Case reports

Primaquine-induced methemoglobinemia: Literature review, case report and pharmaceutical care work-up

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Drugs are the leading cause of methemoglobinemia in North America.[1] A Medline search from 1966 to November 1997 revealed a number of primaquine-induced methemoglobinemia case reports which have been detailed in Table I.[1–4] In all 22 cases reported, the individuals were either concurrently taking or had recently discontinued taking other medications reported to potentially cause methemoglobinemia. The reports involved either soldiers taking primaquine for antimalarial prophylaxis or patients with HIV being treated for pneumocystis carinii pneumonia (PCP). Patients with HIV may be at a higher risk for experiencing methemoglobinemia due to their increased exposure to a number of medications that are known to potentially cause this. Primaquine, used in combination with clindamycin for the treatment of PCP is one of these medications.

The case of a patient who experienced methemoglobinemia secondary to primaquine will be described. This will be followed by a discussion of methemoglobinemia.

CASE REPORT

A 42-year old HIV-positive male (54.5 kg) experienced dyspnea and cyanosis which worsened over a period of 2 to 3 days, but he was still able to walk. On admission to hospital, laboratory findings were as follows: white blood cell (WBC) count 3.7x 10^9/L (normal 4–11 x 10^9/L) with neutrophils 3.0 x 10^9/L (normal 2.5–7.5 x 10^9/L); hemoglobin 113 g/L (normal 140–180 g/L); hematocrit 0.34 (normal 0.33–0.43); serum creatinine 77 µmol/L (normal 75–125 (mol/L); blood urea nitrogen (BUN) 4.9 mmol/L (normal 3–7 mmol/L); aspartate aminotransferase 20 µ/L (normal 0–35 u/L); alanine aminotransferase 12 µ/L (normal 0–35 u/L); alkaline phosphatase 62 µ/L (normal 30–120 u/L); and blood methemoglobin 27% (normal < 1%). Serum lactate dehydrogenase was also elevated at 271 u/L (normal 110–240 µ/L). The patient's absolute CD4 count was 8 cells/mm^3. On admission to hospital, his blood was noted to be a "chocolate-brown" colour.

Medications the patient was taking prior to admission to hospital were: ganciclovir 270 mg IV daily for maintenance treatment of CMV retinitis (for several months), fluconazole 100mg p.o. daily for oral thrush (for several months), clindamycin 450mg p.o. 4 times daily and primaquine 30mg p.o. daily initiated 10 days earlier to complete a course of PCP treatment. Prior to the initiation of clindamycin and primaquine therapy, he was taking dapsone 100mg po every second day for at least one year. The patient's medication allergies include sulfamethoxazole/trimethoprim (Septra) and codeine, with the reactions to each unknown. The patient's social history revealed no history of cigarette smoking, but included occasional marijuana and alcohol use.

Arterial blood gases while the patient was breathing room air were reported as pO_2 13 mmHg (laboratory error likely because this value is incompatible with life) (normal 80–100 mmHg); pCO_2 46 mmHg (normal 35–45 mmHg); bicarbonate content 26 mmol/L (normal 21–28 mmol/L) and pH 7.37 (normal 7.35–7.45). Arterial blood gases while the patient was breathing 100% oxygen were pO_2 197 mmHg (80–100 mmHg); pCO_2 35 mmHg (35–45 mmHg); bicarbonate content 24 mmol/L (21–28

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Table I—Reports of primaquine-associated methemoglobinemia in the literature. Reference numbers relate to the list of references cited at the end of this article.

Ref. no.	Cases	Dose of primaquine therapy	Onset of methemo-globinemia	Concurrent medications	HIV status	Methemo-globinemia concentration	Methylene blue given	Medications before primaquine
2	12	22.5 mg daily x 14 days	n/a	Chloroquine base 3 g over 3 days	n/a	≤10%	no	
3	6	45 mg once wkly	n/a	Chloroquine base 300 mg once wkly + diaminodiphenyl-sulfone 25 mg daily	n/a	22–32%	no	
4	1	30 mg tid x 3 days	3 days	Clindamycin 600 mg tid	+ve	20%	yes	Sulfamethoxazole/ trimethoprim (Septra DS) 8 tabs/day
1	3	a) 30 mg daily	3 days	Clindamycin 900 mg q6h	+ve	28.7%	yes	Dapsone 100 mg/day
1		b) 30 mg daily	9 days	Clindamycin 3600 mg/day	+ve	15.3%	no	Dapsone 100 mg every second day
1		c) 15 mg dailys	>3 days	Clindamycin 1800 mg/day	+ve	26%	yes	Dapsone 100 mg/day

mmol/L) and pH 7.45 (7.35–7.45). Glucose-6-phosphate dehydrogenase (G6PD) was tested and no enzyme deficiency was detected.

Upon demonstration of methemoglobinemia, primaquine and clindamycin therapies were stopped and 80mg of IV methylene blue was administered on the physician's order. However, some of the dose went interstitial and intravenous access was lost. The patient was then placed on ascorbic acid 500 mg p.o. daily. The patient experienced gradual resolution of symptoms over a period of 14 days. He was discharged from hospital 17 days after admission (with a methemoglobin level of 1.5%) and enrolled in an aerosolized pentamidine/ atovaquone study for PCP prophylaxis.

THE PATHOPHYSIOLOGY OF METHEMOGLOBINEMIA

Methemoglobinemia occurs when >1% of the total hemoglobin is in an oxidized form. Chemically, the difference between methemoglobin, deoxyhemoglobin and oxyhemoglobin lies in the oxidation state of the iron.

The iron in deoxyhemoglobin is in the ferrous (Fe++) state which allows oxygen to bind to it easily. Oxygen binds to deoxyhemoglobin to form oxyhemoglobin. Oxyhemoglobin is a superoxo-ferriheme complex ($Fe^{+++}O_{2-}$). When hemoglobin unloads its oxygen, the ferrous state of iron (i.e. deoxyhemoglobin) returns. However, during this process of deoxygenation, a small portion of oxygen leaves as the superoxide (O_{2-}) radical leaving the iron in a ferric state, thus the creation of methemoglobin. Methemoglobin cannot carry oxygen as the ferric iron does not bind oxygen.[5–7]

In normal erythrocytes, small quantities of methemoglobin are formed constantly through the autoxidation of hemoglobin. Several mechanisms exist to restrict methemoglobin levels to less than 1%. The most important system to restore hemoglobin levels is the nicotine adenine dinucleotide (NADH)-dependent cytochrome b_5 reductase system, which uses the hydrogen donor NADH to reduce cytochrome b_5. This in turn reduces methemoglobin to hemoglobin. Up to 95% of the recycling of methemoglobin is accomplished this way.[5,6,8]

The other enzymatic system is the reduced nicotine adenine dinucleotide phosphate (NADPH) diaphorase pathway. This normally accounts for only a very small proportion (<5%) of methemoglobin recycling but is dramatically potentiated in the presence of methylene blue. NADPH-diaphorase only functions in the presence of an artificial electron acceptor such as methylene blue which it reduces to leukomethylene blue. This, in turn, reduces methemoglobin to hemoglobin.[5,6,9]

Antioxidants such as glutathione and ascorbic acid (vitamin C) may reduce methemoglobin non-enzymatically. However, it is more likely that they are involved in the "mopping up" of other radicals within the erythrocyte.[5]

CAUSES OF METHEMOGLOBINEMIA

A genetic deficiency in the NADH-methemoglobin reductase system leads to lifelong methemoglobinemia and cyanosis because this is the major route of methemoglobin reduction in humans. Treatment is usually cosmetic. Treatment alternatives include ascorbic acid, riboflavin or oral methylene blue.

An extremely rare genetic deficiency in NADPH-diaphorase, which accounts for a very small proportion of methemoglobin reduction, results in poor responses to methylene blue therapy in the event of poisoning with oxidizing agents.[5] Also, methylene blue is only clinically effective if there is enough available NADPH.

The most common causes of methemoglobinemia are exogenous substances. The substances can be broken down into 2 major categories: direct methemoglobin formers and methemoglobin formers requiring metabolic activation. Substances in the second category must be metabolized to direct methemoglobin formers. Examples appear in Table II.

Table II—Agents implicated in acquired methemoglobinemia[5,6,8–11,13]

Methemoglobin formers	
Direct	Requiring metabolic activation
Therapeutic agents	Sulfonamides
Alkyl nitrites (e.g. amyl nitrite, isobutyl nitrite)	Co-trimoxazole
Ammonium nitrite	Dapsone
Bismuth subnitrate	Sulfamethizole
Lidocaine	Sulfanilamide
Nitrate esters (e.g. nitroglycerin)	Sulfathiazole
Prilocaine	Prontosil
Silver nitrate	
Sodium nitrite	Aniline dyes
Quinones	Diaper marking ink
	Dyed blankets
Domestic and industrial agents	Laundry markings
Well water high in nitrates	Freshly dyed shoes
Food high in nitrates	
Kerosene	Miscellaneous compounds
Nitrous gases (arc welders, silo fillers)	Acetanilid
Corning extract	Acetylphenylthdrazine
Potassium chlorate	Aminobenzenes
Butyl nitrite ("room deodorizers")	Benzocaine
	Flutamide
	Metoclopramide
	Nitrobenzenes
	Nitrobenzenes
	Nitrotoluenes
	Phenacetin
	Phenazopyridine
	Phenylenediamine
	Prilocaine
	Primaquine
	Resocin
	Toluenediamine
	Trinitrotoluene

DIAGNOSIS

On clinical examination of the patient, if the patient's cyanosis does not resolve following the administration of 100% oxygen, one should suspect methemoglobinemia. Also, at physiologic pH, acid methemoglobin predominates which has a characteristic "chocolate-brown" colour. This results in a bluish or brownish-grey colouring of the skin, lips and nail beds. A methemoglobin level should be drawn which is expressed as a percentage and represents the percentage of total hemoglobin that has been converted to the oxidized form. Most patients tolerate methemoglobin levels up to about 10%.[10] Patient discomfort, however, does depend largely on the rate at which methemoglobin accumulates. If levels increase slowly, patients can tolerate higher levels of methemoglobin.

Levels of methemoglobin and their corresponding clinical symptoms can be summarized as follows:

- *>30%:* fatigue, headache, dyspnea, nausea and/or tachycardia
- *~55%:* lethargy, stupor, deteriorating consciousness
- *55–70%:* cardiac arrhythmias, circulatory failure and neurological depression
- *>70%:* usually fatal.[9]

The severity of a patient's condition must be interpreted with the patient's total hemoglobin level in mind. An anemic patient with a hemoglobin of 80g/L and a methemoglobin level of 25% would have only 60g/L of functional hemoglobin.[5]

Table III—Pharmacist's care plan[14]

Drug-related problem	Outcomes a) clinical outcome b) pharmaco-therapeutic outcome c) pharmaco-therapeutic endpoint	Alternatives and assessment	Therapeutic plan	Therapeutic plan endpoints	Monitoring plan
Which problems will you assume responsibility for and solve for this patient? Shortness of breath and cyanosis due to methemo-globinemia, secondary to primaquine	What are the clinical outcome, pharmaco-therapeutic outcomes and pharmaco-therapeutic endpoints? a) Decreased shortness of breath and improvement in cyanosis; ensure patient is receiving appropriate therapy to treat methemo-globinemia; decrease methemoglobin level to <2%.	List, assess all reasonable drug and nondrug therapies that could produce desired pharmaco-cotherapeutic outcome(s) For each alternative drug or nondrug regimen, consider efficacy, toxicity, timeframe of effect, convenience, drug interactions and cost. 1) Administer 100% O_2; discontinue primaquine/ dapsone. 2) Administer 100% O_2; discontinue primaquine/ dapsone; start ascorbic acid. 3) Administer 100% O_2; discontinue primaquine/ dapsone; start methylene blue.	For this patient, which drug or nondrug regimen should be instituted or which changes should be made in existing drug therapy? Option 1: Discontinue primaquine or Option 2: Discontinue primaquine and start ascorbic acid.	What are potential benefits or problems associated with this therapeutic plan? Determine desired endpoints for the therapeutic plan. Endpoint is defined as parameter, degree of change and desired time-frame for change. Avoid possible adverse effects and cost associated with methylene blue administration. Decrease methemoglobin level to <2% within several days. Counsel patient to avoid primaquine in future. Discuss risks association with other agents known to cause methemoglob-inemia.	For pharmaco-therapeutic and therapeutic plan endpoints, determine what parameters have to be followed, when to start monitoring, how frequently, when to stop and who will take responsibility for monitoring. Monitor methemoglobin level daily until level falls below 2%. Monitor for decreased dyspnea and increased exercise tolerance. Monitor for possible gastrointestinal disturbances if ascorbic acid is initiated.

Accurate assessment of oxygenation in the presence of methemoglobin can only be obtained from the analysis of an arterial or venous blood sample by a CO-oximeter.[5] Pulse oximetry tends to overestimate oxygen saturation in the presence of methemoglobin.

TREATMENT

The treatment of methemoglobinemia is dependent on its severity. Most cases are mild and require only withdrawal of the responsible agent. Other than observation, no treatment is thought to be necessary in patients with methemoglobin levels below 30%.[5]

In more severe cases (methemoglobin >35%), 100% oxygen should be administered and if the patient's level of consciousness deteriorates, airway control may become necessary as well as hemodynamic support. Caution is advised in patients with chronic obstructive airway disease who retain CO_2 and operate on a hypoxic respiratory stimulus, because high concentrations of oxygen may cause respiratory depression.[5]

The mainstay of treatment in patients with severe methemoglobinemia is IV methylene blue given at a dose of 1–2 mg/kg as a 1% solution over 5–10 minutes. Repeated doses can be given if the methemoglobinemia persists after 1 hour, or if the patient relapses. However, cumulative doses of over 7 mg/kg should be avoided because dyspnea, chest pain, tremours, cyanosis and hemolytic anemia can occur in these patients.[5,11]

Methylene blue is contraindicated in patients with G6PD deficiency because there is insufficient G6PD for erythrocytes to generate an adequate amount of NADPH to reduce methylene blue. Oxidative hemolysis can result in these patients. Thus, a non-enzymatic methemoglobin-reducing agent such as ascorbic acid at a dose of 500 mg/day may be beneficial.[5,11] Methylene blue is also contraindicated in patients with severe renal impairment.[11]

PHARMACEUTICAL CARE WORK-UP OF CASE 14

How might the patient's care have differed if pharmaceutical care had been in place?

What are the patient's undesirable signs and symptoms?

This patient is experiencing shortness of breath and cyanosis.

How urgent is the situation?

The situation is not currently life-threatening. However, it can be potentially life-threatening if left untreated. Thus, treatment should begin as soon as possible.

Is the problem caused by drug therapy?

Given the age of the patient, genetic enzyme deficiencies are unlikely to be the cause of the methemoglobinemia. It is most likely to be toxin-related because the patient was recently started on primaquine therapy, which is known to potentially cause this problem. Although the patient was previously taking dapsone (an agent which is known to potentially cause methemoglobinemia), it is unlikely to be the sole cause because the patient had been taking it for over a year. It is possible that the combination of dapsone and primaquine in the patient's system may be blamed. Although dapsone therapy was discontinued before initiating primaquine, dapsone may not have been completely eliminated from the patient's system; its half-life can be as long as 83 hours. Also, hydroxylation of dapsone into hydroxylated monoacetyl metabolites is thought to be responsible for methemoglobin production, and these metabolites can linger on for up to 35 days after the drug is discontinued.[1]

Statement of the drug-related problem

This patient is experiencing shortness of breath and cyanosis secondary to methemoglobinemia, an adverse effect of primaquine.

Pharmacy care plan

After considering the options (Table III), it is decided that discontinuation of the primaquine is required. Ascorbic acid may be added. It is relatively inexpensive, usually well-tolerated and may provide some benefit in reducing methemoglobin non-enzymatically or mopping up radicals. Methylene blue administration is not needed because the patient's methemoglobin level is below 30%. The pharmacist will monitor the methemoglobin level daily until the level falls below 2%, which normally occurs within days but depends on clearance of the drug from the patient's system.[12] Dapsone's half-life is quite long, as discussed previously. The patient should be counselled to avoid primaquine in the future and to monitor for similar symptoms should he be prescribed any other agents known to cause methemoglobinemia.

The agent chosen for PCP prophylaxis also needs to be discussed with the patient. Sulfamethoxazole/trimethoprim, followed by dapsone, are the most efficacious agents. However, depending on the patient's allergic reaction to sulfamethoxazole/trimethoprim and whether he would like to be re-challenged with either of these agents, aerosolized pentamidine may be another option.

CONCLUSIONS

Methemoglobinemia may be caused by a number of different agents, notably primaquine with or without dapsone in this case. When detected early, this can be managed quite easily by removing the causative agent. However, if it is not, this adverse effect can be lethal. Physicians, pharmacists and nurses need to be made more aware of this condition and its potential causes, allowing for quicker diagnosis and treatment.

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