Author's response to reviews

Title: Benzocaine and Lidocaine Induced Methemoglobinemia After Bronchoscopy

Authors:

Sophie Kwok (sophiekwok@yahoo.com)
Jacqueline L Fischer (jlfl@uicomp.uic.edu)
John D Rogers (jdr64@uic.edu)

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Author's response to reviews: see over
Dear Editors,

I would like to thank you for reviewing our case report entitled “Benzocaine and Lidocaine Induced Methemoglobinemia After Bronchoscopy.” I appreciate the feedback from the two reviewers. Please see below for point-by-point responses to their concerns.

**Rajesh Gutta’s comments:**

**General Comment**

I would also like for the authors to clarify as to why they did not use methylene blue, despite the patient’s oxygen saturation being only in the low 90’s. Also they report the patient having bilateral ground glass opacities and this should even be a good reason to be aggressive in management of this potentially fatal condition.

Methylene blue was not used because the patient’s methemoglobin level was 17.5% (methemoglobin levels less than 30% usually resolve spontaneously over 15-20 hours when the offending agent is removed and oxygen is administered) and our patient indeed improved quickly with oxygen supplementation.

**Revisions necessary for publication**

1. Correct the 3rd line of the abstract - "methemoglobinemia secondary to benzocaine and lidocaine”. These drugs are are only suspected to cause methemoglobinemia, however were not proved in the paper as the reason for the reported condition.

3rd line of abstract has been corrected to “A 62-year-old male developed methemoglobinemia after benzocaine and lidocaine were used for bronchoscopy.”

2. Please clarify as to whether the chest CT was performed to evaluate the desaturation episode or to evaluate the pulmonary opacities. If the CT was done for evaluating the desaturation episode, was it necessary after ABG diagnosis of methemoglobinemia and improved O2 saturation with 100% oxygen.

There were two chest CT’s done. First, to evaluate the monocystosis. A second chest CT was performed to evaluate the desaturation episode to rule out a pulmonary embolism. In retrospect, that this was not necessary if the ABG was done immediately for the diagnosis of methemoglobinemia.

**Melinda J Throm’s comments:**

**Background section:**

1) It is stated that methemoglobinemia is “uncommon” and “most often reported …when topical anesthetics are used during bronchoscopy…”. Provide
statistics/references supporting these statements. What is the incidence of methemoglobinemia with lidocaine vs. benzocaine?

References (Douglas, Khan) have been cited regarding methemoglobinemia being “uncommon.” The third sentence has been corrected and now reads: “This condition is often reported in the perioperative period when topical anesthetics are used during bronchoscopy, laryngoscopy, or upper gastrointestinal endoscopy.” The incidence of methemoglobinemia with lidocaine vs. benzocaine is discussed in the Discussion, beginning of paragraph 4: Review of literature on lidocaine as a cause of methemoglobinemia is rarely reported [Karim]. It almost always occurs in the setting of other agents and comorbidities [Weiss]. Benzocaine is a more common cause of methemoglobinemia because it is more lipophilic and may continue to enter the blood stream from adipose tissue stores after methylene blue blood concentrations are no longer therapeutic [Rodriquez].

Patient case section:

2) The 1st paragraph describes the patient. Include the patient’s race, weight, and baseline H/H. As certain ethnicities may be more predisposed to inherited vs. acquired methemoglobinemia and patient’s with baseline anemia are at a higher risk of developing more severe symptoms of methemoglobinemia, the author needs to establish risk factors for development of methemoglobinemia. As gold standard dosing of methylene blue is weight-based, include baseline weight. Although patient did not require methylene blue, still include weight.

In paragraph 1, 2nd and 3rd sentences, the patient’s race (Caucasian), weight (106.59 kg), baseline H/H (11.1 grams/dL and 33.6%) have been included.

3) 2nd paragraph, 3rd line: suggest change “done” to “performed.”
2nd paragraph, 3rd line, “done” has been changed to “performed.”

2nd paragraph, 6th line: Per JCAHO, #g is an unapproved abbreviation in the healthcare/hospital setting. If this patient was in the hospital, consider using microgram or mcg.
2nd paragraph, 6th line, has been changed to mcg.

2nd paragraph, 7th line: consider adding “non-metered dose” Hurricaine (double check spelling) as newer topical anesthetics with metered dosing, have less risk of methemoglobinemia.
2nd paragraph, 7th line, has been changed to “non-metered dose” and “Hurricaine” spelling has been corrected.

As there are other medications that may cause methemoglobinemia, it is important to include other concomitant medications that the patient was receiving in order to establish
the likelihood of caine-induced disorder. Author reviews other medications that may cause methemoglobinemia in the discussion section, so need to tie back to presented patient.

Other concomitant medications have been added at the end of the 1st paragraph (last sentence). These include: cephalexin, amitryptyline, amlodipine, enoxaparin, gabapentin, pantoprazole, oxycodone, and pravastatin.

4) 3rd paragraph, clarify whether the oxygen saturation was via pulse oximetry, co-oximetry, or ABG.
3rd paragraph, oxygen saturation via pulse oximetry has been clarified.

3 paragraph, 3rd line, add ‘beats/minutes’ for heart rate units.
3rd paragraph, 3rd line, “beats/minute” has been added.

Clarify why “uncomfortable” is in quotations.
Quotations have been deleted around “uncomfortable.”

5) 4th paragraph, oxygen administration rates should read 10 (add space) L/minutes. Change throughout patient case.
4th paragraph, a space has been added after 10 (ie. 10 L/minute). This has been changed throughout the patient case.

Clarify if the oxygen saturation, methemoglobin level, and pH/PCO2, were obtained via pulse oximetry, co-oximetry, or ABG. Both co-oximetry (used to measure methemoglobin levels) and ABG require an arterial blood sample, whereas pulse ox is non-invasive. When the methemoglobin level is > 10%, pulse ox and ABG are inaccurate.

Oxygen saturation, methemoglobin level, pH, PCO2 has been clarified throughout the case.

Include what the color of the blood sample was since a ‘chocolate’ brown blood is characteristic of methemoglobinemia. If the color of blood was not noted for this patient, then state this.

The color of the blood was not observed and this has been added to the case (paragraph 4, 5th sentence).

6) 5th paragraph, state if the patient’s cyanosis resolved (ie. What was his coloring?). Also, clarify how the methemoglobinemia level was obtained (via co-oximetry?).
5th paragraph, 1st sentence, added that the patient’s cyanosis resolved. It is clarified how methemoglobinemia level was obtained (via co-oximetry) in sentence 2.
Discussion section:

7) 2nd paragraph, incorporate the incidence of inherited methemoglobinemia.

After extensive literature searches, the exact incidence of inherited methemoglobinemia is unknown, however is reported to be rare. This has been added to 2nd paragraph, 2nd sentence.

8) 3rd paragraph, incorporate the incidence of acquired methemoglobinemia. In Table 1, consider adding celecoxib and EMLA.

After extensive literature searches, the exact incidence of acquired methemoglobinemia is unknown. However it is more common than hereditary causes and this is included in the 3rd paragraph, 1st sentence. In Table 1, celecoxib and EMLA have been added.

9) 4th paragraph, discuss the differences in the incidence of methemoglobinemia with lidocaine (only a handful of case reports) vs. benzocaine (numerous case reports). Also, discuss pharmacologic differences between the two agents (benzocaine more lipophilic; therefore, may require repeat doses of methylene blue, prolonged duration).

4th paragraph, added a discussion in the incidence of methemoglobinemia with lidocaine vs. benzocaine and the pharmacologic differences between the two agents. The literature on lidocaine as a cause of methemoglobinemia is rarely reported. It almost always occurs in the setting of other agents and comorbidities [Weiss]. Benzocaine is a more common cause of methemoglobinemia and reported more frequently in the literature. Because benzocaine is more lipophilic, it may continue to enter the blood stream from adipose tissue stores after methylene blue blood concentrations are no longer therapeutic [Rodriquez]. Benzocaine is a more powerful oxidizing agent than lidocaine in animal studies, and a dose-response relationship has been demonstrated between benzocaine and methemoglobin [Guertler, Martin].

Define what is considered an elderly patient (age > x years). Is this patient truly elderly at age 62 years?

Patient is not elderly at age 62 and this has been deleted (original manuscript, 4th sentence).

Discuss other risk factors for methemoglobinemia ie. Anemia at baseline/concomitant disease states/concomitant medications/metered dose vs. non-metered dose topical anesthetics.

Other risk factors for methemoglobinemia have been discussed: anemia, infants, concomitant diseases and medications, and metered dose vs. non-metered dose topical anesthetics. Our patient received a combination of topical lidocaine and benzocaine, perhaps rendering him more susceptible to methemoglobinemia. Another risk factor for developing pharmacologic-induced methemoglobinemia is concomitant illnesses, such as cardiac and respiratory diseases [Wright].
Although hemoglobin level does not directly affect the production of methemoglobin, it does affect the amount of functional anemia. Our patient did have baseline anemia, which put him at a higher risk of developing more symptoms of methemoglobinemia. Furthermore, a non-metered dose Hurricaine topical anesthetic aerosol spray (20% benzocaine) was used in our patient, rather than a metered dose spray. The manufacturer recommends a dose of benzocaine 20% half-second spray that delivers 30 mg, so our patient probably received a relative overdose of benzocaine [Fitzsimons]. Infants are more susceptible than adults because hemoglobin F is more susceptible to oxidation [Nilsson].

This would be a good place to discuss the probability of caine-induced methemoglobinemia utilizing the Naranjo adverse drug event scale (Clin Pharmacol Ther 1981;30(20):239-45). Authors need to better establish the likelihood of caine-induced methemoglobinemia.

The probability of caine-induced methemoglobinemia utilizing the Naranjo adverse drug event scale. In our case, the likelihood of an adverse drug reaction using the Naranjo probability scale was calculated to be probable (score of 6). Our conclusion was based on previous reports on this reaction; the adverse event appearing after the suspected drugs were administered; the adverse reaction improving when the drugs were discontinued; the drug being detected in the blood in a toxic concentration, and confirmation with objective evidence.

10) 5th paragraph, define what methemoglobin level/signs and symptoms are defined as mild methemoglobinemia.

5th paragraph, we have removed the word “mild” in defining methemoglobinemia. The symptoms are now described based on the level of methemoglobinemia. Clinical symptoms and signs depend on the level of methemoglobin. Levels greater than 15% are associated with cyanosis. Concentration of methemoglobin is reported as the percentage of total hemoglobin, therefore anemic individuals may experience more severe symptoms for a given percentage of methemoglobin. Levels of 20-45% cause headache, anxiety, lethargy, tachycardia, lightheadedness, weakness, and dizziness. Dyspnea, acidosis, cardiac dysrhythmias, heart failure, seizures, and coma occur at levels above 45%. Methemoglobin levels above 60% are associated with a high mortality rate, and levels greater than 70% are fatal [Udeh].

11) 6th paragraph, discuss in more depth the tests used to diagnosis and monitor methemoglobinemia (pulse oximetry, co-oximetry, or ABG).

6th paragraph, we have discussed in depth the tests used to diagnosis and monitor methemoglobinemia. The diagnosis of methemoglobinemia is made by analysis of an arterial blood sample, using co-oximetry, which demonstrates a discrepancy between a low arterial oxyhemoglobin saturation (SaO₂) and a relatively high arterial oxygen partial pressure (PaO₂). A standard arterial blood gas analyzer measures the partial pressure of oxygen and calculates the oxygen saturation from this value. This is inaccurate because the methemoglobin level is assumed to be zero. However, a co-oximetry is a simplified spectophotometer that measure light absorbency at four different wavelengths and these wavelengths correspond to specific absorbency characteristics of deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, and hemoglobin. In the presence of methemoglobinemia, oxygenation obtained by pulse oximetry is
inaccurate because it does not reflect the degree of desaturation and can under or over estimate oxygenation depending on the severity of methemoglobinemia. The diagnosis should be suspected if cyanosis develops suddenly after the administration of oxidizing agents, or if chocolate brown arterial blood does not turn red on exposure to air [Khan].

12) 7th paragraph, put more emphasis on how to differentiate when to administer methylene blue vs. not to administer.

7th paragraph, we have emphasized how to differentiate when to administer methylene blue vs. not to administer. In the absence of serious underlying illness, methemoglobin levels less than 30% usually resolve spontaneously over 15-20 hours when the offending agent is removed and oxygen is administered.

What is mild methemoglobinemia defined as?

We have decided remove the word “mild” and define the symptoms based on the level of methemoglobinemia. This has been clarified in paragraph 5. Clinical symptoms and signs depend on the level of methemoglobin. Levels greater than 15% are associated with cyanosis. Concentration of methemoglobin is reported as the percentage of total hemoglobin, therefore anemic individuals may experience more severe symptoms for a given percentage of methemoglobin. Levels of 20-45% cause headache, anxiety, lethargy, tachycardia, lightheadedness, weakness, and dizziness. Dyspnea, acidosis, cardiac dysrhythmias, heart failure, seizures, and coma occur at levels above 45%. Methemoglobin levels above 60% are associated with a high mortality rate, and levels greater than 70% are fatal [Udeh].

Are there any risks (side effects, contraindications) to administering methylene blue to patients with mild methemoglobinemia?

We have included the risks to administering methylene blue. Sentences 6-9: “Higher doses of methylene blue (> 7 mg/kg) may cause hemolysis and persistent cyanosis because the agent will oxidize hemoglobin to methemoglobin, instead of acting as a reducer at lower doses [Fitzsimons]. Methylene blue itself has side effects, which include nausea, vomiting, diarrhea, dyspnea, burning sensation in the mouth and abdomen, restlessness, and perspiration. Methylene blue should not be used in patients with G6PD deficiency because it would be ineffective. The agent is an ineffective treatment for G6PD-deficient patients because G6PD generates NADPH, which acts as the reducing agent to convert methemoglobin to hemoglobin. Therefore, methylene blue would lead to the formation of more methemoglobin because of its oxidant potential, leading to hemolysis [Udeh].”

This patient did not require the antidote, further justify why.

Our patient’s methemoglobin level was 17.5% (methemoglobin levels less than 30% usually resolve spontaneously over 15-20 hours when the offending agent is removed and oxygen is administered) and he improved quickly with oxygen administration, therefore the antidote was not given. (Paragraph 7).
State route of administration of methylene blue (slow IV push); at low doses acts as a reducing agent, at high doses (> 7 mg/kg) can act as an oxidizer and cause methemoglobinemia (Table 1).

We added that slow IV push is the route of administration (4th sentence). Added 6th sentence: Higher doses of methylene blue (> 7 mg/kg) may cause hemolysis and persistent cyanosis because the agent will oxidize hemoglobin to methemoglobin, instead of acting as a reducer at lower doses.

13) 8th paragraph (conclusion), state if caine-induced methemoglobinemia is rare or common. Clarify if this patient is elderly.

8th paragraph (conclusion), stated that caine-induced methemoglobinemia is not a very common cause of acquired methemoglobinemia (2nd sentence). Deleted that this patient is not elderly (originally 1st sentence).

Please let me know if I can re-format it to your specifications if needed.

Thank you very much in advance for your time and kind attention. I look forward to hearing from you soon.

Sincerely,

Sophie Kwok, MD
University of Illinois College of Medicine at Peoria
OSF Saint Francis Medical Center
530 NE Glen Oak Avenue
Peoria, IL 61637
United States
Phone: (985) 791-7368
Email: sophiekwok@yahoo.com