Methemoglobinemia Related to Local Anesthetics: A Summary of 242 Episodes

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BACKGROUND: The purpose of this article is to summarize all episodes of local anesthetic-related methemoglobinemia found in the medical literature.
METHODS: I performed a search of the American National Library of Medicine's PubMed with the following key words: "local anesthetic" and "methemoglobinemia."
RESULTS: Two-hundred-forty-two episodes (40.1% published in year 2000 or after) were found. Chocolate-colored blood suggests methemoglobinemia but other colors may be found. A discrepancy between the pulse oximeter saturation (≤90%) and the arterial oxygen partial pressure (≥70 mm Hg) was present in 91.8% of the episodes. The difference between oxygen saturation measured by pulse oximetry and co-oximetry varied from −6.2% to 44.7%. Plain prilocaine may induce clinically symptomatic methemoglobinemia in children older than 6 mo at doses exceeding 2.5 mg/kg. In adults, the dose of prilocaine should be kept lower than 5.0 mg/kg, which is reduced to 3.2 mg/kg in the presence of renal insufficiency and to 1.3 mg/kg if other oxidizing drugs are used concurrently. A single spray of benzocaine may induce methemoglobinemia. Clinical symptoms may be observed at relatively low methemoglobin values, including coma at 32.2 and 29.1% in children and adults, respectively. Rebound methemoglobinemia (benzocaine on mucous membranes) with methemoglobin values as high as 59.9% may occur up to 18 h after methylene blue administration. Complications of methemoglobinemia include hypoxic encephalopathy, myocardial infarction, and death.
CONCLUSION: Benzocaine should no longer be used. Prilocaine should not be used in children younger than 6-mo-old, in pregnant women, or in patients taking other oxidizing drugs. The dose should be limited to 2.5 mg/kg.
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Methemoglobin describes the oxidized form of the iron moiety ($Fe3^+$) within the hemoglobin molecule. It is formed in the presence of an oxidizing substrate and is useless for oxygen carrying. In addition, methemoglobin shifts the oxygen-hemoglobin dissociation curve to the left and changes the sigmoid shape of the curve into a more hyperbolic one, thus hindering unloading of oxygen to tissues.[1] These effects are proportional to the concentration of methemoglobin and are reversible. The concentration of methemoglobin is usually kept low (1%–2%) by the effect of cytochrome b5 methemoglobin reductase, which is dependent on reduced nicotine adenine dinucleotide (NADH) and is also known as NADH-diaphorase. Cytochrome b5 methemoglobin reductase is also dependent to a lesser degree on the presence of reduced nicotine adenine dinucleotide phosphate diaphorase, which reduces a flavin that in turn reduces methemoglobin to deoxyhemoglobin. The latter reaction usually accounts for <5% of the reduction of methemoglobin to deoxyhemoglobin, but its activity can be greatly enhanced by methylene blue, which is reduced to leukomethylene blue by nicotine adenine dinucleotide phosphate-diaphorase. Leukomethylene blue then reduces methemoglobin to deoxyhemoglobin.[2]

An abnormally high level of methemoglobin will occur when the production exceeds the capacity of the methemoglobin reduction processes. This may happen after exposure to various toxic substances and drugs which may be divided into direct oxidizers, which are capable of inducing methemoglobin formation when added to erythrocytes *in vitro* or *in vivo*, and indirect oxidizers, which do not induce methemoglobin formation when exposed to erythrocytes *in vitro*, but do so after metabolic modification *in vivo*.[2] Local anesthetics are indirect oxidizers. Reactions involved

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Table 1. Distribution of Local Anesthetics-Related Methemoglobinemia Episodes and Maximal Methemoglobinemia Level Measured According to the Local Anesthetic Used

	Children	Adults	Pregnant women	Unspecified	Total	Maximal methemoglobin measured in this category (%)
Benzocaine	41	117		1	159	84
Alone	40	65			105	84
In combination	1	52		1	54	
Prilocaine	37[a]	23	7	1	68	42
Alone	18	19	6	1	44	42
In combination	19[a]	4	1		24	
Lidocaine		11	1		12	51.4
Alone		9	1		10	51.4
In combination		2			2	
Tetracaine		1			1	10.8
Cocaine mixed with aniline	1				1	35.2
Unidentified (teething preparation)	1				1	55.2
	80	152	8	2	242	

Numbers within each column except the last are total numbers of patients.

[a] One child received both a high dose (24 mg/kg) prilocaine and an unspecified amount of benzocaine, her data are counted under prilocaine.

for local anesthetic-induced methemoglobinemia are: hydrolysis of the amide to the corresponding amine, metabolism of the amine to the appropriate species, and direct oxidation of hemoglobin by the amine metabolite.[3] The nature of the amine liberated on hydrolysis is the major determining factor in the methemoglobin-forming ability of amides.[3]

First clinical descriptions of toxic methemoglobinemia date at least as far back as 1886.[4] Steele and Spink reported using methylene blue (also known as methylthionine chloride) to treat methemoglobinemia in 1933.[5] Ockliz reported a case of methemoglobinemia attributed to a local anesthetic, and its treatment with thionine in 1949.[6]

The literature contains numerous cases of local anesthetic-related methemoglobinemia. The purpose of this article is to summarize those cases and define safety rules to prevent local anesthetic-induced methemoglobinemia.

METHODS

Articles were found from a search of the American National Library of Medicine's PubMed with the following keywords: "methemoglobinemia" and "local anesthetic" on April 6, 2007. The reference lists of all articles retrieved were also checked. When the weight was not available, for children (<18 yr), the average weight for age (as found according to charts or formulae appropriate for the age group) was applied. For adults (≥18 yr), the mean weight of the subgroup (women or men) was used. To determine the signs and symptoms of methemoglobinemia, all patients known to have received a total dose of local anesthetic higher than the equivalent of 10 mg/kg of lidocaine regardless of the route (not counting benzocaine) were excluded. Equivalences were calculated as follow: lidocaine = 1, bupivacaine = 4, cocaine = 4, mepivacaine = 0.8, prilocaine = 0.9, and tetracaine = 4.

RESULTS

Identification of the Episodes

Two-hundred-seventeen episodes of local anesthetic-related methemoglobinemia were identified by PubMed of which 19 were rejected for the following reasons: underlying congenital methemoglobinemia ($n = 2$), partial glucose-6-phosphate dehydrogenase (G-6-PD) deficiency ($n = 1$), no clear relationship to local anesthetics ($n = 2$), doubtful diagnosis ($n = 3$), no article published in English nor French ($n = 10$), or concomitant drug street abuse ($n = 1$). Forty-four more case reports could be retrieved from the reference lists. Two neonatal cases secondary to a paracervical block were excluded because this block is no longer recommended for labor analgesia. The search returned 242 individual episodes in 233 patients (9 repeated episodes) published between 1949 and 2007. The search results are available as Appendix 1, which is available as a Web supplement at www.anesthesia-analgesia.org.

The distribution of the episodes according to the drug used and the subpopulation is given in Table 1. The age distribution for benzocaine, prilocaine, and lidocaine is given in Figure 1. Details of the clinical setup in which those episodes happened are provided in Table 2. Types of anesthesia implicated and doses administered are given in Table 3. Four patients (1 child and 3 adults) developed methemoglobinemia (methemoglobin = 29.1%–40.0%) with only 1 spray of benzocaine (20% = 3, unknown concentration = 1).

For EMLA®, when it is not accompanied by the administration of any other local anesthetic, the following rules should be used to guide maximal doses:

1. Infants ≤3 mo of age or <5 kg: 1 G, 10 cm^2 for ≤1 h,

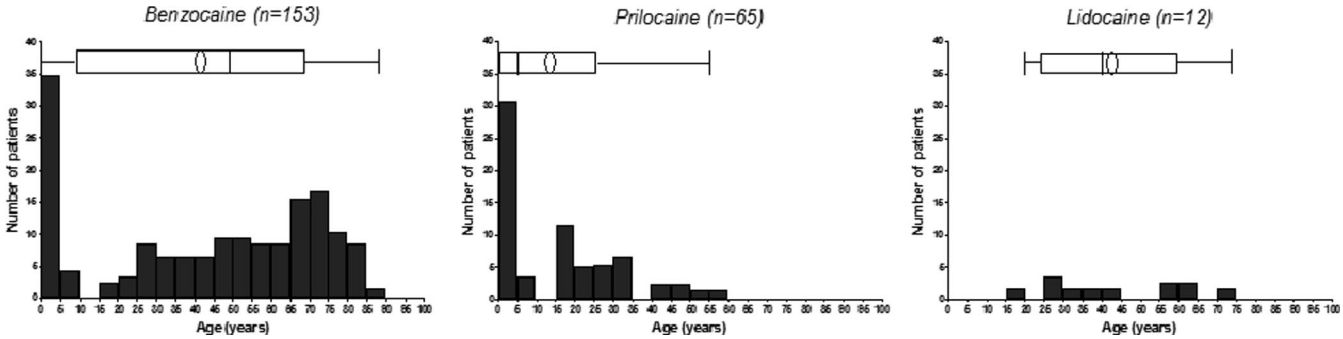

Figure 1. Age distribution of local anesthetic-related methemoglobinemia episodes by the type of local anesthetic used. There were 18 infants 6-mo-old or less with the benzocaine episodes (11.3%) and 26 (38.2%) with the prilocaine episodes. Boxes indicate median and quantiles (25th–75th). Ellipses within the boxes stand for means. Age was not available for 9 patients (benzocaine = 6 and prilocaine = 3).

Table 2. Number of Local Anesthetic-Related Methemoglobinemia Cases, Divided by Clinical Scenario and Patient Type

	Children	Adults	Pregnant women	Unspecified	Total *n* (%)
Pre- or intraoperative use by the anesthesiologist	14	28			42 (17.4%)
Benzocaine	6	14			
Prilocaine	8	12			
Lidocaine		2			
Pre- or intraoperative use by the surgeon	2	5		1	8 (3.3%)
Benzocaine	1	1			
Prilocaine	1	3		1	
Lidocaine		1			
Medical or dental procedure outside the operating room	33	105[a]	8	1	147 (60.7%)
Benzocaine	4	93		1	
Prilocaine	28	6	7		
Lidocaine		6	1		
Cocaine mixed with aniline	1				
Over the counter medication used without medical prescription	11	3			14 (5.8%)
Benzocaine	11	2			
Tetracaine		1			
Accidental ingestion	7				7 (2.9%)
Benzocaine	6				
Teething preparation	1				
Other	13	11			24 (9.9%)
Benzocaine	13	7			
Prilocaine		2			
Lidocaine		2			

[a] In this subgroup, there were 40 transesophageal echocardiographies (reported between 1991 and 2006), 34 gastrointestinal endoscopies (reported between 1987 and 2006) and 12 tracheobronchial endoscopies (reported between 1977 and 2002). In all but 3 of these 86 episodes of methemoglobinemia, benzocaine was the primary local anesthetic.

2. Infants from 4 to 12 mo of age and 5 to 10 kg: 2 G, 20 $cm^2$for ≤4 h,
3. Children from 1 to 6 yr of age and >10 kg but ≤20 kg: 10 G, 100 cm^2,
4. Children from 7 yr of age and >20 kg: 20 G and 200 cm^2.

In all 11 episodes involving EMLA these guidelines were not followed.

Diagnosis

The diagnosis was based on at least one methemoglobin measurement over 2% or 0.24 G/100 mL (n = 206), blood test showed positive but value not specified (n = 2), positive spectroscopic examination (n = 8), positive Kronenberg "red-brown" test (drop of blood with suspicious color not changing to air and different from one drop of normal blood) or suspiciously colored blood not changing with the addition of oxygen or air (n = 4), cyanosis or low oxygen saturation value after exposure to a drug known to produce methemoglobinemia that reverted after injection of methylene blue or thionine (n = 15) or cyanosis appearing within few hours after a drug known to produce methemoglobinemia (n = 7).

A formal measurement of the quantity of NADH (or cytochrome b5 reductase) was done and reported as normal for 31 episodes (benzocaine = 24, prilocaine = 4, lidocaine = 2, cocaine mixed with aniline = 1), present for 1 episode and 0.6 IU per G of hemoglobin

Table 3. Minimal Dose of Local Anesthetic with Which Methemoglobinemia has been Reported According to the Type of Anesthesia for Benzocaine and Prilocaine

Type of anesthesia	With predisposing factor[a] dose in mg/kg	Without predisposing factor dose in mg/kg
Children		
Benzocaine[b]		
Oropharynx with or without oesophagus or stomach or enterostomy	22.2	24.8
Other mucosa	7.5	9.7
Transcutaneous	133.5	
Prilocaine		
Peripheral nerve block or local infiltration without adrenaline	2.5	2.9
Peripheral nerve block or local infiltration with adrenaline	6.7	8.6
Transcutaneous	8.9	
Transplacental passage[c]	5.2	
Adults		
Benzocaine[b]		
Oropharynx with or without esophagus or stomach or enterostomy	4.4	2.2
Other mucosa	35.4	
Prilocaine		
Peripheral nerve block or local infiltration without adrenaline	1.3	3.2[d]
Peripheral nerve block or local infiltration with adrenaline		7.4
Epidural single shot without epinephrine		12.2
Epidural single shot with epinephrine		14.2
Transcutaneous	75	
Pregnant women		
Prilocaine		
Epidural multiple boluses or infusion		6.3

[a] Predisposing factor = any of the following: younger than or 6-mo-of-age or abnormal mucous membrane (including oro- or nasogastric or tracheal tubes within one week of event) or skin or concomitant use of dapsone, nitrates, nitroprusside, antimalarials, nitrofuran, trimethoprim-sulfamethoxazole, nitric oxide, 8-hydroxiquinoleine, phenacetin, aniline dyes, environmental exposure, nitric oxide 40 ppm, phenazopyridine, or resorcin.

[b] Doses were not calculated for benzocaine spray; 4 patients (1 child and 3 adults) developed methemoglobinemia (29.1%–40.0%) with only 1 spray of benzocaine (20%: $n = 3$; unspecified concentration: $n = 1$).

[c] For transplacental passage, the dose is the dose given to the mother.

[d] The patient who developed methemoglobinemia after a dose of 3.2 mg/kg of prilocaine had chronic renal failure. Excluding this patient, the lowest prilocaine dose of this subgroup would be 5.0 mg/kg.

in a 2-day-old newborn. A hemoglobin electrophoresis was reported as normal for 26 episodes (benzocaine = 18, prilocaine = 5, lidocaine = 2, cocaine mixed with aniline = 1). A normal G-6-PD level was reported in 19 episodes (benzocaine = 8, prilocaine = 9, lidocaine = 1, cocaine mixed with aniline = 1).

Apart from being cyanotic, patient skin color was reported as black ($n = 3$), gray ($n = 30$), chocolate ($n = 1$), brownish ($n = 2$), purple ($n = 4$), tinged with yellow ($n = 2$; signs of hemolysis present before any treatment), and/or pale ($n = 19$; 17 of 19 were children). The color of the blood was described as chocolate ($n = 44$), brown ($n = 27$), black ($n = 11$), burgundy or purple or red ($n = 7$), or cyanotic or blue ($n = 5$). There was no apparent relationship between the color of the patient's skin or the color of the blood and the first methemoglobin concentration.

The oxygen saturation measured with the pulse oximeter varied between 50% and 94% (median 85%, mean ± SD 81.2 ± 8.8%). The discrepancy between the saturation measured on the pulse oximeter and the saturation as measured on the co-oximeter varied from −6.2% to 44.7%. When both values were measured simultaneously ($n = 85$) a pulse oximetry oxygen saturation ≤90% and an arterial Pao_2 ≥70 mm Hg was present in 78 episodes (91.8%). Signs and symptoms associated with methemoglobinemia can be found in Table 4 and Figure 2.

Episodes Associated with Local Anesthetics other than Benzocaine and Prilocaine

Twelve episodes were related to lidocaine without the association of prilocaine or benzocaine. For seven patients, an oxidative drug was administered concomitantly (nitrate therapy = 3, trimethoprim-sulfamethoxazole = 1, dapsone = 1, phenazopyridine = 1, phenacetin = 1). For one patient, the episode occurred within 24 h of an episode related to the application of benzocaine on mucosa, so a rebound episode from benzocaine cannot be excluded. One man developed methemoglobinemia after chronic abuse of lidocaine gel for palatal cancer pain. Finally, three patients developed methemoglobinemia after appropriate clinical use of lidocaine. None were tested for NADH deficiency. Cocaine mixed with aniline was associated with methemoglobinemia in one patient. Aniline is the most probable culprit in this case. Tetracaine (3.6 mg over a week) has been reported to cause methemoglobinemia once, but again NADH deficiency was not excluded.

Repeated and Rebound Episodes

Nine cases were repeated episodes. One infant had 2 surgical procedures in which prilocaine was administered caudally (estimated doses between 5.4 and 6.7 mg/kg) after application of EMLA (estimated doses 0.5 G) and developed symptomatic methemoglobinemia with maximal measured methemoglobin of 4.8% and 8.8%. Four patients developed methemoglobinemia when re-exposed to benzocaine after a

Table 4. Minimal Value at Which Signs and Symptoms of Methemoglobinemia Have Been Reported

Signs and symptoms	Without anemia, pulmonary disease or congestive heart failure			With anemia or pulmonary disease or congestive heart failure[a]		
	MTG in percentage	MTG in absolute value (G/dL)	Residual functional hemoglobin value (G/dL)[b]	MTG in percentage	MTG in absolute value (G/dL)	Residual functional hemoglobin value (G/dL)[b]
Children						
Cyanosis (n = 41)	12.6	2.3	11.4			
Tachypnea (n = 13)	10.7	1.8	14.8			
Respiratory compromise[c] (n = 5)	35.2	5.4	7.5			
Tachycardia (n = 14)	10.7	1.8	14.8			
Hypertension (n = 1)	54.0					
Myocardial ischemia at Electrocardiogram[d] (n = 1)	55.2					
Shakiness (n = 2)	10.7	1.8	14.8			
Seizures (n = 2)	32.2	3.3	6.9			
Altered consciousness (n = 14)	10.7	1.8	14.8			
Coma[e] (n = 6)	32.2	3.3	7.5			
Adults						
Cyanosis (n = 101)	5.0	0.8	15.3		0.6	
Tachypnea (n = 30)	11.4	2.8	12.2	7.4	0.6	
Apnea (n = 1)	59.7					
Respiratory compromise[c] (n = 13)	40.0			19.4	3.8	8.1
Tachycardia (n = 34)	10.3	1.1	12.2	7.4	0.6	
Hypertension (n = 8)	17.0	2.8	12.2			
Hypotension (n = 5)	23.6	3.0	9.6			
Orthostatic hypotension (n = 1)	28.0					
Chest pain[d] (n = 2)	17.0	4.4	9.0			
Signs of myocardial ischemia at electrocardiogram[d] (n = 5)	17.0	4.4	9.0			
Shakiness (n = 1)	18.8	2.8	12.2			
Syncope (n = 3)	28.0	5.7	6.7	10.8	0.8	
Altered consciousness (n = 22)	19.0	4.0	9.6	11.2	0.6	
Coma[e] (n = 4)	29.1	4.0	9.6			

MTG = methemoglobin value; n = the number of patients in whom this symptom was reported as present excluding all patients who received more than the equivalent of 10 mg/kg of lidocaine (not counting benzocaine)(n = 63 for children and 141 for adults).

[a] Hemoglobin value lower than 10 G/dL or if not available hematocrit lower than 30% or stated as anemic by the authors; any respiratory problem other than asthma history. Values for this category are given only if the value was beyond the limits (lower or higher) of the patients without any of those underlying conditions.

[b] Highest value at which this symptom is reported.

[c] Requiring tracheal intubation or attempt to or emergent tracheotomy.

[d] None of these patients were said to suffer from coronary heart disease or having suffered a previous myocardial infarction.

[e] Responsive only to painful stimuli or not responsive at all. Methemoglobin value in percentage or in G/dL and residual hemoglobin for a single symptom do not necessarily originate from the same patient. NA = Information not available.

benzocaine-related episode (from 0 to 10 days after). One child developed four episodes of benzocaine-related methemoglobinemia. The two first episodes each followed lubricating an endotracheal tube with a preparation containing benzocaine. The two last episodes were intentional exposure for diagnostic purposes. At the fourth episode, methemoglobinemia was produced by touching the child's oral mucosa with benzocaine crystals. Finally, one man developed a possible lidocaine-related episode within 24 h of a benzocaine-related episode, which could have been rebound from the benzocaine. Rebound methemoglobinemia was reported 5 times (benzocaine on mucous membrane) and occurred between 2.5 and 18 h after methylene blue administration with rebound methemoglobin values ranging from 9.1% to 59.9%.

Treatment

The treatment included IV methylene blue (n = 155), IV thionine (n = 2), oral, IV, or IM ascorbic acid (n = 8), IV methylene blue plus oral, IV, or IM ascorbic acid (n = 14), or no antidote (n = 53). In 10 cases, the treatment was not listed. The first dose of methylene blue varied between 0.5 and 5.5 mg/kg. The total dose of methylene blue varied between 0.6 and 9.4 mg/kg. The doses of ascorbic acid varied from 7.6 to 10 mg/kg for the oral route, 3.1 to 63.3 mg/kg for the IV route, 1.6 to 56.2 mg/kg for the IM route, and 200 mg/kg for an unspecified route of administration for the first dose. The total doses of ascorbic acid varied from 7.6 to 10 mg/kg for the oral route, 3.1 to 253.2 mg/kg for the IV route and 3.2 to 56.2 mg/kg for the IM route. Excluding one patient with chronic lidocaine gel

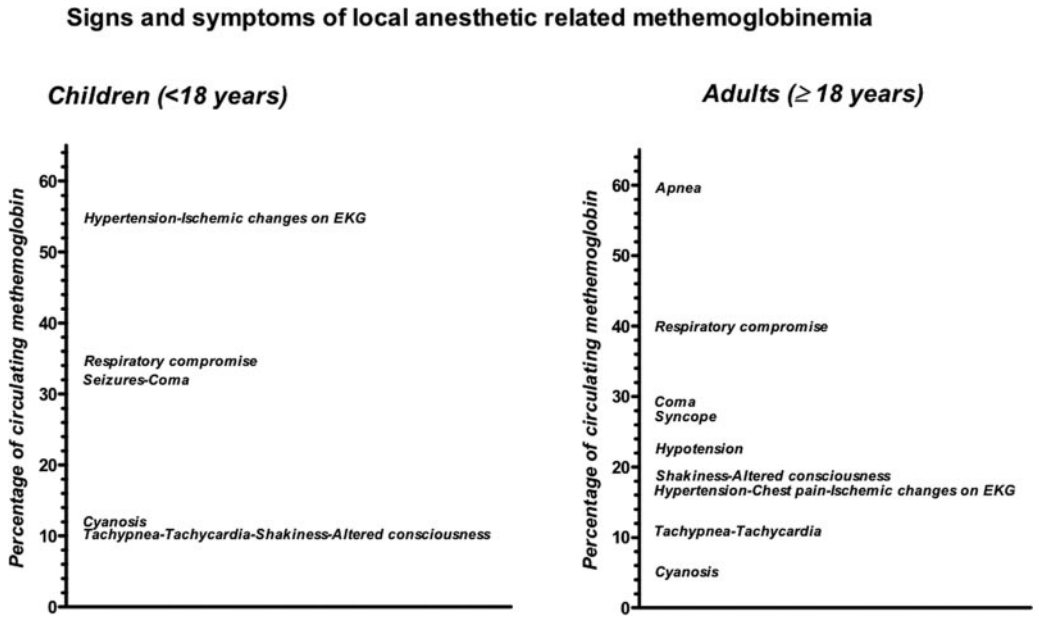

Figure 2. Minimal methemoglobin value (in percentage of circulating hemoglobin) at which various signs and symptoms associated with local anesthetic-related methemoglobinemia have been reported in patients without anemia, pulmonary disease or cardiac heart failure for children (<18 yr) and adults (≥18 yr). Respiratory compromise means that patients required tracheal intubation or attempt to or emergent tracheotomy.

abuse, the time to a methemoglobin level of ≤2.0% varied from 0.33 to 36.2 h in patients who received either methylene blue or thionine with or without ascorbic acid, and 15 to 36 h in those who received no treatment. The time to disappearance of clinical cyanosis varied from 0.25 to 9 h in those who received the previously mentioned treatment, and from 2 to 19.8 h in those who received no treatment. A decrease in Sao_2 measured with pulse oximetry with the administration of methylene blue was documented in five patients. Hemolysis attributed to methylene blue administration (hemoglobin decrease of 1.8 G/dL) was observed in a 1-day-old newborn who received a single dose of 1.0 mg/kg.

Adverse Outcomes

Three patients had lasting electrocardiogram changes or enzyme elevation compatible with a non-Q wave myocardial infarction (methemoglobin = 17.0%–67.8%). One 83-yr-old man who received benzocaine spray for tracheal intubation and who had a peak methemoglobin level of 54.1% was left with severe neurological impairment (electroencephalogram compatible with diffuse hypoxic injury). One 52-yr-old man investigated for increasing dyspnea on exertion developed a methemoglobin value of 51% after receiving pharyngeal benzocaine spray. Despite therapy (including tracheal intubation and administration of methylene blue), respiratory failure, renal failure, liver dysfunction, and deteriorating mental status ensued, and the patient died after a cardiac arrest. A 4-mo-old child with acute upper respiratory tract infection (including signs compatible with laryngitis) was found dead in his bed after having received 3 times the prescribed dose of ear drops containing 1.4% of benzocaine and 5.4% antipyrine on the day before his death. His postmortem blood levels of methemoglobin and benzocaine were 36.0% and 3.48 μg/mL, respectively. The pathologist determined the cause of death as sudden infant death syndrome. One woman, who lost her fetus, received a total dose of 1000 mg of prilocaine as intermittent epidural injection for labor analgesia and was noted to be markedly cyanosed at the time the fetal heart rate ceased. The term newborn weighed <2.7 kg and the placenta was unusually small.

DISCUSSION

Local anesthetic-related methemoglobinemia is an important clinical problem. Forty percent (97 of 242) of these episodes have been published in 2000 or after (benzocaine = 77, prilocaine = 12, lidocaine = 6, tetracaine = 1, unidentified = 1). The diagnosis of clinical methemoglobinemia relies mainly on the co-oximeter measurement of an elevated circulating level of methemoglobin (>1% or 2%). Chocolate-colored blood is suggestive of methemoglobinemia, but its absence does not exclude it. The drop on filter paper test (Kronenberg "red-brown" test), which reflects the capacity of an individual to visually differentiate blood containing an elevated amount of methemoglobin from normal blood, is identified correctly by 30 of 32 subjects at 10%, 19 of 32 at 5%, and 0 of 3 at 10% if they are red-green color-blind.[7]

A discrepancy between the pulse oximeter saturation (Sao_2 ≤90%) and the measured arterial oxygen partial pressure (Pao_2 ≥70 mm Hg) suggests methemoglobinemia. This discrepancy was present in 91.8%

of the episodes where both values were simultaneously measured. Oxygen saturation is not accurately measured on most pulse oximeters in patients with methemoglobinemia and may grossly underestimate the degree of hypoxia (gradients from −6.2% to 44.7% in the present review). The Rainbow-SET Rad-57 Pulse CO-Oximeter (Masimo, Irvine, CA) (not used in any of the episodes reported here) uses eight wavelengths of light instead of the usual two and theoretically would have returned a more accurate estimation of both the true Sao_2 and the percent of methemoglobin.[8]

Four types of local anesthetic have been reported as possibly causing methemoglobinemia: prilocaine, benzocaine, lidocaine, and tetracaine. For prilocaine, the condition seems well understood. A metabolite, orthotoluidine, is responsible for hemoglobin oxidation.[9] Although increasing the dose would increase the chances of developing measurable methemoglobinemia, there would be a large interindividual variability in the amount of methemoglobin developed for any prilocaine dose administered.[10–12] Methemoglobin values anywhere from 0.9% to 15.4% may be present at 3 h when 300 to 400 mg of prilocaine (2.6–7.4 mg/kg) is used for peripheral nerve blocks in adults (≥18 yr of age).[12] The dose in mg/kg, young age, female gender, and concentration used explained only 36% of the variance observed, making an exact and reliable prediction of methemoglobin formation impossible.[12] From the cases reported here, a dose as low as 1.3 mg/kg in the presence of concomitant administration of other oxidizing drugs (isosorbide dinitrate) or 2.5–2.9 mg/kg in children, or 3.2 mg/kg in adults with chronic renal insufficiency, or 5.0 mg/kg in adults without any obvious predisposing factor would be sufficient to induce clinically symptomatic methemoglobinemia in some individuals (Table 3). Thus, the actual recommendations that allow a dose up to 8 mg/kg should be reduced. Adding epinephrine to prilocaine may modify the time course, but not the magnitude of the response.[11] Fetuses and infants of <6-mo-of-age seem more susceptible to oxidation, possibly because their enzymatic system is immature (lower level of NADH up to 3–6 mo) or possibly because neonates are easily overdosed (small weight). Thus, infants of 6 mo or less represent 38.2% of the prilocaine-related episodes reported here, some of them from transplacental passage (Fig. 1).

When prilocaine was used for epidural analgesia, Climie et al.[13] found that the methemoglobin value in the cord blood may exceed the venous maternal value by as much as 5.6%. Prilocaine should probably be avoided in children younger than 6-mo-old (except for transcutaneous administration), in pregnant women, and in patients taking other oxidizing drugs.

The problem of benzocaine-related methemoglobinemia is not as well understood, but benzoic esters are hydrolyzed by a mechanism similar to anilides.[3] Only some patients seem to be susceptible (maximum 95%CI for incidence = 1 of 370 exposures for the first exposure and 1 in 28 for repeated exposure within a week).[14] Some patients have developed the syndrome with a single 1 s or short spray of 20% solution on mucous membrane (exact dose impossible to determine: anywhere from <76 mg to 212 mg).[15] Conversely, some children failed to develop any clinically significant problem with doses higher than 200 mg/kg.[16] In a multicenter (regional poison centers) retrospective chart review, Spiller et al.[16] reported only one clinically symptomatic episode of methemoglobinemia (methemoglobin = 19.0%) in 188 accidentally exposed children (mean and median doses of benzocaine of 86.8 ± 89.5 and 50 mg/kg, respectively). Finally, some patients who have developed methemoglobinemia after benzocaine exposure have done so on subsequent exposure (up to four episodes in one child). A variation in the metabolism and/or elimination has been advocated to explain this phenomenon.[17] Some animal species have responder and non- or poor-responder animals.[17] To explain the whole picture, the inherent possibility for this metabolic variation would have to be present in certain humans and not in others and to be inducible by previous exposure in some patients.

Because it is impossible to predict which individuals will be susceptible to develop methemoglobinemia after benzocaine exposure, and also because there is no therapeutic window(between the doses required to produce a therapeutic effect and those producing toxicity) in susceptible individuals, the clinical use of benzocaine should be abandoned.

The capability of lidocaine to induce methemoglobin formation with appropriate clinical use is less well demonstrated. If lidocaine does cause methemoglobinemia, it must be quite rare, given the paucity of reports and the huge clinical exposure. In the present review, only three cases of lidocaine-associated methemoglobinemia were found when lidocaine was administered at clinical doses without the concomitant administration of other oxidative drugs. Young children (≤18 mo) might be more susceptible to methemoglobin formation after lidocaine exposure at high doses. A recent retrospective study found an incidence of 20% of methemoglobin elevation (median 6%; range 2.2%–18%) after scalp infiltration with lidocaine 13 mg/kg.[18] Lidocaine or any respiratory depressant drug may worsen the clinical picture without necessarily increasing the methemoglobin level in patients with underlying congenital methemoglobinemia (NADH deficiency).[19] Whenever feasible, lidocaine should probably be replaced by another local anesthetic in patients taking other oxidative drugs and in patients with congenital methemoglobinemia.

Tetracaine has been related to methemoglobinemia only once. However, because the dose was relatively small (3.6 mg over a week) and the clinical picture quite broad (including fever, anemia and jaundice),

Table 5. Recommendations to Prevent and Treat Local Anesthetic-Induced Methemoglobinemia

1. Benzocaine should no longer be used. Although it is well tolerated by the majority of individuals, some patients will develop methemoglobinemia upon exposure. It is not possible to predict who will be at risk. In susceptible individuals, there is no "therapeutic window" between the doses required to produce a therapeutic effect and those producing toxicity. Sensitive individuals may develop methemoglobinemia after a single benzocaine spray
2. Prilocaine should not be used in infants of less than 6-months-of-age (except for transcutaneous anesthesia), in pregnant women, patients receiving other oxidizing drugs and patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency
   a. When prilocaine is used for transcutaneous anesthesia, strict adherence to the manufacturer's recommendations (amount, surface and length of exposition) is mandatory and it should not be administered at the same time by any other route
   b. When prilocaine is administered for peripheral nerve blocks or IV regional anesthesia, limiting the dose to 2.5 mg/kg should probably decrease the risk of inducing clinically symptomatic methemoglobinemia but may not abolish it entirely
3. Lidocaine has induced methemoglobinemia in patients receiving other oxidizing drugs (nitrate therapy, trimethoprim-sulfamethoxazole, dapsone, phenazopyridine, phenacetin), from chronic abuse, at high doses in young children (≤18 mo) and also possibly rarely at clinical use without any obvious predisposing factor. Whenever feasible, lidocaine should probably be replaced by another local anesthetic in patients taking other oxidative drugs and in patients with congenital methemoglobinemia
4. Chocolate-colored blood is suggestive of methemoglobinemia but its absence does not exclude methemoglobinemia. There are many variations in the reported color blood with high concentrations of methemoglobinemia
5. A discrepancy between the pulse oximeter saturation and the measured Pao_2 (Sao_2 ≤90% with Pao_2 ≥70 mm Hg) after exposure to a hemoglobin oxidizing drug is strongly suggestive of methemoglobinemia. Other possible causes of a discrepancy between oximeter-measured oxygen saturation and measured Pao_2 include carboxihemoglobinemia, sulfhemoglobinemia, and congenital or acquired diseases with abnormal O_2-Hb dissociation curve, or congenital methemoglobinemia
6. The definitive diagnosis of methemoglobinemia is direct methemoglobin measurement by co-oximetry (normal < 1%–2.2%)
7. The treatment is both symptomatic (optimization of oxygen delivery to tissues including oxygen administration as well as respiratory and hemodynamic support as required) and specific (methylene blue and/or ascorbic acid)
8. Methylene blue (which acts faster than ascorbic acid) should be administered to symptomatic individuals with local anesthetic-induced methemoglobinemia except in those with G-6PD deficiency, where it will be ineffective (low level of NADPH) and it may possibly induce hemolysis. It should be used with caution in patients with severe renal impairment and in pregnant or breast-feeding women
   a. For newborns (up to 2 mo old), the first dose should be limited to 0.5 mg/kg IV. This dose may be as effective as the 1.0 mg/kg dose which has sometimes induced hemolysis in this subpopulation
   b. For older patients, the first dose may be 1.0–2.0 mg/kg IV (concentration≤1%) administered over 5 min (preferentially diluted in 5% dextrose)
   c. The same dose may be repeated every 60 min as required up to a total dose of 7 mg/kg
   d. A transient false decrease of the $PSaO_2$ value may be observed after methylene blue administration
9. For severe or refractory cases, red blood cells transfusion (anemic patients) or exchange transfusion has been reported to be effective
10. Hyperbaric oxygen administration has not been demonstrated to be effective
11. For patients who have developed methemoglobinemia after benzocaine administration on a mucous membrane, the methemoglobin concentration should be monitored for at least 24 h after methylene blue administration to prevent rebound methemoglobinemia
12. Investigation to detect ischemic damage, including myocardial injury, may be warranted in susceptible individuals and/or severe cases
13. Hemolysis may happen with or without the administration of methylene blue. Hemolysis should be aggressively treated if it occurs

other cases would be needed before a clear relationship could be established.

Local anesthetic-related methemoglobinemia may lead to life-threatening events (including coma, seizures, respiratory compromise, shock state etc.), permanent injury (hypoxic encephalopathy, myocardial infarction), and death. The Food and Drug Administration has recently published a second alert on benzocaine-related methemoglobinemia.[20] In a retrospective review of methemoglobinemia episodes of various etiologies, Ash-Bernal et al.[21] found that most patients with a methemoglobin ≥8% were symptomatic. Some or many of their patients, however, were anemic. In the present review, even excluding patients with clinically significant anemia, pulmonary disease and/or cardiac failure, it can be seen from Table 4 and Figure 2 that symptoms may occur below the critical 30% level often quoted as the cut-off point for methylene blue administration.[22] It is highly improbable that the symptoms observed in the present review were due to high blood concentrations of local anesthetic and not to methemoglobinemia because patients known to have received a high local anesthetic dose were not included when those signs and symptoms were reviewed. Benzocaine was not included in the determination of the total dose of local anesthetic administered but, if methemoglobinemia is not produced, benzocaine rarely produces severe signs and symptoms of local anesthetic toxicity. In their 188 cases of massive benzocaine overdose in children,

Spiller et al.[16] reported that 92% of the children remained asymptomatic and the rest had only minor symptoms (oral numbness = 8, vomiting = 3, oral irritation = 1, dizziness = 1, and nausea = 1).

Organ and tissue damage may be induced by methemoglobinemia by mechanisms other than tissue hypoxia. The heme in methemoglobin would be more likely to dissociate from the pocket in the protein and, in animals, heme release or heme administration would increase vasopermeability, adhesion molecule expression, and infiltration of tissues by leukocytes.[23]

Table 5 presents an outline of the treatment of methemoglobinemia, based on this review. The treatment of methemoglobinemia should include both symptomatic (optimization of oxygen delivery to tissues) and specific (methylene blue and/or ascorbic acid) therapy. Methylene blue is the treatment of choice, except in patients with G-6-PD deficiency, in whom it would not work. Ascorbic acid, which acts more slowly, is the preferred treatment in patients with G-6-PD deficiency. At clinical doses, methylene blue does not seem to cause any serious side effects except in infants and in patients with G-6-PD deficiency in whom it can induce hemolytic anemia (one case of methylene blue-related hemolysis in a neonate with the administration of 1.0 mg/kg of methylene blue in the present review). For neonates, a retrospective chart review suggested that for methemoglobinemia not related to local anesthetic a dose of 0.3 to 0.9 mg/kg would be as effective as a dose of 1.0 to 1.6 mg/kg (both dosages induced a 69% reduction in methemoglobin concentrations in 1 to 2 h).[24] Patients who develop methemoglobinemia after the application of benzocaine on a mucous membrane should be carefully monitored since rebound methemoglobinemia occurring up to 18 h after methylene blue administration with methemoglobin values as high as 59.9% has been reported.

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