Induced Methemoglobinemia Secondary to an Exposure to a Measurable Quantity of Topical Anesthetics During a Transesophageal Echocardiogram

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Abstract

Introduction: Most instances of anesthetic-induced methemoglobinemia are believed to be due to excessive systemic exposure to the topical anesthetic benzocaine. Unfortunately, minimal information exists regarding the dosing thresholds of benzocaine associated with methemoglobinemia.

Case Report: This report describes a 38-year old Native American male with local anesthetic-induced methemoglobinemia who received quantifiable amounts of benzocaine and lidocaine during a transesophageal echocardiogram and was successfully treated with methylene blue.

Discussion: The patient exhibited multiple known risk factors for induced methemoglobinemia and he was exposed to 500 mg of benzocaine, which is two and a half times greater than the manufacturer's recommendation dose. Based on the Naranjo scale it is probable that the patient experienced an adverse drug reaction to benzocaine.

Conclusion: Although extremely rare, the risk of methemoglobinemia reinforces the importance of adhering to the recommended dose of benzocaine. Even though a relatively new unit-dose formulation of benzocaine spray exists, lidocaine has an established therapeutic index, minimal risk of induced-methemoglobinemia when used alone, and is more effective than benzocaine when used in accordance to the dosing recommendations.

Methemoglobinemia is a hematologic emergency characterized by an excessive level of methemoglobin, requiring immediate intervention to prevent patient harm.[1] Methemoglobin, an oxidized form of hemoglobin, is unable to provide adequate tissue oxygenation due to an electrochemical alteration of heme-bound iron atoms.[2] In its normal state, heme-bound iron exists in a reduced, ferrous (Fe+2) form which is readily capable of transporting oxygen. However, when this iron is oxidized to a ferric (Fe+3) state, the oxygen-hemoglobin dissociation curve is shifted to the left, resulting in a hypoxic state. Methemoglobinemia may be congenital (i.e. enzyme deficiency) or induced (i.e. medications). Certain local anesthetics, which are ubiquitously used to minimize the discomfort associated with various superficial procedures, are a recognized cause of induced methemoglobinemia.[3,4] These medications are remarkably safe when properly administered with adverse effects typically confined to the site of administration. Most instances of anesthetic-induced methemoglobinemia are believed to be due to excessive systemic exposure.[5] Minimal information exists, however, regarding the typical dosing thresholds that are associated with the occurrence of methemoglobinemia. This is caused, in part, because the dose of certain aerosolized local anesthetic formulations cannot be measured and quantified in a reliably accurate manner. The following case report describes an incident of local anesthetic-induced methemoglobinemia in a patient, who received quantifiable amounts of lidocaine and benzocaine.

Case Report

A 38-year old Native American male presented to the emergency department with diffuse low back pain and intermittent fevers. His past medical history was significant for intravenous methamphetamine use and tobacco use. Prior to presenting, the patient was not taking any prescription medications, over-the-counter medications, or herbal preparations. After an initial exam, the patient was admitted with sepsis secondary to intravenous drug use. Blood cultures were obtained, and the patient was empirically started on broad spectrum antibiotics. Magnetic resonance imaging of the patient's lower back confirmed the presence of an epidural abscess.

On hospital day 2, the patient underwent multiple lumbar lamintomies with concurrent abscess drainage. The patient remained stable postoperatively, experiencing some transient weakness in his lower right extremity which resolved without intervention. The following morning, his blood and lumbar abscess cultures were found to be positive for methicillin-resistant Staphylococcus aureus. The Infectious Disease service recommended that the patient undergo a transesophageal echocardiogram (TEE) to rule out the presence of any bacterial vegetation on his cardiac valves. Given the patient's continued postoperative stability, the TEE was scheduled for the morning of hospital day 4.

Upon arrival to the echocardiography lab, routine pre-procedural medications were administered to the patient. To

provide topical anesthesia, the patient was given 15 mL of lidocaine 4% solution to swish and spit out, followed by the recommended amount of two unit dose sprays of benzocaine 20% (HurriCaine ONE™). The patient verbalized an insufficient response to the topical anesthetic, and was subsequently given three additional unit doses of benzocaine 20% spray to the pharyngeal region. Conscious sedation was then induced using intravenous midazolam 1 mg, administered at 5 minute intervals for a total of 3 mg.

Approximately 20 minutes later, the TEE was aborted as the patient developed perioral cyanosis with an oxygen saturation of 75% (refer to Table 1 for normal values). Supplemental oxygen was provided but failed to improve patient status, so the patient was transferred to critical care for further evaluation. Arterial blood gases yielded a partial pressure of oxygen (pO2) value of 328 mmHg (normal value 80-100 mmHg), partial pressure of carbon dioxide (pCO2) value of 28.7 mmHg (35-45 mmHg), pH 7.51 (7.35-7.45), and bicarbonate level of 22.6 mmol/L (22-26 mmol/L). His oxygen saturation dropped to 61%, and it was noted upon collection that his blood was a chocolate brown color. Methemoglobinemia was suspected and subsequently confirmed by laboratory analysis showing a methemoglobin level in excess of 30% (<1.5%).

The Hematology service was emergently consulted, and after confirming that the patient had no known personal or family history of glucose-6-phosphate dehydrogenase deficiency (G6PD), methylene blue 1 mg/kg was administered as an intravenous bolus. Three hours after administration, a repeat arterial blood gas showed a pO2 68.2 mmHg, pCO2 26.5 mmHg, pH 7.52, and bicarbonate level of 21.7 mmol/L (Table 2). Oxygen saturation increased to 92%, methemoglobin levels were undetectable, and the patient was clinically stable. Subsequent TEEs were not attempted after this event. Given the high clinical index of suspicion for infective endocarditis, the patient was discharged on hospital day 15 with an oral regimen of doxycycline 100 mg twice daily and rifampin 300 mg twice daily.

Discussion

Typically, hypoxia resulting from methemoglobinemia presents with clinical cyanosis, occurring at methemoglobin levels around 20%. Cyanosis is generated from a reduction in active hemoglobin binding sites secondary to the oxidation of iron.[2] As the level of methemoglobin increases so does the severity of symptoms, with serious effects like lethargy, dizziness, stupor, circulatory failure, cardiac arrhythmias, seizures, coma and possibly death occurring at levels exceeding 50%. At the onset of methemoglobinemia, our patient showed minor signs of cyanosis and hypoxia, but he denied shortness of breath. His methemoglobin level of greater than 30%, however, warranted the treatment with methylene blue as an antidote to prevent further complications.[6,7]

Methylene blue is the only known antidote for methemoglobinemia, with a time of onset of about 60 minutes. To avoid paradoxical reactions, it should be administered slowly at a dose of 1-2 mg/kg intravenously.[6,7] Excess methylene blue can worsen methemoglobinemia through excessive oxidation of iron in hemoglobin. Although methylene blue is an oxidizing agent, its metabolite, leukomethylene blue, provides a reductive environment.[2,8] Leukomethylene blue and the enzyme methemoglobin reductase form an alternate pathway to convert methemoglobin back to hemoglobin. Administration of methylene blue in G6PD deficient patients has been associated with hemolytic anemia, which presents with symptoms of tachycardia, hypertension, and tachypnea due to the hemolysis of red blood cells.[9] Other monitoring parameters for methylene blue include adjusting for renal impairment

TABLE 1. Normal Laboratory Values

Laboratory Test	*Normal Range*
Oxygen Saturation	94-100%
Partial pressure of oxygen (pCO2)	80-100 mmHg
Partial pressure of carbon dioxide (pCO2)	35-45 mmHg
pH	7.35-7.45
Bicarbonate	22-26 mmol/L
Methemoglobin level	< 1.5%

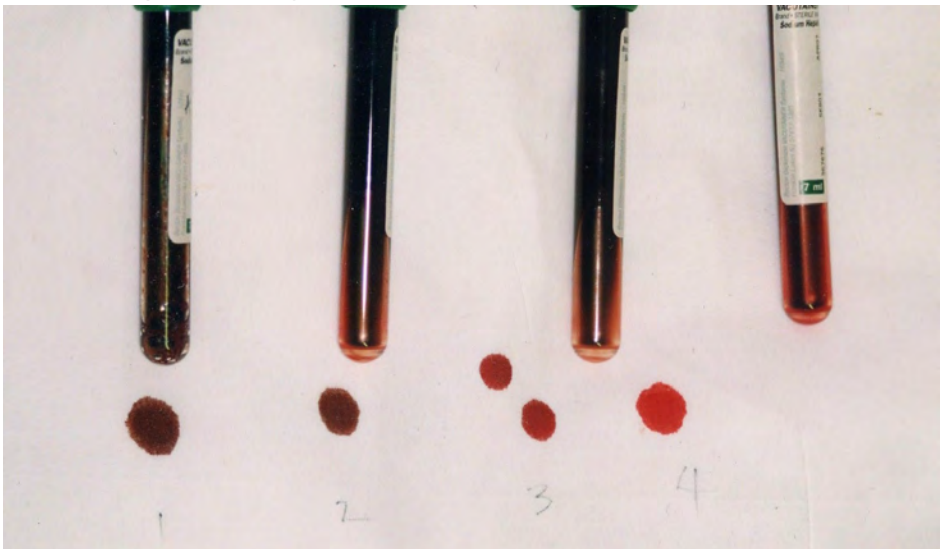
Table 1 overviews the normal values for laboratory tests in this case report.

TABLE 2. Timeline of Patient's Methemoglobinemia

Time	*1300*	*1315*	*1330*	*1345**	*1400*	*1415*	*1430*	*1445*	*1500*	*1530*	*1545*	*1600*	*1645*	*1700*	*1845*	*2015*
HR (bpm)	88	94	93	91	95	111	112	114	110	118	118	114	116	117	121	87
SBP (mmHg)	168	160	158	205	215	204	169	144	183	168	177	172	-	158	128	136
DBP (mmHg)	105	100	82	110	142	105	85	86	99	89	90	91	-	80	72	92
RR (breaths/min)	26	27	26	22	30	24	36	35	30	32	30	34	31	30	30	23
SpO2 (%)	92	91	88	91	88	96	96	96	97	96	96	97	95	94	94	98
O2 delivery	CPAP 100%	CPAP 100%	CPAP 100%	CPAP 100%	CPAP 100%	NC 4L	NC 4L	NC 4L	NC 4L	NC 4L	NC 4L	NC 3L	NC 2L	NC 2L	Room air	Room air

Table 2 expands upon the vitals around the time of administration of methylene blue. Abbreviations: CPAP = continuous positive airway pressure, DBP = diastolic blood pressure, HR= heart rate, NC = nasal cannula, O2 = oxygen, RR = respiratory rate, SBP = systolic blood pressure, SpO2 = saturation of the partial pressure of oxygen. Benzocaine and lidocaine administration took place at 1045.
**Methylene blue antidote was given at 1342.*

FIGURE 1. Examples of Methemoglobinemia



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and monitoring for alterations in blood pressure.[6]

Topical anesthetic use is one known cause of induced methemoglobinemia with benzocaine considered the highest risk agent, because it has an oxidizing metabolite unlike other topical anesthetics.[2] In fact, the FDA issued safety alerts in 2011 and 2012 for the continued submission of benzocaine-induced methemoglobinemia reports. Benzocaine is often used with lidocaine due to their varied pharmacokinetic properties.[10,11] Unit dose benzocaine sprays like the one used in this case are replacing the less accurate continuous dosing aerosolized sprays to reduce the risk of acquired methemoglobinemia. Most of the reported cases of benzocaine-induced methemoglobinemia occurred when dosing exceeded the manufacturer recommendation, although those cases often do not report the specific amount of benzocaine administered.[5] In this case, the 500 mg of benzocaine administered was two and a half times greater than the manufacturer's maximum recommendation dose.[10] Since the frequency of methemoglobinemia in topical procedures is well below 1%, the low incidence rate may decrease the clinical concern of induced methemoglobinemia and promote misuse of topical anesthetics. Practicing proper administration techniques (i.e. following recommended manufacturer dosing limits and avoiding additional administrations in a short timeframe) reduces the misuse of topical anesthetics and could thereby lower the incidence of methemoglobinemia. While benzocaine-induced methemoglobinemia is well documented in over 200 known case reports, more research is needed to determine dosage thresholds of benzocaine and to prove that unit dose sprays actually decrease the risk of methemoglobinemia.[5,10]

On the other hand, topical lidocaine has a much lower risk of methemoglobinemia when used alone in part due to the lack of an oxidizing metabolite.[11] While central nervous system toxicities from lidocaine are a major concern, serum concentrations with a known therapeutic index are already established.[5] Other rare side effects of lidocaine include visual disturbances, muscle twitching, unconsciousness, seizures, coma, and respiratory/cardiac arrest. However, a maximum volume of 15 mL of lidocaine 4% topical solution to swish and spit out is recommended to prevent complications.

The primary genetic disposition for methemoglobinemia is a deficiency in cytochrome b5 reductase, most common in neonates, elderly, and Native Americans.[1] When available in the body, cytochrome b5 reductase converts methemoglobin back to regular hemoglobin. In the presented case the patient's ethnicity increased his risk of methemoglobinemia. Unfortunately, a cytochrome b5 reductase deficiency could not be ruled out without genetic testing. Chowdhury and colleagues found the following patient characteristics increase the risk of methemoglobinemia: hospitalization, a history of cardiac or pulmonary disease, active tobacco use, topical benzocaine use over other topical anesthetics, and TEE over other oropharyngeal procedures.[4] Although our patient displayed many of these risk factors of induced methemoglobinemia no scale exists to measure an individual patient's risk. Furthermore, the liberal use of five sprays of benzocaine, instead of the recommended 1-2 sprays, may have compounded the risk for our patient. The Naranjo scale is a systematic evaluation designed to determine the likelihood of the occurrence that an adverse drug reaction is due to a medication. The scale probability can be definite, probable, possible, or doubtful. Overall, the Naranjo adverse drug reaction probability scale score was 7 in relation to the benzocaine and lidocaine use in this case report indicating a probable possibility that this was an adverse drug reaction (Table 3).[12]

After this case, the institution updated the echocardiography standing orders to

TABLE 3. Naranjo Adverse Drug Reaction Score Breakdown

Laboratory Test	*Normal Range*
Conclusive reports on this reaction	1
Event after medication administered	2
Improvement after discontinuation	1
No re-administration, dose change, placebo effect, blood level, or past use	0
No alternative causes	2
Objective evidence	1
Total Score:	**7**

Table 3 is a visual breakdown of the individual components for the Naranjo ADR Probability Score for this case report.

include an as needed order for methylene blue, and added it to the nearby automated dispensing cabinet for quick access. The dosing of the benzocaine was updated and clarified to explicitly state that two sprays may be administered to oropharyngeal area. No new cases of methemoglobinemia have occurred (not necessarily because of the measures that were taken).

Conclusion

The risk of methemoglobinemia reinforces the importance of adhering to the dosing recommendations with topical anesthetics. The specific quantifiable amount of both benzocaine and lidocaine in conjunction with the detailed time course of events surrounding the episode of methemoglobinemia expands the current literature on methemoglobinemia secondary to exposure to unit-of-use benzocaine in combination with lidocaine during a TEE. Beyond the inherent risk factors of each patient, the use of benzocaine increases the risk of induced methemoglobinemia. Many institutions, including the Veteran's Affairs Hospitals, have removed topical benzocaine leaving lidocaine as the topical anesthetic of choice for oropharyngeal procedures. Even with new unit-dose sprays of benzocaine solution, dosing of lidocaine is more accurate, safer, and more effective than benzocaine when used in accordance to the dosing recommendations. •

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Acknowledgements: We thank Magdalena Siodlak for her help with editing the manuscript. We thank Adam Gregg, PharmD, BCPS for his advice and assistance while preparing this case report.

Disclosures: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Case reports submitted to The Journal should contain valuable clinical lessons. We invite case reports that present a treatment, ethical or management challenge, or that highlight aspects of medicinal treatment of educational value. Moreover, case reports should represent unique or informative findings with objectively evaluated causality; they should expand the clinician's understanding of contemporary drug therapy. Case reports that detail a purported drug-induced effect or a drug-drug interaction are required to use and report the results of an objective assessment algorithm, such as the Naranjo algorithm.[1] Case report manuscripts should contain a complete review of the relevant literature. The references below can be used for additional guidance in the writing of case reports.[2,3]

Case reports should fulfil at least one of the following criteria:

1. Reminder of important clinical lessons
2. Unusual adverse drug reaction or drug-drug interaction from a common medication
3. Rare or new medication
4. Novel medication treatment (new drug/intervention or an established drug/procedure in new situation)
5. Unusual association of disease/medication
6. Unexpected outcome (positive or negative) including adverse drug reactions

Total Word Limits: 2500 including abstract, references, and any tables or figures
Abstract Word Limits: 250

Patient Consent

Ideally signed informed consent from the patient (or relatives/guardians) should be obtained prior to submitting a case report for consideration. Patient's details and identifiers should be anonymized as much as possible and the patient should not be identifiable. If you cannot obtain consent, the head of your medical team, legal team, or Institutional Review Board must provide permission for the case report to be published.

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