convulsions. On Day 3 of admission, hemoglobin was 9,5 g/dL, haptoglobin <15 mg/dL. Lactate dehydrogenase was 513 unit/L and total creatine kinase was 180 unit/L, reticulocyte count elevated 6.3%, Peripheral blood smear showed microcytes, macrocytes, Burr cells, Heinz bodies, bite cells, anisocytosis, and poikilocytosis. Creatinine was also noted at 28 mg/L, and there was some improvement in methemoglobin that decreased to 1.8%. with carboxyhemoglobin level at 1.4%. On Day 4 of admission, the patient began clinically improving and after withdrawal of Noradrenaline he was extubated after a control scan that showed a clear regression of cerebral edema, he continues hemodialysis. Methylene blue was considered but was not given to the patient as the patient was clinically improving and methemoglobin levels were trending down, he received ascorbic acid (225 mg) orally three times a day. The patient was oliguric during the hospital stay and continued to be hemodialyzed daily with rare amounts of brown urine, which improved to an amber color on the day of discharge. His hemoglobin decreased the fourth day to 8,8 g/dL after one units of packed red blood cells during the last hemodiafiltration it remained stable at 9,7 g/dL. The methemoglobin level trended down to 1,5% on the day 5. Creatinine and total bilirubin trended down to 19 mg/L and 16 mg/dL, respectively (Table 1). The patient discharged in the fifth days after admission with good outcome but he was still oligo-anuric requiring daily hemodialysis session.

Table 1:

Progression of parameters during hospital admission in a patient with naphthalene exposure.

ND - not drawn, * - transfused units packed red blood cells.

Labs tests	Day 1	Day2	Day3	Day4	Day5
Hemoglobin g/dL	4.3	*11.5	9.5	8.8	*9.7
Total Bilirubin mg/dL	56	40	28,9	23,4	16
Creatinine mg/L	50	30	28	23	19
Methemoglobin %	11,5	2,6	1,8	ND	1,5
Urine color	Dark brown	Dark brown	Dark brown	brown	amber

III. DISCUSSION

Naphthalene, a widely used industrial and household chemical, is an uncommon agent of poisoning worldwide, and may be a diagnostic challenge if naphthalene exposure is unknown. Naphthalene causes oxidative stress by enhancing the production of free oxygen radicals, which then results in lipid peroxidation and deoxyribonucleic acid damage to cells. [8] Hemolysis is thus particularly seen in patients who have a low tolerance to oxidative stress, such as patients with G6PD deficiency. [9] G6PD is essential in red cell metabolism due to its role in the pentose phosphate pathway. It provides resistance for oxidative stresses on the cell, as it leads to the generation of the reduced form of nicotinamide adenine dinucleotide phosphate. [10] The presence of G6PD likely reduces the severity of naphthalene poisoning. [11] The oxidative stress produced by naphthalene results in methemoglobinemia—the oxidized form of hemoglobin. In methemoglobin, the iron (Fe) moiety of unoxygenated hemoglobin is in the ferric (Fe +3) state and does not bind oxygen. The affinity of oxygen for the partially oxidized portion of hemoglobin is thus increased. The patient becomes cyanotic if the methemoglobin level is above 1.5 g/dL. The arterial blood changes to dark brown color. [12] In such patients with methemoglobinemia, pulse oximetry is not reliable. The conventional pulse oximeters use two wavelengths of light, which cannot detect methemoglobin and cannot accurately determine oxygen saturation when methemoglobinemia is present. Pulse oximetry readings in such patients may consistently show an oxygen saturation of 85% despite arterial blood gas oxygen saturation values. [13] The most important metabolite of naphthalene in human urine is alpha-naphthol. Beta-naphthol and alpha- and beta-naphthol quinone occur in small concentrations.

Patients initially present jaundice, pallor with Headache, abdominal pain, nausea, recurrent vomiting, and dark urine. [1] The color may vary from patient to patient or in the same patient during the course of illness. In most but not all persons with naphthalene induced hemolysis, a deficiency of G6PD, sickle cell anemia, or sickle trait can be demonstrated. [14] There may be hematuria, hemoglobinuria and dysuria, progressing to oliguria or anuria. Methemoglobinemia and cyanosis can occur. In severe poisoning, excitement, coma and convulsions can occur as was the case with our patient. [15-17] Thus, hemolytic anemia and methemoglobinemia are characteristic of naphthalene poisoning. The clinical suspicion of methemoglobinemia should be raised when there is cyanosis that doesn't respond to high flow oxygen with no obvious cardiorespiratory causes like right to left shunting. The neurologic symptoms of naphthalene ingestion include, confusion, altered sensorium, listlessness, lethargy, and vertigo. Muscle twitching, convulsions, Status epilepticus (SE), decreased responses of painful stimuli, and coma occurred prior to death in individuals who ingested naphthalene.[3] The Neurologic symptomatology results from cerebral edema which is probably secondary to acute hemolysis. Rapid progression to coma and convulsions indicated poor prognosis. [3,4], our patient had repetitive seizures that were reported as status epilepticus, with diffuse cerebral edema on the scan. In the absence of adequate supportive treatment, death may result from acute renal failure or kernicterus in infants [1]. Status epilepticus (SE) is defined as the occurrence of continuous seizures or seizures recurring without recovery of consciousness, for more than thirty minutes, except for the generalized convulsive SE which is considered after 5 minutes. Subtle SE is defined by the cessation of motor activity with a coma and the persistence of the electrical epileptic activity. It is the evolution of an insufficiently treated or untreated convulsive SE. [18] Respiratory failure and pulmonary edema have also been reported. This poisoning may cause acute renal failure and hyperkalemia, due to hemolysis. [19] Metabolic acidosis may develop due to acute renal failure. Hyperbilirubinemia, with indirect predominance, elevated lactate dehydrogenase and decreased haptoglobin levels are seen.[11] The hematological findings may include leukocytosis, a rapid fall in erythrocyte count, hemoglobin concentration and hematocrit followed by a temporary increase in reticulocytes and normoblast in the peripheral blood. During a hemolytic crisis the fragility of the remaining cells is increased. Hemoglobin is present in the plasma. Red cells may contain Heinz bodies and the cells may be fragmented showing anisocytosis and poikilocytosis. Serum bilirubin is elevated.

If a significant amount is ingested, cautious gastric lavage can be considered. Lavage is Contraindicated in patients with convulsions and is not likely to be effective if more than 2 hours have passed since ingestion. [20] Give activated charcoal 1 gram per kilogram up to 50 grams as a slurry in water.

Treatment of naphthalene toxicity is supportive, including mechanical ventilation and blood pressure support with the use of inotropes. [19] Underlying cardiac, pulmonary, or hematologic disease may worsen the toxicity of methemoglobinemia.[21] Ascorbic acid, which acts as a free radical scavenger, can be used to decrease the oxidative stress of naphthalene.[22]

A severe anemia due to hemolysis may require small repeated blood transfusions preferably with red cells from a non-sensitive individual. Give repeated small blood transfusions until the hemoglobin concentration is 60 to 80% of normal. A patient who had ingested naphthalene with suicidal intent and who was treated promptly with 100mg of cortisone daily developed Heinz bodies and excreted naphthalene derivatives but did not become ill. Corticosteroids appear to have been beneficial in a few cases of naphthalene hemolysis. [14,15] But the value of cortisone in naphthalene poisoning remains to be confirmed.[14]

Control convulsions with diazepam 5 to 10mg intravenous (IV) slowly (pediatric dose 0.2mg/kg). Repeat if necessary. Therapeutic protocols recommend benzodiazepine in first-line and valproate, phenytoin, phenobarbital or levetiracetam in second-line. Refractory SE treatment requires general anesthesia. Midazolam is a particularly suitable alternative to clonazepam, either intrabuccal, intranasal, through intramuscular way for the SE, or through intravenous way for the refractory SE. [23-25] Osmotic therapy, diuretics, hyperventilation and barbiturates can be used to reduce the brain swelling

Give sodium bicarbonate 5g orally every 4 hours or as necessary to maintain alkaline urine. Give fluids up to 15 mL/kg/h with furosemide 1mg/kg to produce maximum diuresis and reduce injury to the kidney from hemoglobin prod. [15] Anticipate and treat renal failure. If methemoglobin levels are greater than 30% treatment may be required. In the event of intravascular hemolysis with hemoglobinuria, protect the kidneys by promoting a brisk flow or dilute urine; an osmotic diuretic such as mannitol is often used for this purpose.[9] Alkalinization of urine may be helpful by giving small amounts of sodium bicarbonate but many investigators doubt the efficacy of this measure in preventing blockade of renal tubules.[9] Hemodialysis should be used in the presence of severe central nervous system symptoms such as kernicterus.[15]

Specific treatment of methemoglobinemia includes the use of methylene blue, concentrated red blood cells transfusion and ascorbic acid.[11] Methylene blue increases the rate of reduction of methemoglobin to hemoglobin.[19] Recommended doses of methylene blue for the treatment for methemoglobin is 2 mg/kg body weight for infants, 1.5 mg/kg body weight for older children, and 1 mg/kg body weight for adults, in a 1% sterile aqueous solution via slow intravenous infusion.[26] Methylene blue may, however, induce hemolysis and result in paradoxical methemoglobinemia in patients with G6PD deficiency. G6PD testing should be performed prior to administration. Empiric treatment of methemoglobinemia with methylene blue is contraindicated in patients with G6PD deficiency.[6] N-acetylcysteine (NAC) may also be used in the treatment of methemoglobinemia as a reducing agent, especially in patients with G6PD deficiency.[21] Exchange transfusion is an alternative option in these patients.[21] And finally the combination of red blood cell transfusion, intravenous methylene blue, NAC, and ascorbic acid has also been used all together for the treatment for naphthalene ingestion with good results.[1]

IV. CONCLUSION

Naphthalene toxicity should be suspected in patients with acute onset dark brown urine, nausea, vomiting and diarrhea, combined with acute hemolytic anemia, methemoglobinemia, and acute kidney injury. The neurologic symptoms as such convulsions, and Status epilepticus (SE) can complicate the evolution but rarely constitute the initial mode of presentation when the patients consults early. Exact guidelines for the treatment of naphthalene poisoning based on the mode and severity of toxicity are unknown. Treatment includes supportive care, with intravenous hydration, respiratory and blood pressure support, Control convulsions and possibly renal replacement therapy. Specific management options include ascorbic acid, methylene blue, and NAC. Care should be individualized based on the severity of the clinical picture.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

all the authors contributed to the realization of this article, the read and approved the final manuscript.

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Patient consent

Obtained by his family

REFERENCES

- [1] Rahman MM, Mogni Mowla SG, Rahim A, Chowdhury FR, Jahan S, Hasan MN. Severe haemolytic anaemia due to ingestion of naphthalene (mothball) containing coconut oil. *J Coll Physicians Surg Pak.* 2012;22(11):740-741.
- [2] Sillery JJ, Lichenstein R, Barrueto F Jr, Teshome G. Hemolytic anemia induced by ingestion of paradichlorobenzene mothballs. *Pediatr Emerg Care.* 2009;25(4):252-254.
- [3] GIDRON E, LEURER J. Naphthalene poisoning. *Lancet.* 1956;270(6910):228-231.
- [4] Nash FL. Naphthalene poisoning. *BMJ* 1903; 1: 251-259.
- [5] MACKELL JV, RIEDERS F, BRIEGER H, BAUER EL. Acute hemolytic anemia due to ingestion of naphthalene moth balls. I. Clinical aspects. *Pediatrics.* 1951;7(5):722-728.
- [6] Chun T, Perrone J, Osterhoudt K, Ugur S, Henretig F. Mothball blues: confusion in naphthalene toxicities and treatment. *Clin Toxicol* 1998; 36(5): 465.
- [7] Lim HC, Poulouse V, Tan HH. Acute naphthalene poisoning following the non-accidental ingestion of mothballs. *Singapore Med J.* 2009;50(8):298-301.
- [8] Bagchi M, Bagchi D, Balmoori J, Ye X, Stohs SJ. Naphthalene-induced oxidative stress and DNA damage in cultured macrophage J774A.1 cells. *Free Radic Biol Med.* 1998;25(2):137-143.
- [9] Chugh KS, Singhal PC, Sharma BK, et al. Acute renal failure due to intravascular hemolysis in the North Indian patients. *Am J Med Sci.* 1977;274(2):139-146.
- [10] Hassan KS, Al-Riyami AZ, Al-Huneini M, Al-Farsi K, Al-Khabori M. Methemoglobinemia in an elderly patient with glucose-6-phosphate dehydrogenase deficiency: a case report. *Oman Med J.* 2014;29(2):135-137.
- [11] Trevisan A, Rossi di Schio M, Pieno M. Haemolytic anaemia after oral self-giving of naphthalene-containing oil. *J Appl Toxicol.* 2001;21(5):393-396.
- [12] do Nascimento TS, Pereira RO, de Mello HL, Costa J. Methemoglobinemia: from diagnosis to treatment. *Rev Bras Anesthesiol.* 2008;58(6):651-664.
- [13] Annabi EH, Barker SJ. Severe methemoglobinemia detected by pulse oximetry. *Anesth Analg.* 2009;108(3):898-899.
- [14] Hayes WJ. Pesticides studies in man. Williams and Wilkins: Baltimore; 1982. pp. 136-137.
- [15] Dreisbach RH, Robertson WO. Handbook of Poisoning: Prevention, Diagnosis and Treatment. Los Altos California: Appleton and Lange; 1987. pp. 194-195.
- [16] Reynolds JEF (1996). Martindale The Extra Pharmacopoeia. 31th ed. London: The pharmaceutical Press.
- [17] Windholz M ed. The Merck Index: an encyclopaedia of chemicals, drugs and biologicals. 10th ed. Rahway, New Jersey: Merck & Co., Inc; 1983. pp. 2-67.
- [18] Kreisman NR, Magee JC, Brizzee BL. Relative hypoperfusion in rat cerebral cortex during recurrent seizures. *J Cereb Blood Flow Metab.* 1991; 11:77-87.
- [19] Kundra TS, Bhutatani V, Gupta R, Kaur P. Naphthalene Poisoning following Ingestion of Mothballs: A Case Report. *J Clin Diagn Res.* 2015;9(8):UD01-UD2.
- [20] Siegel E, Wason S. Mothball toxicity. *Pediatr Clin North Am.* 1986;33(2):369-374.
- [21] Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med.* 1999;34(5):646-656.
- [22] Niki E. Action of ascorbic acid as a scavenger of active and stable oxygen radicals. *Am J Clin Nutr.* 1991;54(6 Suppl):1119S-1124S.
- [23] Outin H, Blanc T, Vinatier I; le groupe d'experts. Prise en charge en situation d'urgence et en réanimation des états de mal épileptiques de l'adulte et de l'enfant (nouveau-né exclu). Recommandations formalisées d'experts sous l'égide de la Société de réanimation de langue française [Emergency and intensive care unit management of status epilepticus in adult patients and children (new-born excluded). Société de réanimation de langue française experts recommendations]. *Rev Neurol (Paris).* 2009;165(4):297-305.
- [24] Glauser T, Shinnar S, Gloss D, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr.* 2016;16(1):48-61.
- [25] Chapman MG, Smith M, Hirsch NP. Status epilepticus. *Anaesthesia* 2001;56:648-59.
- [26] Obeagu E I.A Review on Methaemoglobinaemia: From Diagnosis to Treatment. *Curr Trends Biomedical Eng & Biosci.* 2018; 14(2): 555884.