Reminder of important clinical lesson

Acquired methaemoglobinaemia related to phenazopyridine ingestion

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Summary

Methaemoglobin is an altered state of haemoglobin in which the ferrous ions of haeme are oxidised to the ferric state. This results in increased affinity to the bound oxygen and decreasing its availability to tissues. Most cases of methaemoglobinaemia are acquired, resulting from an increased methaemoglobin formation by various exogenous agents. The authors report an elderly patient presenting to the emergency department with a 1-month history of shortness of breath. Around the same time she had started using over-the-counter (OTC) phenazopyridine tablets for urinary symptoms. The patient was hypoxic and cyanotic; however, lacked evidence of hypoxaemia on the arterial blood gas. The presence of abnormal haemoglobin was suspected and confirmed by elevated levels of methaemoglobin. Phenazopyridine was proposed to be the likely aetiology of the methaemoglobinaemia, which the patient was not aware of. This case highlights the importance of always inquiring the OTC drug use especially in geriatric population.

BACKGROUND

Methaemoglobin is an altered state of haemoglobin in which the ferrous (Fe^{2+}) ions of haeme are oxidised to the ferric (Fe^{3+}) state. The ferric hemes of methaemoglobin are unable to bind oxygen and subsequently the oxygen affinity of any remaining ferrous hemes in the haemoglobin tetramer is increased.¹ This results in increased affinity to the bound oxygen and decreasing its availability to tissues. Most cases of methaemoglobinaemia are acquired, resulting from an increased methaemoglobin formation by various exogenous agents. The classical drugs causing methaemoglobinaemia include analgesics (lidocaine and phenazopyridine), antibiotics (sulphonamides and dapsone), nitrites/nitrates, nitroprusside and metoclopramide.² The clinical presentations of methaemoglobinaemia include cyanotic appearance, unresponsive to oxygen therapy; low oxygen saturation on pulse oximeter, which does not match high PaO_2 .

CASE PRESENTATION

The authors report a 74-year-old woman presenting to the emergency department with a 1-month history of shortness of breath. The patient mentioned that her shortness of breath was progressive and had been worsening over the past month. The shortness of breath was constant and did not have any correlation with activity or position. No exacerbating or relieving factors were associated with shortness of breath. The symptoms were not associated with cough, cold or fever. The patient had complaints of urinary urgency as well as pain in her bladder area for the past few months. She mentions seeing a primary care physician on multiple occasions for the same and has received courses of sulphamethoxazole/trimethoprim and levofloxacin; however, it had not responded to antibiotics. Her last dose of any antibiotic was 5 weeks ago. Recently a month ago she had started using over-the-counter (OTC) phenazopyridine tablets to

relieve her urinary symptoms. The patient had previous medical history significant for hypertension, hyperlipidaemia and chronic obstructive pulmonary disease and was on appropriate medication for the same. She had a 30-pack-year history of smoking, however, denied any drug or alcohol use.

On examination the patient appeared in moderate respiratory distress with a respiratory rate of 30/min and had oxygen saturation of 92% on her pulse oximetry on 10 litres oxygen via a non-rebreather mask. There was cyanosis appreciated in her nail beds and perioral area. Her cardiopulmonary examination was normal on auscultation. Yellowish discolouration of the skin was appreciated in the absence of scleral icterus. The patient's urine seen in the bedpan was bright orange in colour suggesting us some toxin ingestion.

INVESTIGATIONS

Laboratory investigation revealed the presence of acute renal failure (ARF) with a serum creatinine of 4.5 mg/dl and glomerular filtration rate of 10 ml/min/1.73 m². In order to evaluate her hypoxia an arterial blood gas was ordered which showed blood pH=7.32, pCO_2 =47 mm Hg and pO_2 =234 mm Hg on FiO_2 of 60%.

Considering the clinical picture of hypoxia in the absence of hypoxaemia and the presence of cyanosis, presence of abnormal haemoglobin such as methaemoglobin was considered. Methaemoglobin levels were measured using a multiple wavelength co-oximeter and were found to be elevated at 18.9% confirming our clinical suspicion. The only offending agent on the patient's current medication list at this time was phenazopyridine. Her symptoms had started a month ago and had gradually worsened which correlated temporally with the initiation of the phenazopyridine tablets. The patient had a Naranjo algorithm score of 7 indicating a probable association between phenazopyridine and methaemoglobinaemia.³

TREATMENT

The patient was administered 70 mg of intravenous methylene blue (1 mg/kg dose) and her methaemoglobin levels decreased to 10.8% after 2 h of the medication. The intravenous methylene blue dose was repeated which completely resolved her methaemoglobinaemia.

OUTCOME AND FOLLOW-UP

This patient's hypoxia improved the next day where she was breathing comfortably and her oxygen saturation was normal on room air. Concomitantly, her renal failure resolved in the next 48 h with adequate hydration. The patient on discharge was explained about the side effects of the phenazopyridine tablets and explained the importance of discussing the safety of OTC tablets with her physician.

DISCUSSION

The authors report a case where the patient developed toxicity with phenazopyridine at therapeutic doses. The patient developed renal failure most likely due to the phenazopyridine and later with drug accumulation developed methaemoglobinaemia. ARF is a rare but reported side effect of phenazopyridine and methaemoglobinaemia and skin pigmentation along with orange discolouration of the urine accompanies the transient renal failure in some of the reported cases.⁴⁻⁷ In a healthy individual, there is a reducing enzyme cascade which converts the methaemoglobin back to haemoglobin. Phenazopyridine toxicity is suggested to result in either overproduction of oxidised haemoglobin or interruption of the reducing cascade resulting in methaemoglobinaemia.⁶ Acute tubular necrosis secondary to phenazopyridine and interstitial damage secondary to methaemoglobinaemia are the proposed mechanisms contributing to renal injury.⁷

New prescription drugs are continually introduced, and older drugs are increasingly available OTC, making self-medication common. Adverse reactions to drugs are among the leading causes of hospitalisation and death in the USA.⁸ Healthcare professionals are often not informed of OTC drug use by their patients and hence patients remain unaware of the adverse reaction associated with the drug. This case further highlights the importance of always inquiring the OTC drug use especially in the geriatric population.

Learning points

- ▶ Methaemoglobin is an altered state of haemoglobin in which the ferrous ions of heme are oxidised to the ferric state. This results in increased affinity to the bound oxygen and decreasing its availability to tissues.
- ▶ Most cases of methaemoglobinaemia are acquired, resulting from an increased methaemoglobin formation by various exogenous agents. The classical drugs causing methaemoglobinaemia include analgesics (lidocaine and phenazopyridine), antibiotics (sulphonamides and dapsone), nitrites/nitrates, nitroprusside and metoclopramide.
- ▶ The clinical presentations of methaemoglobinaemia include cyanotic appearance, unresponsive to oxygen therapy; low oxygen saturation on pulse oximeter, which does not match high PaO₂.
- ▶ Adverse reactions to drugs are among the leading causes of hospitalisation and death in the USA.

Competing interest None.

Patient consent Obtained.

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