


A Rare Culprit of Methemoglobinemia

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Abstract

Methemoglobinemia is a rare cause of hypoxia and can be a diagnostic challenge early in the disease course. The incidence of medication-induced methemoglobinemia is more common than congenital-related methemoglobinemia. The most common cause of methemoglobinemia is exposure to household detergents, illicit drugs, or medications with nitrate or sulfonamide chemical groups. The 2 main medications accounting for up to 45% of medication-induced cases are dapson and benzocaine. We report a case of hypoxia and diarrhea with an arterial blood gas (ABG) showing methemoglobinemia at 26%. Infectious and autoimmune workup were negative. Methemoglobinemia level returned to normal level within 2 weeks of hydrochlorothiazide discontinuation, suggesting medication-induced methemoglobinemia at appropriate hypertension dosage. In this case, there was an acute rise in methemoglobin levels following initiation of an hydrochlorothiazide-losartan combination, which improved following the discontinuation of hydrochlorothiazide. Extensive workup ruled out cytochrome b5 reductase (Cb5R) and Glucose-6-phosphate dehydrogenase (G6PD) deficiency, which raised the suspicion of hydrochlorothiazide-induced methemoglobinemia, as it is part of the sulfa drug family.

Keywords

methemoglobinemia, drug-induced, hypoxic

Introduction

While methemoglobinemia may be inherited, its acquired form occurs when hemoglobin is exposed to oxidizing agents and is far more prevalent. Nitrate-containing compounds have been classically described as causing methemoglobinemia, ranging from aniline dyes and pesticides to medications, such as nitroglycerin, nitroprussides, and silver nitrite.^{1,2} Other commonly used drugs include sulfonamides, dapson, and benzocaine—the latter 2 accounting for up to 45% of all drug-induced methemoglobinemia cases.³ There is no exhaustive list of agents that may predispose to methemoglobinemia and new predisposing agents are constantly being discovered. In this case report, we present a case of a 64-year-old female patient with methemoglobinemia, likely induced by the commonly prescribed diuretic, hydrochlorothiazide.

Case Presentation

A 64-year-old female with an active medical history of hypertension presented with chronic diarrhea of 1 month duration. On physical examination, she was afebrile, normotensive, with no heart rate or respiratory rate abnormalities.

However, she was hypoxic on room air and was requiring 2 to 3 L of supplemental oxygen to maintain an oxygen saturation of 90%. Abdominal examination was unremarkable as the abdomen was soft, scaphoid, non-tender, no rigidity or guarding, and bowel sounds were heard in 4 quadrants. Neurologic examination was unremarkable.

She reported starting a combination of hydrochlorothiazide and losartan 3 to 4 weeks prior to presentation. She reported no known exposure to any chemicals other than the appropriate use of bleach at home for laundry. She denied any chronic over-the-counter medication or supplements use. In addition, she denied any illicit drug use. Arterial blood gas (ABG) showed methemoglobinemia at 23.8% (Table 1), and the patient was placed on a 15 L of supplemental oxygen through non-rebreather mask. An extensive workup was

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Table 1. Serial Arterial Blood Gas (ABG) Shows Methemoglobinemia Level During Hospitalization.

| Blood gases | Reference ranges | Arrival | 72 hours later | Discharge | Follow-up |
|-------------------|------------------|---------|----------------|-----------|-----------|
| pH | (7.35-7.45) | 7.433 | 7.456 | 7.428 | 7.465 |
| PCO ₂ | (35-45 mmHg) | 34.5 | 36.2 | 39.7 | 41.0 |
| PO ₂ | (80-100 mmHg) | 147 | 139 | 185 | 76.4 |
| HCO ₃ | (22-26 mEq/L) | 23.0 | 25.5 | 26.2 | 29.5 |
| tHB | (12-16 g/dL) | 12.8 | 12.3 | 11.5 | 12.6 |
| O ₂ Hb | (85%-95%) | 76.3 | 85.4 | 89.5 | 90.3 |
| COHb | (0%-1.5%) | <0.3 | <0.3 | <0.3 | <0.3 |
| MetHb | (0%-2%) | 23.8 | 14.4 | 10.3 | 5.9 |

Abbreviations: COHb, carboxyhemoglobin; HCO₃, bicarbonate; MetHb, methemoglobinemia; O₂Hb, oxyhemoglobin; PCO₂, partial pressure of carbon dioxide; pH, potential of hydrogen; PO₂, partial pressure of oxygen; tHB, tetrahydrobiopterin.

done and was unremarkable. The workup included fecal leukocytes, *Clostridium difficile* (*C. diff*) antibodies/toxins, stool ova, parasites, hepatitis panel, urine drug screen (UDS), antinuclear antibody (ANA), Immunoglobulin A, anti-Smith antibodies (Sm), Sjogren syndrome A antibodies (SSA), Sjogren syndrome B antibodies (SSB), tissue transglutaminase antibodies, and anti-double-stranded Deoxyribonucleic Acid antibodies (anti-dsDNA). Outpatient follow-up 10 days later showed no recurrence of hypoxia or diarrhea. Methemoglobinemia level continued to improve within 2 weeks of hydrochlorothiazide discontinuation. Outpatient ABG showed methemoglobinemia level of 5.9% (Figure 1) and the patient was on room air with oxygen saturation of 96%.

Follow-Up

The patient followed up in the clinic 3 months afterward with no recurrent symptoms. She electively underwent surveillance endoscopy and colonoscopy with biopsy findings of chronic inactive gastritis and was negative for *Helicobacter pylori* but otherwise normal mucosa tissues. Further lab work was done to test for G6PD deficiency and Cb5R deficiency using quantitative test measures. The G6PD deficiency was reported to be 17.2 U/g Hb (normal range = 7-20.5 U/g Hb) and Cb5R deficiency was noted to be 10.1 U/g Hb (normal range = 7.8-13.1 U/g Hb). The above tests supported that our patient did not suffer a deficiency in either of these metabolic processes.

Discussion

Methemoglobinemia is characterized by the oxidation of iron in the hemoglobin from the ferrous state (Fe²⁺) to the ferric state (Fe³⁺), which increases the oxygen affinity and impairs oxygen release from the hemoglobin. There are 2 main categories of methemoglobinemia, and the presentation of this disease depends primarily on the acuity of the rise in methemoglobin levels. The first category is hereditary methemoglobinemia, a chronic condition caused by cytochrome b5 reductase (Cb5R) deficiency, which is

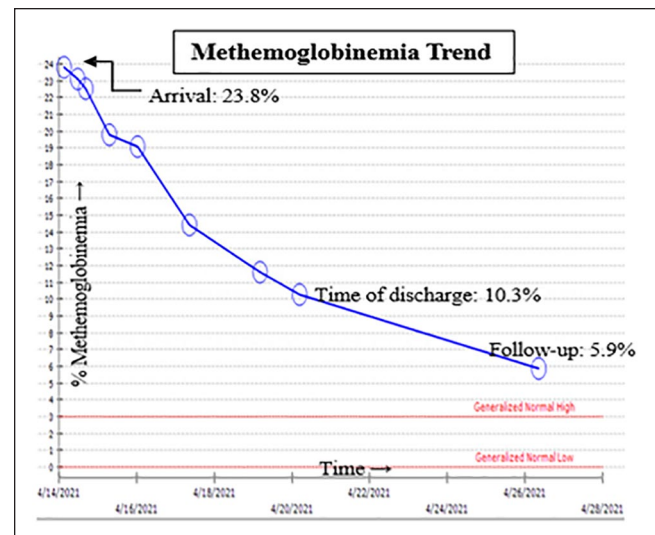


Figure 1. Shows methemoglobinemia trends over time.

generally asymptomatic and causes cyanosis that is only bothersome aesthetically.² The second cause, is the acute rise that can be seen with the introduction of compounds that contain nitrate or sulfonamide groups, which are strong oxidants, especially in those with G6PD deficiency, with or without Cb5R deficiency.³

However, an acute rise in methemoglobin levels is generally associated with worse outcomes due to the lack of compensation with erythrocytosis. The symptoms may range from fatigue and light-headedness to shock, seizures, or even death.⁴⁻¹⁰ It has been reported that the rate at which symptoms can arise is variable and can either be immediate or delayed.¹¹

A case series analyzing 138 cases of methemoglobinemia retrospectively found that 42% of patients with methemoglobinemia had a history of dapsone use, with a mean level of methemoglobin found to be at 7.6%. Benzocaine was a less likely cause of methemoglobinemia in this case series, with only 3.6% with exposure to benzocaine; however, the mean methemoglobin level was found to be 43.8%.¹⁰ Moreover, amid the COVID-19 pandemic, the use of the quinine-based

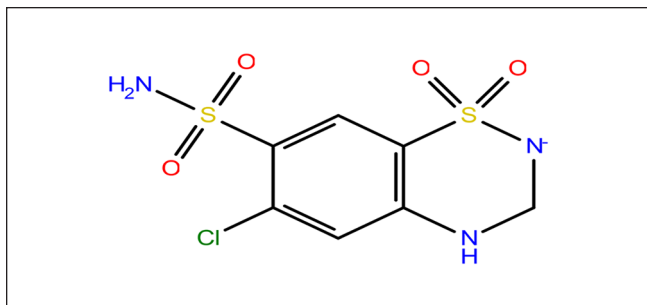


Figure 2. The 2 groups in question for a probable cause are the sulfa groups (yellow S) connected to 2 oxygens (red O) and 1 nitrogen (blue N).

medication, hydroxychloroquine, was on the rise and anti-malarials have been linked in the past to methemoglobinemia, after a study done on soldiers in Vietnam receiving malarial chemoprophylaxis revealed an association with methemoglobinemia.¹² Although there is no official consensus as to common causes of methemoglobinemia, it is estimated that the vast majority of cases are caused by topical anesthetics.^{10,13} Table 2 list the most reported common and rare causes of methemoglobinemia.

The compounds that contain strong oxidant components, such as nitrates and sulfonamides, are expansive and range from antibiotics to food dyes.¹⁹ Hydrochlorothiazide, a thiazide diuretic and one of the first-line medications in the management of essential hypertension, at a chemical level contains 2 sulfonamide groups (Figure 2). Moreover, another medication that the patient reported starting in the same time period was losartan (Figure 3). However, losartan is unlikely to be the culprit cause of methemoglobinemia as it lacks nitrate or sulfonamide components.

There are a handful of hypotheses as to why it affected our patient as such. First, it could be that the patient has a mutated form of her CYP enzymes, which are explicitly known in the literature as cytochrome enzymes and to be numerous. The possible mutated cytochrome enzyme could have metabolized hydrochlorothiazide (HCTZ) into a free radical form that can result in hemoglobin oxidation. It could be that her specific batch of HCTZ medication was degraded through patient error in storage by light, heat, water, pH changing chemical exposure, and thereby a powerful oxidizing sulfonamide group was released.²⁰ Finally, it has been reported that some human microbiome bacteria can metabolize medications, which could be the cause of our patient's methemoglobinemia as HCTZ could have been metabolized to an oxidizing form.^{21,22} Hydrochlorothiazide was found to bind the NADPH binding site of dihydrofolate reductase in the gut microbiome, which suggested potential antimicrobial effects of HCTZ. The literature regarding the interactions between the gut microbiome, chronic diseases, and medications is rapidly expanding the frontier of medicine that still has areas full of unknowns and future research might clarify the interactions between medications and the

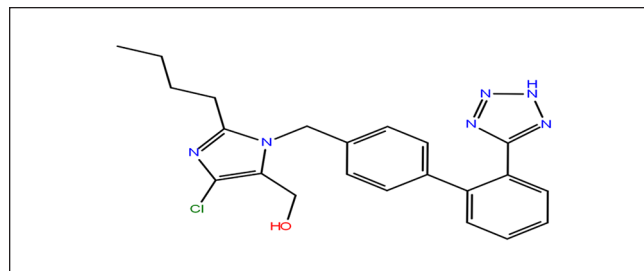


Figure 3. Losartan chemical structure that lacks highly oxidative molecules.

Table 2. Shows Common and Uncommon Causes of Methemoglobinemia.

| | Common | Uncommon |
|---------------------------------|---|---|
| Analgesic/ antipyretics | Phenazopyridine ¹⁴ Phenacetin ¹⁴ | |
| Antiepileptic | | Phenytoin ¹³ Sodium valproate ¹³ |
| Anti-infective agents | Dapsone ¹⁵ Primaquine ¹³ | Chloroquine ¹⁵ Sulfonamide ¹⁵ |
| Local or topical anesthetics | Benzocaine ^{1,16} Prilocaine ^{16,17} | Amethocaine ¹³ Tetracaine ¹⁷ |
| Vasodilator agents | Nitrate derivatives ¹⁸ | |

gut microbiome. Moreover, we searched the FDA's website for any recall of her specific medication or any medication batch in the same time frame and found that no such recall or warning was issued. The chemical degradation of her product is on the top of the list of causes because one of the side effects of ingesting sulfates/sulfonamides is diarrhea that our patient experienced.

Methemoglobinemia does not necessarily require methylene blue for resolution. Mild cases are self-resolving with supportive care once the offending agent is isolated and removed. This resolution occurs in part due to the short half-life of methemoglobin through the enzymatic reduction action by G6PD or Cb5R.^{12,16}

Due to the relative stability of our patient, as evidenced by the absences of seizures, dizziness, palpitations, and methemoglobin levels that never exceeded 30%, our recommendation was to discontinue hydrochlorothiazide. Instead, this patient was continued on losartan for hypertension management at a higher dose with close monitoring.^{7,15} Methemoglobin levels were followed even after discharge and the steady downtrend of levels closely correlated to the removal of what is hypothesized as the offending agent, hydrochlorothiazide.

To our knowledge, this is the first case of hydrochlorothiazide-induced methemoglobinemia and it is not known whether this adverse event has arisen from degraded products due to manufacture error or expired medication. Our patient's medication was recently filled and there was no obvious reason to doubt expiration. Ideally, analyzing these medications for unknown chemical structures might provide a better understanding of the causative agent with certainty.

Conclusion

Methemoglobinemia is very rare; however, early recognition and treatment potentially would prevent fatal complications. Nonetheless, thorough history-taking and careful evaluation of the medication list can improve morbidity and mortality significantly and might be a life-saving measure as in our case where the causative agent was identified and discontinued, which allowed for early recovery. In this case, we describe a 64-year-old female presenting with medication-induced methemoglobinemia after HCTZ initiation. The medication was promptly held with symptomatic and laboratory parameters improvement. This case also sheds light on the importance of clinical pharmacists' participation in the identification of potential drug interactions and drug reactions in those with no known toxin exposure.

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Ethics Approval


Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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