CASE REPORT

Sulphaemoglobinaemia caused by ferrous sulfate

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SUMMARY

A 78-year-old man was referred from his primary care clinic to the emergency department due to bluish discoloration of his lips and decreased oxygen saturation on pulse oximetry. The patient was asymptomatic. Physical exam was normal except for lip cyanosis. A CT pulmonary angiogram was negative for pulmonary embolism. Arterial blood gas (ABG) analysis with co-oximetry showed low oxyhaemoglobin, normal partial pressure of oxygen and methaemoglobinaemia, but an unexplained 'gap' in total haemoglobin saturation. This gap was felt to be due to sulphaemoglobinaemia. After a thorough review of his medications, ferrous sulfate was stopped which resulted in resolution in patient's cyanosis and normalisation of his ABG after 7 weeks.

oximetry was 88% on ambient air. The patient was alert and oriented. No use of accessory muscles of respiration were noted. His lips were dark blue. Extremities were warm and well perfused with no finger clubbing. Cardiopulmonary examination was essentially normal with no audible murmurs or wheezes.

Past medical history includes prostate cancer, pulmonary embolism, iron deficiency anaemia, chronic recurrent *Clostridium difficile* colitis for which he had a recent faecal microbiota transplant, seizure disorder and early Alzheimer's disease.

Medications were warfarin, ferrous sulfate, tamsulosin, atorvastatin, cyanocobalamin, finasteride, loperamide, bethanechol, levetiracetam, fluticasone and memantine.

BACKGROUND

Sulphaemoglobin is a rare haemoglobin species characterised by reduced affinity to oxygen resulting in cyanosis and ultimately compromised tissue oxygenation.¹ It is formed first by oxidation of iron atoms in haemoglobin to the ferric state followed by sulfur incorporation into haemoglobin molecules.² Medications that have been implicated as causes of sulphaemoglobinaemia include dapsone, nitroglycerin, sulfonamides and phenazopyridine.³⁻⁴ Sulphaemoglobin and methaemoglobin share similar absorptive peak wavelengths on co-oximetry making the diagnosis challenging.⁵⁻⁷ To our knowledge, this is the first report implicating ferrous sulfate as a likely cause for sulphaemoglobinaemia. Thus, the incidence has never been previously reported.

CASE PRESENTATION

A 78-year-old Caucasian male retired electrical engineer was found to have lip cyanosis with a reduced oxygen saturation (88%) on pulse oximetry during a regular clinic visit. The patient had no symptoms. His daughter had noticed that his lips were turning blue in the preceding weeks, but they did not seek any medical attention at that time because the patient was feeling well. The patient denied any recent exposure to toxic chemicals or fume exhaust and stated that he had a carbon monoxide alarm at home that never went off.

Given the persistent lip cyanosis, the patient decided to see his primary care physician who sent him to the emergency department. In the emergency room, his vital signs were: blood pressure of 138/79 mm Hg, respiratory rate of 17/min, pulse rate of 67 bpm and temperature of 36.8°C. Pulse

INVESTIGATIONS

1. Pulse oximetry was performed on ambient air and showed oxygen saturation of 88%.
2. Haemoglobin level: 9.5 g/dL with a hematocrit of 30%.
3. CT angiogram of the chest was performed with no evidence of acute pulmonary embolism.
4. Arterial blood gas (ABG) with cooximetry was as follows:

-Baseline ABG performed 6 months previously, on ambient air showed: (oxyhaemoglobin 95.2%) and normal PaO₂ of oxygen.

-A sample obtained in ED on ambient air showed oxyhaemoglobin of 86.7%, normal PaO₂ of oxygen (89 mm Hg) and low SpO₂ (88%).

-Second sample obtained on 3L/min of oxygen via nasal cannula showed oxyhaemoglobin of 89.8%, an increase of PaO₂ of oxygen to 191 mm Hg and SpO₂ 90%.

-Co-oximetry revealed methaemoglobin concentration of 2.0% and carboxyhaemoglobin level of 0%. The blood gas analyser did not report sulphaemoglobin levels.

(5) Cyanide level was less than 0.050 mg/L.

A concern was raised due to the gap in saturated haemoglobin levels on co-oximetry. The oxyhaemoglobin, carboxyhaemoglobin and methaemoglobin levels fell well short of 100%. This raised concern for sulphaemoglobinaemia. The laboratory was then called, and the technician stated that there was an error message that accompanied the co-oximetry results that stated sulphaemoglobin was present in levels up to 10%. The diagnosis of sulphaemoglobinaemia was then made.

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TREATMENT

His medications were thoroughly reviewed and ferrous sulfate was the only identified likely cause for sulfhaemoglobinaemia. The decision was made to stop this medication and the patient was discharged from the hospital on supplemental oxygen with follow-up scheduled in the pulmonary clinic.

OUTCOME AND FOLLOW-UP

At follow-up, the patient's lip cyanosis had resolved and repeat ABG with co-oximetry—on ambient air—revealed the following:

Oxyhaemoglobin 94.3%, carboxyhaemoglobin 0.2%, methaemoglobin 0.7% and a normal PaO₂ of oxygen.

This shows return of oxyhaemoglobin back to near baseline level 6 months ago which was 95.2% after 7 weeks of discontinuing ferrous sulfate.

DISCUSSION

Sulfhaemoglobin is formed by oxidation of iron atoms in haemoglobin to the ferric state followed by sulfur incorporation into the haemoglobin molecule.² Drugs that cause sulfhaemoglobin share two characteristics: first, they provide the source for sulfur and second they cause oxidation of iron in haemoglobin.⁸ The mechanism by which oral ferrous sulfate may have caused sulfhaemoglobin in our patient is unclear but the two characteristics named above are present in ferrous sulfate. First, it provides a source for sulfur and second, literature has shown that it can cause oxidative damage in toxic levels.⁹ It remains unclear however, whether the oxidation could occur in normal ferrous sulfate levels or whether the patient actually had toxic levels at some point. In our patient, the sulfhaemoglobinaemia is clearly linked to ferrous sulfate by the temporal relationship. The ferrous sulfate had been the only new medication added since his baseline ABG. The ABGs in the hospital, on further investigation, were consistent with sulfhaemoglobinaemia, and discontinuation of the ferrous sulfate led to essential resolution at 7 weeks (full resolution would be anticipated at 90–120 days, the life of the typical red blood cell).

Management includes removing the causative agent. In this situation, removing the suspected offending agent and getting a follow-up ABG after several weeks established a definitive answer. Ideally, follow-up ABG should be done after 120 days which reflects the life span of red blood cell. By this time, new generation of red blood cells will have replaced old red blood cells that carried the abnormal sulfhaemoglobin.¹⁰

The presence of cyanosis, low saturation on pulse oximetry and normal arterial oxygen tension on ABG point requires obtaining co-oximetry to analyse different types of haemoglobin molecules other than oxyhaemoglobin such as methaemoglobin or sulfhaemoglobin. However, differentiating between sulfhaemoglobin and methaemoglobin on co-oximetry can be sometimes difficult because they share similar absorptive peak wavelengths, and most blood gas analysers do not report sulfhaemoglobin levels.

Clinicians should be aware of this overlap which is crucial to save the patient from improper treatment with methylene blue, a commonly used treatment for methaemoglobinaemia,⁵ and to arrive at the correct diagnosis if there is a 'gap' in saturated haemoglobin as there was in our case.

Certain types of co-oximeters are designed to differentiate between sulfhaemoglobin and methaemoglobin. Most, however, are not.

In our case, co-oximetry showed normal PaO₂ of oxygen, oxyhaemoglobin (89.8%), methaemoglobin (2.0%). It is important to know the normal reference range for

oxyhaemoglobin in the lab which is (95%–100%). As shown above, the patient had a normal oxygen tension and notable decrease in total haemoglobin saturation reported (91.8%)—*which is the sum of oxyhaemoglobin and methaemoglobin*. If we subtract this per cent (91.8%) from the normal reference range for oxyhaemoglobin, the net result will be (3.2%–8.2%). This value represents a deficit in haemoglobin molecules not reported in our preliminary report. This prompted us to call the lab, who then informed us of an error code. The blood gas analyser we used was EM-4000. The error code was investigated by the laboratory technician and was found to be due to the presence of sulfhaemoglobin of 'less than 10%', which is near the per cent range we calculated as deficit.

Some drugs that cause sulfhaemoglobinaemia can also cause methaemoglobinaemia.³ The presence of methaemoglobin (2.0%) in this was almost certainly a false positive due to similarity in wavelength detection (a 'cross reaction') by the blood gas analyser with sulfhaemoglobin. The decrease in methaemoglobin levels (in this case falsely elevated in the first place) on follow-up testing, the increase in oxyhaemoglobin and near-elimination of the oxygen saturation 'gap' or 'deficit' and the resolution of cyanosis show that sulfhaemoglobinaemia was the diagnosis in this case. In the patient with cyanosis, it is very important to scrutinise co-oximetry when the oxygen tension is normal. If there is a gap in haemoglobin saturation, an alternative haemoglobin species needs to be considered.

The authors are unaware of any other reports of ferrous sulfate causing sulfhaemoglobinaemia. Clinicians should consider any agent that is sulfur-containing as a possible cause of sulfhaemoglobinaemia if present.

Learning points

- Co-oximetry is needed when patient presents with cyanosis, decreased oxygen saturation on pulse oximetry and normal PaO₂ of oxygen on arterial blood gases.
- Sulfhaemoglobinaemia is a rare disease and can be missed because sulfhaemoglobin shares similar spectral wavelength with methaemoglobin. Sulfhaemoglobin levels are not typically reported on blood gas analysers. Concern should be raised for the presence of another haemoglobin species such as sulfhaemoglobin when the degree of methaemoglobinaemia does not explain the low level of oxyhaemoglobin in its entirety.
- Review of recently introduced medications can be helpful to find the cause for sulfhaemoglobinaemia.

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