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Survival After Methemoglobinemia Associated with Massive Paracetamol Ingestion: A Case Report and Review of the Literature

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Abstract

Introduction: Paracetamol is a frequently used agent in intoxications and known to cause hepatic failure. However, methemoglobinemia secondary to paracetamol toxicity has only been described in a handful of case reports and may be an important determining factor for morbidity and mortality. Methemoglobinemia results in functional anemia with cellular hypoxia. Severe cases are usually fatal.

Case Presentation: We present a case of survival after severe methemoglobinemia in a 67-year-old female. She was admitted to the Intensive Care Unit after auto-ingestion of a large amount of paracetamol. Hemoglobin-oximetry showed a methemoglobin level of 24.6%, treated with intravenous methylene blue, exchange-transfusion, ascorbic acid, and riboflavin. Toxicological screening revealed a high plasma concentration of paracetamol (611.7 mg/L). Treatment with N-acetylcysteine (NAC) was initiated. The patient deteriorated and developed acute liver failure, but refused liver transplantation. Furthermore, she developed septic shock with multi-organ failure and bowel ischemia. In spite of her severe condition and her refusing transplantation, the patient survived. There was a complete resolution of acute liver failure and she fully recovered from her critical condition.

Conclusions: A case of survival after paracetamol-induced methemoglobinemia is presented. Paracetamol-induced methemoglobinemia seems to be a rare (but possibly under-diagnosed) condition. With this report, we would like to focus more attention on the possibility of methemoglobinemia associated with paracetamol intoxication and emphasize the possible impact on morbidity and mortality. Therefore, we think there should be a low threshold for screening for this rare but hazardous problem when there is clinical suspicion.

Keywords: Methemoglobinemia, Methemoglobin, Methemoglobin, Acetaminophen, Intoxication, Acute Liver Failure, Survival

1. Introduction

Paracetamol is a well-known agent that is frequently used in intoxications and suicide attempts. Mainly because it is an over-the-counter drug and the most widely used analgesic drug in the world (1). Paracetamol poisoning is often seen in the Emergency and Intensive Care departments and has been known to cause hepatic failure due to hepatic necrosis for many years since its clinical introduction in 1955 (2). Methemoglobinemia secondary to paracetamol toxicity however, has only been described in 4 previous case reports (3-6) and may be an important determining factor for morbidity and mortality. Acquired methemoglobinemia is a rare disease that has its classic drug-related causes such as various antibiotics (dapsone and sulfonamides), local anesthetics and nitrates. Paracetamol might be a rare, but important cause should be added to this list. It could also be a contributing factor to the severity of methemoglobinemia caused by other agents. In acquired methemoglobinemia, there is an altered state of hemoglobin, where the Fe^{2+} ions of the heme group have been oxidized to Fe^{3+} ions, which results in the inability of methemoglobin to bind oxygen resulting in functional anemia with cellular hypoxia that is often fatal. In this report, we present a case of survival after severe paracetamol-induced methemoglobinemia and acute liver failure, complicated with septic shock and multi-organ failure. Our key objective is to raise awareness for this possible under-diagnosed problem and emphasize the effect that it might have on our critically ill patients.

2. Case Presentation

A 67-year-old woman was found in her home by a mobile medical team after her husband contacted the emergency services when he could not reach her by phone for

several hours. The patient was found on her bed in an altered mental state. Scattered in the apartment and on the patient's body, there was a white substance, which a sample was immediately taken and sent to the lab for analysis. The patient had no significant medical history. She did not take any medication on a regular basis. It was later revealed that the patient had ingested a large quantity of paracetamol (more than 10 boxes) mixed with water and with the intention of committing suicide. At the time of arrival of the mobile medical team, the patient was confused and had a Glasgow Coma Scale of 9/15 (E3 M5 V1). She was brought to the emergency department, where she was further monitored: non-invasive blood pressure was 138/97 mmHg, heart rate 55 beats/minute, saturation 77% on pulse oximetry with an increased respiratory rate and body temperature of 36.1°C. Her chest X-ray and electrocardiogram (ECG) were within normal limits. Initial arterial blood gas analysis showed a high anion gap metabolic acidosis (pH 7.23, Anion Gap 25, Na 148 mmol/L, K 3.8 mmol/L, Cl 115 mmol/L, HCO3- 8.6 mmol/L, pO_2 103 mmHg, pCO_2 20 mmHg, Base Excess-16, Lactate 5 mmol/L, and glycemia 136 mg/dL). A non-rebreathing mask with 12 L/min of oxygen was given as well as 1 litre of intravenous (IV) fluids in bolus (crystalloids). The patient was then transferred to the intensive care unit (ICU) for further diagnostic workup and monitoring, here a striking blue color of the skin and a chocolate brown color of the blood was noticed. Therefore, hemoglobin oximetry was performed that showed a high methemoglobin level (18.2%). Toxicological screening (serum and urine) revealed a very high paracetamol concentration (> 300 mg/L in urine and 611 mg/L in serum) after that the treatment with N-acetylcysteine (NAC) was initiated with a loading dose of 150 mg/kg IV over 30 minutes, followed (30 minutes later) by 50 mg/kg IV over 4 hours, followed by 100 mg/kg IV over 16 hours. Other lab results at the time of the admission showed elevated hepatic enzymes (alanine aminotransferase (ALT) 252 U/L, aspartate aminotransferase (AST) 451 U/L, lactate dehydrogenase (LDH) 1715 U/L, ALP 95 U/L, and total bilirubin 1.3 mg/dL). Coagulation tests were normal at that point (international normalized ratio (INR) 0.97, platelets 362 10E9/L, and activated partial thromboplastin time (APTT) 38). Renal function was normal (with a rather low creatinine 0.21 mg/dL) and myoglobin was markedly elevated (24,910 ng/mL). After that hemoglobin oximetry revealed significant methemoglobinemia, the administration of IV methylene blue (1 mg/kg over 5 minutes) was initiated. Since the toxic components at the time of presentation were unknown, 5 g of hydroxycobalamine (Cyanokit) was supplementary administered in light of a high anion gap metabolic acidosis possibly due to cyanide poisoning. Further tests showed no signs of cyanide poisoning. The initial response was a decrease in methemoglobin from 18 to 8%. However, the next morning the methemoglobin level was once again increased to 13.3% thus the second dose of methylene blue (1 mg/kg IV) was given. Meanwhile, the paracetamol concentration decreased to 308 mg/L at 12 hours post-admission. After reviewing the available literature, the decision was taken to start intermittent hemodialysis for clearance of paracetamol concomitantly the dose of NAC was doubled. After hemodialysis, the paracetamol concentration in plasma decreased from 308 to 68 mg/L. Nevertheless, methemoglobin continued to increase to 24.6%. Therefore, riboflavin (3×1 g) and ascorbic acid (3×500 mg) infusions were associated as well as transfusion of 2 units red packed cells after bloodletting of 300 mL after that methemoglobin levels remained stable around 12%. After 24 hours post-admission the patient developed acute liver failure with hepatic enzymes and coagulation tests further deteriorating (INR > 10, APTT > 1300, platelets 130 10E9/L, AST 700 U/L, ALT 566 U/L, and LDH 3496 U/L) as well as acute kidney injury. She was transferred to a tertiary care (university) hospital, where liver transplantation could be provided if necessary. Further treatment of methemoglobinemia with high dose ascorbic acid was provided there, resulting in further declining levels that eventually normalized. The patient however, who was still struggling with depression, refused liver transplantation and further deteriorated to a septic shock and a state of multi-organ failure with bowel ischemia. Broad spectrum antibiotics (piperacillin-tazobactam) and antifungal prophylaxis (fluconazole) were associated and a sigmoid resection with abdominal lavage was performed. Prolonged ventilation was required and during placement of a tracheostomy an iatrogenic perforation of the trachea and esophagus occurred with a need for repair surgery. Furthermore, a critical illness polyneuropathy was diagnosed.

Despite of this long period of severe illness with multi-organ failure and all the complications mentioned above (and the patient's refusal for liver transplantation), the acute liver failure recovered completely with supportive treatment and the patient's critical condition resolved. She was transferred to the rehabilitation department of our hospital 83 days after admission and was discharged from the hospital 196 days after the admission.

3. Discussion

There are two known forms of methemoglobinemia: congenital and acquired. The most common congenital methemoglobinemia is Cytochrome-b5 reductase deficiency, an autosomal recessive genetic disorder that is caused by a deficiency in the cytochrome-b5 reductase enzyme. This enzyme is the key factor in one of the

body's hemoglobin-reducing pathways, reducing methemoglobin back to its healthy form (as further explained below). Acquired methemoglobinemia is a rare disease. Its precise incidence and mortality is difficult to be ascertained from the available literature because the occurrence of this disease is quite rare and most cases are presented only as case reports. Pharmacological agents are the most common cause of methemoglobinemia in clinical practice. The best known causative agents are local anesthetics (benzocaine, procaine), antibiotics (dapsone and sulfonamides), and nitrates (such as nitroglycerin, nitric oxide) (7). Nitrates can also be present in vegetables or well water (contaminated with agricultural fertilizers) and cause methemoglobinemia in newborns and children (8). Other toxic products such as paint thinner are also well known causative agents of methemoglobinemia (9). Normal hemoglobin contains four heme groups with iron in the reduced ferrous state (Fe^{2+}). There is an altered state of hemoglobin in acquired methemoglobinemia, where the Fe^{2+} ions of the heme group have been oxidized to Fe^{3+} ions, which results in the formation of methemoglobin. Methemoglobin is unable to bind oxygen. Furthermore, the hemoglobin that is left in the reduced state therefore, will have a higher affinity for oxygen and case a left-shift in the oxygen/haemoglobin dissociation curve. These mechanisms result in functional anemia with cellular hypoxia that can be fatal when severe. In healthy individuals, the formation of methemoglobin from hemoglobin is an ongoing oxidative process that results from exposure of hemoglobin to a variety of highly reactive molecules (oxygen free radicals), produced during normal cell metabolism. Yet normal methemoglobin levels are usually low (< 1%) and are maintained low by endogenous protective pathways such as the cytochrome-b5 reductase pathway in red blood cells (responsible for the majority of reduction), NADPH methemoglobin reductase pathway, as well as the ascorbic acid and glutathione enzyme systems. When we are exposed to a strong oxidative agent or large quantities of these agents, methemoglobin levels rise and methemoglobinemia occurs, when these protective pathways become saturated and/or deficient. In newborns cytochrome-b5 reductase pathway is not yet completely developed, which makes these children more prone to the accumulation of excess methemoglobin (8, 10). Typical clinical features of methemoglobinemia are cyanosis, confusion, anxiety, headache, and tachycardia. These may be present in methemoglobin levels > 10%. Other signs are an alteration of skin color and brownish color of the blood. Blood levels > 50% may induce seizures, coma and levels > 70% are usually fatal. Diagnosis is made using hemoglobin oximetry, which is available on standard arterial blood gas analysis (11). Treatment should be considered when methemoglobin levels are > 20% and/or when patients are symptomatic (or when levels are > 10% if risk factors are present such as anemia or ischemic heart disease). First line treatment consists of IV methylene blue, which acts as a cofactor for nicotinamide adenine dinucleotide (NADH) methemoglobin reductase (cytochrome-b5 reductase), rendering methemoglobin back to its normal form (12). High doses of ascorbic acid can also be used as a second line therapy because it is an effective anti-oxidizing agent (13). Most case reports with ascorbic acid were settings, where methylene blue was not readily available. Second line treatment options are hyperbaric oxygen therapy and exchange transfusion in patients who do not respond to methylene blue therapy (14). The scarcity of literature on this subject is striking. There are four cases of paracetamol induced methemoglobinemia in the literature. Despite its frequent use as an analgesic drug (and frequent use in intoxication), the occurrence of significant methemoglobinemia seems to be rare. There is somewhat more literature available on this subject in veterinary medicine (more specifically in cats and dogs). However, since the pathophysiologic mechanisms leading to disease in these animals are somewhat different compared with those in humans, we will not discuss the details of these cases (15-18). In humans however, the first report dates back to 1968 when a case report was published in the British Medical Journal describing a case of methemoglobinemia after intake of a normal dose of paracetamol for post-partum pain. The level of methemoglobin is not mentioned in this case report. The patient made an uneventful recovery (6). In 2000, another survived case of methemoglobinemia was described in Japan, which reported an initial methemoglobin level of 57%; however, this case described a combined use of paracetamol and sodium nitrate (5). The most recent reports are comprised of Kanji et al. who reported a similar case to ours, describing a patient with coma, metabolic acidosis, and methemoglobinemia after a paracetamol intoxication and reported a methemoglobin level of 9.4%, while no acute liver failure was found (4) and Queiros et al. who reported methemoglobinemia (3, 3%) in a hemodialysis-dependent patient with daily use of 1g paracetamol 3 times a day (3). As it can be seen, the levels of methemoglobin referred to in these recent reports are remarkably lower than the level in our report, which peaked at 24.6%. We assume that ingestion of larger quantities of paracetamol and the presence of acute liver failure (with depletion of glutathione storages) may have resulted in higher levels of methemoglobin in our case. However, why this does not occur in all patients after paracetamol intoxication with acute liver failure remains unclear. We did not find any other reports of survival in patients with such high levels of methe-

moglobinemia associated with paracetamol ingestion.

The exact pathogenesis of paracetamol-induced methemoglobinemia is not well understood. Since paracetamol is a metabolite of acetanilide, which is an aniline derivate - and one of the first analgesic drugs on the market - that was banished because of its important toxicity, the mechanism in current paracetamol intoxications could be related and the causative molecule could be phenylhydrolamine, which is an oxidant metabolite of these aniline derivatives (18). The reason why this can be more toxic in some patients is not well understood and genetic traits could be a key factor in this subject. It is likely that methemoglobinemia in paracetamol intoxication is under-diagnosed since mild methemoglobinemia is typically subclinical. Measuring levels of methemoglobin is not traditionally included in the standard work-up of a patient with a paracetamol intoxication. Mild methemoglobinemia itself is subclinical and emphasis on patients with paracetamol intoxication lies typically on the risk and prevention of acute liver failure (19). It might also be important to realize paracetamol could also be a contributing factor to the severity of methemoglobinemia caused by other agents. As paracetamol is one of the most frequently used over-the-counter pharmacological agents in suicide attempts, the importance of a better understanding of its toxicity and the mechanisms by which this toxicity occurs are paramount for ensuring the best treatment for these patients. Therefore, we advocate one-off hemoglobin oximetry in all patients with a severe paracetamol intoxication. Furthermore, clinicians should have a suspicion for methemoglobinemia in patients with hypoxia that does not improve with an increased fraction of inspired oxygen (FiO_2), abnormal coloration of blood or skin or new onset cyanosis after ingestion of an unknown agent.

3.1. Conclusions

In the present report, a case of survival after paracetamol-induced methemoglobinemia was presented. Due to abnormal blood and skin color, the diagnosis was confirmed by hemoglobin oximetry. Treatment with IV methylene blue, ascorbic acid, exchange transfusion, and riboflavin was given with beneficial clinical effect and decline of the methemoglobin to normal levels. Paracetamol induced methemoglobinemia seems to be rare in humans, but may also be under-diagnosed. With this case report, we would like to focus the attention on the possibility of methemoglobinemia associated with paracetamol intoxication and emphasize the possible impact on morbidity and mortality. Therefore, there should be a low threshold for screening for this rare but hazardous problem, when there is clinical suspicion. Furthermore, our suggestion would be to evaluate the possible advantages of systematic screening for methemoglobinemia in paracetamol intoxications in future studies.

Footnotes

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