ORIGINAL INVESTIGATION

Benzocaine-Induced Methemoglobinemia Based on the Mayo Clinic Experience From 28 478 Transesophageal Echocardiograms

Incidence, Outcomes, and Predisposing Factors

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Background: The potentially life-threatening condition of methemoglobinemia is characterized by cyanosis, low pulse oximetric readings, and normal arterial PO2 values. Acquired methemoglobinemia has been linked to the use of the topical anesthetic benzocaine in endoscopic procedures, including transesophageal echocardiography (TEE). Yet, the incidence of benzocaine-induced methemoglobinemia with TEE and the clinical factors associated with its development are unclear.

Methods: All cases of methemoglobinemia complicating TEE at our institution (from January 1, 1999, to July 1, 2006) were identified by a comprehensive review of medical records and echocardiography and pharmacy databases.

Results: During 90 months among 28 478 TEEs, 19 cases of methemoglobinemia were identified, with a mean±SD methemoglobin level of 32%±15%. All patients were cyanotic, with low oxygen saturations. Eighteen of 19 patients received methylene blue (mean±SD dose, 1.3±0.4 mg/kg of body weight), with resolution of symptoms and signs. One of 19 cases resolved spontaneously. Compared with a random sample of 190 patients undergoing TEE, the age, sex, body mass index, left ventricular systolic function, and dose of sedation (midazolam hydrochloride, fentanyl citrate, or both) were similar in the 2 groups. However, study patients who developed methemoglobinemia were more likely to be hospitalized (89.5% vs 57.6%, P=.005), be anemic (84.2% vs 44.7%, P=.002), and have active systemic infection (68.4% vs 6.8%; P<.001) at the time of TEE compared with the random control cohort.

Conclusions: In a large series of patients undergoing TEE, the incidence of methemoglobinemia is low (1 case per 1499 [0.067%; 95% confidence interval, 0.040%-0.100%]) and has a good outcome if promptly recognized and treated. Clinical factors associated with the development of methemoglobinemia include sepsis, anemia, and hospitalization. Minimizing or avoiding the use of benzocaine in these patients is recommended.


METHEMOGLOBINEMIA IS a rare, potentially life-threatening medical condition that occurs due to increased methemoglobin production or decreased elimination and can be hereditary or acquired. Methemoglobin is a derivative of hemoglobin in which the normal ferrous iron state (Fe2+) is oxidized to the ferric state (Fe3+) (Figure). These ferric heme molecules are unable to bind oxygen, substantially reducing the oxygen-carrying capacity of the blood. Hence, excessive replacement of hemoglobin with methemoglobin leads to functional anemia and tissue hypoxia. Clinically, acquired methemoglobinemia is characterized by cyanosis, low pulse oximetric readings, and chocolate-brown blood on arterial blood gas sampling with normal arterial PO2 values. Symptoms can range from nonspecific to cardiopulmonary collapse; the occurrence of neurologic abnormalities and death is proportional to the degree of methemoglobinemia. The diagnosis of methemoglobinemia is confirmed by measurement of elevated methemoglobin levels on arterial blood sampling. Treatment is effective and includes oxygen therapy, discontinuation of causative medications, and intravenous administration of the antidote methylene blue, a thiazine dye that acts as an electron donor activating the nicotinamide adenine dinucleotide phosphate methemoglobin reductase pathway.

Benzocaine (ethyl aminobenzoate), used routinely as a topical oropharyngeal anesthetic for transesophageal echocardiography (TEE), has been reported to rarely cause methemoglobinemia. Estimates of methemoglobinemia incidence following TEE vary from 0.4 to 3 cases per 1000;
globinemia during or following TEE. Furthermore, we aimed to identify the outcomes associated with the development of methemoglobinemia. Clinical factors related to the development of methemoglobinemia have been difficult to date unsuccessful.

The objectives of this study were to establish the incidence of benzocaine-induced methemoglobinemia in a large cohort of patients undergoing TEE and to evaluate the outcomes associated with the development of methemoglobinemia. Furthermore, we aimed to identify the clinical factors related to the development of methemoglobinemia during or following TEE.

METHODS

Following approval of the institutional review board, all cases of methemoglobinemia complicating TEE at our institution during a 90-month period (January 1, 1999, to July 1, 2006) were identified by review of the echocardiography and pharmacy databases and the outpatient, inpatient, and emergency department medical records. All subjects agreed to the use of their medical records for research purposes.

METHEMOGLOBINEMIA CASES

Cases of benzocaine-induced methemoglobinemia following TEE were defined as those with documentation of each of the following criteria: (1) pre-TEE use of topical benzocaine spray, (2) clinical suggestion of methemoglobinemia (cyanosis, substantial drop in oxygen saturation by pulse oximetry during or following TEE, or observance of brown-appearing arterial blood on arterial Po2 sampling), and (3) a methemoglobin level of greater than 1.5% of the total hemoglobin concentration on arterial blood sampling.

BENZOCAINE USE

All patients at the Mayo Clinic receive topical local anesthetic to the oropharyngeal area before TEE with a combination of 2% viscous lidocaine hydrochloride, 20% benzocaine spray, or both based on physician preference. Most patients receive both agents, with a typical administered dose of 20% benzocaine spray being 1 to 2 brief (0.5-1.0 second) sprays.

Figure. Methemoglobin is a derivative of hemoglobin in which the normal ferrous iron state (Fe2+) is oxidized to the ferric state (Fe3+). Factors contributing to the oxidation of hemoglobin to methemoglobin include oxidizing agents such as benzocaine and states of oxidative stress such as sepsis. The predominant endogenous reducing mechanism of methemoglobin is the enzyme cytochrome b5 reductase. A secondary mechanism of nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase is the target of methylene blue.

however, these estimates are based on studies with small sample sizes (≤5 cases). Furthermore, because of the few cases in these studies, evaluation for clinical factors that might be associated with the development of benzocaine-induced methemoglobinemia has been difficult and to date unsuccessful.

To investigate clinical and procedural characteristics that might be associated with the development of methemoglobinemia, we randomly identified a subgroup of all subjects undergoing TEE. For every case of methemoglobinemia, we randomly identified 10 patients who underwent TEE in the same clinical year as the patient with methemoglobinemia. Medical records were reviewed in detail, including TEE procedural records of these 190 subjects in addition to those of the 19 patients with methemoglobinemia. Clinical factors associated with the development of methemoglobinemia and characteristics of the control group were then compared. For the purposes of this study, anemia was defined as a hemoglobin level of less than 13 g/dL (to convert to grams per liter, multiply by 10.0).

STATISTICAL ANALYSIS

Data were stored and statistical analyses performed using JMP version 6.0 (SAS Institute, Cary, North Carolina) by means of simple descriptive statistics and analysis of variance. P <.05 was considered statistically significant.

RESULTS

During the 90-month study period, 28 478 TEEs were performed at our institution. Intraoperative studies were not included in this analysis because patients do not receive local anesthetic for intraoperative TEE. Of 28 478 TEEs, 12 068 (42.4%) were performed on outpatients and 16 410 on inpatients (57.6%), including precadioversion TEEs. The distribution during the 90-month study period was uniform.

During the study period, 19 patients with clinical presentation of methemoglobinemia were identified, for an incidence of 1 case per 1499 (0.067%; 95% confidence interval, 0.040%-0.100%). All 19 patients received topical 20% benzocaine spray as a pre-TEE anesthetic, although per routine practice the exact administered dose was unrecorded because it is not sufficiently quantifiable. Seventeen of 19 patients also received 2% viscous lidocaine to swish, gargle, and swallow. The 19 TEEs were performed by 14 different cardiologists. In 5 of 19 cases, a senior cardiology fellow was also involved in the pro-
procedure. All 19 patients were clinically suspected of having methemoglobinemia on the basis of cyanosis and low oxygen saturation on pulse oximetry and had arterial blood gas sampling that confirmed the diagnosis of methemoglobinemia. The mean ± SD methemoglobin level was 32%±15% (range, 15%-60%) of the hemoglobin level. The mean ± SD time to arterial blood gas sampling (and confirmation of the diagnosis) from the time of benzocaine administration was 85±37 minutes.

Seventeen of 19 patients (89.5%) who developed methemoglobinemia were inpatients at the time of their TEE vs 57.6% of the 190 control subjects (P=.005). In 12 of 17 cases occurring in inpatients, the diagnosis of methemoglobinemia was made while the patient was still in the echocardiography laboratory, and in 1 case the procedure was a bedside TEE in an intensive care unit. In the remaining 4 cases, the diagnosis of methemoglobinemia was made after return of the patient to their hospital rooms. In 3 of 4 of these cases, the patients were cared for on a midlevel intensive care monitored floor setting and potentially had an abbreviated post-TEE observation in the echocardiography laboratory. In the remaining case, the diagnosis of methemoglobinemia was suspected in the echocardiography laboratory just before transfer and was confirmed and treated immediately on arrival in the patient’s room. Two of 19 patients who developed methemoglobinemia were outpatients when TEE was performed. One case was confirmed in the echocardiography laboratory; in the other case, the diagnosis was not made until the patient was noted to be cyanotic when seen by the physician a few hours later.

Given the disparity between inpatient vs outpatient status with regard to the number of methemoglobin cases, we assessed the frequency at which outpatients are seen in the hours and days immediately following TEE. In a review of the medical records of a random sampling of 190 TEEs, 80.0% of patients undergoing TEE as outpatients are seen by a physician within 8 hours, 88.9% within 24 hours, and 96.3% within 48 hours of their TEE.

Eleven of 19 patients who developed methemoglobinemia received intravenous methylene blue at a mean ± SD dose of 1.3±0.4 mg/kg of body weight (range, 0.7-2 mg/kg). Two patients received only 50 mg initially, and both required a second dose. All 18 patients receiving methylene blue had resolution of their symptoms and signs within an hour, frequently within 20 to 30 minutes. The remaining patient was noted to be hypotensive, dyspneic, and cyanotic. Despite a methemoglobin level of 36%, the diagnosis was initially unrecognized, and the patient was managed with supportive care only. Methemoglobinemia resolved overnight, and the patient made a full recovery.

In addition to their physical location at the time of TEE, other clinical factors were sought regarding those patients who developed methemoglobinemia compared with those who did not. Age, sex, body mass index, serum albumin level, left ventricular systolic function, and the dose of sedation (midazolam, fentanyl citrate, or both) were similar between patients who developed methemoglobinemia and the random group of TEE patients who did not (Table). However, compared with the control subjects, those subjects who developed methemoglobinemia were more likely to be anemic (84.2% vs 44.7%, P=.002) at the time of their TEE. The mean ± SD hemoglobin level in the methemoglobinemia cohort was 11.4±2.0 g/dL vs 12.6±2.0 g/dL in the controls (P=.02). There was also a difference in the prevalence of active systemic infection (the presence of bacteremia or the clinical suspicion of infective endocarditis) between the groups. Sixty-eight percent (13 of 19) of the methemo-

### Table. Characteristics of the Study Cohorta

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Developing Methemoglobinemia (n = 19)</th>
<th>Control Subjects (n = 190)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.8 ± 16.0</td>
<td>63.8 ± 12.0</td>
<td>.78</td>
</tr>
<tr>
<td>Male sex</td>
<td>10 (52.6)</td>
<td>87 (45.8)</td>
<td>.6</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>56.9 ± 12.0</td>
<td>58.1 ± 9.0</td>
<td>.65</td>
</tr>
<tr>
<td>Sedative use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam hydrochloride dose, mg</td>
<td>3.6 ± 2.4</td>
<td>3.7 ± 2</td>
<td>.7</td>
</tr>
<tr>
<td>Fentanyl citrate dose, µg</td>
<td>44.9 ± 33.0</td>
<td>50.9 ± 24.0</td>
<td>.43</td>
</tr>
<tr>
<td>Benzocaine use</td>
<td>19 (100.0)</td>
<td>185 (97.5)</td>
<td>.6</td>
</tr>
<tr>
<td>Viscous lidocaine hydrochloride use</td>
<td>18 (94.7)</td>
<td>183 (96.5)</td>
<td>.6</td>
</tr>
<tr>
<td>Body mass indexb</td>
<td>28.6 ± 7.0</td>
<td>28.9 ± 5.0</td>
<td>.6</td>
</tr>
<tr>
<td>Serum albumin level, g/dLc</td>
<td>3.33 ± 0.80</td>
<td>3.28 ± 0.70</td>
<td>.9</td>
</tr>
<tr>
<td>Gastric acid suppression</td>
<td>12 (63.2)</td>
<td>72 (37.9)</td>
<td>.03</td>
</tr>
<tr>
<td>Serum hemoglobin level, g/dL</td>
<td>11.4 ± 2.0</td>
<td>13.1 ± 2.0</td>
<td>.02</td>
</tr>
<tr>
<td>Anemic, hemoglobin level &lt;13 g/dL</td>
<td>16 (84.2)</td>
<td>85 (44.7)</td>
<td>.002</td>
</tr>
<tr>
<td>Indication for transesophageal echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>11 (57.9)</td>
<td>36 (18.9)</td>
<td></td>
</tr>
<tr>
<td>Cardiac source or clot</td>
<td>5 (26.3)</td>
<td>131 (68.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Other</td>
<td>3 (15.8)</td>
<td>23 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Active systemic infection</td>
<td>13 (68.4)</td>
<td>13 (6.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0.

a Data are given as mean ± SD or as number (percentage).

b Calculated as weight in kilograms divided by height in meters squared.

c Available in 60% of patients.
globinemia group had evidence of active systemic infection, compared with only 6.8% of the control group (P < .001). An additional patient had active systemic cancer and was receiving ifosfamide chemotherapy at the time of TEE. Finally, more patients (12 of 19 [63.2%]) in the methemoglobinemia group were receiving a form of gastric acid suppression at the time of TEE (histamine blockers or proton pump inhibitors) than in the control group (37.9%, P = .03). No other pattern of medication use previously linked with methemoglobinemia was present among identified patients with methemoglobinemia.

**COMMENT**

The potentially life-threatening condition of methemoglobinemia has been linked to the use of the topical anesthetic benzocaine in endoscopic procedures. In the present study among a large cohort of patients undergoing TEE, we evaluated the incidence of clinically manifested methemoglobinemia and the clinical characteristics associated with its development. Benzocaine is an ester type of anesthetic that is rapidly absorbed from the pharyngeal mucosa. The amount of drug administered is proportional to the duration of the administered spray. A typical 1-second spray provides 150 to 200 mg of drug. Investigations in healthy volunteers indicate that a 2-second spray marginally affects systemic methemoglobin levels (0.8%-0.9%). Although benzocaine use is a recognized cause of methemoglobinemia in patients, reports on the safety of TEE have not mentioned methemoglobinemia as a complication. Since the first reported case of benzocaine-induced methemoglobinemia in 1950, there have been approximately 65 cases reported in the literature, with more than half of these associated with topical anesthesia for TEE. However, the incidence is unclear, with the 2 largest series each reporting only 5 TEE-related cases of benzocaine-induced methemoglobinemia. Ash-Bernal et al reviewed the overall experience of methemoglobinemia at The Johns Hopkins University, Baltimore, Maryland, from 1999 to 2002. Although most cases were related to dapsone therapy, 5 cases were related to benzocaine administration in patients undergoing endoscopic procedures. Of 5 patients, 1 died, and 3 others had “near-fatal” outcomes. Novaro et al reviewed the TEE experience at the Cleveland Clinic, Cleveland, Ohio, from 1999 to 2001. During 32 months, there were 4336 TEEs performed (excluding intraoperative studies). Among these, there were 5 cases of methemoglobinemia, for an incidence of 0.12% (95% confidence interval, 0.04%-0.27%), with methemoglobin levels between 23% and 55%. Unlike The Johns Hopkins University cases, these patient outcomes were good. Three patients had received methylene blue, 2 received observation treatment only, and all 5 recovered. With this as a background, the objectives of our study were to identify the incidence of methemoglobinemia in a large cohort of patients and to identify clinical characteristics that were associated with its development.

Our review of 28,478 patients undergoing TEE identified 19 cases of methemoglobinemia, for an incidence of 0.067% (95% confidence interval, 0.04%-0.1%), which is slightly lower although statistically equivalent to the rate reported by Novaro et al at the Cleveland Clinic. Eighteen of 19 cases received methylene blue, and all did well, with no long-term sequelae. A novel finding in our study was the identification of clinical characteristics that may have been contributing factors and that suggest a plausible biologic basis for the development of methemoglobinemia.

Most cases (89.5%) of TEE-associated methemoglobinemia occurred in hospitalized patients. The reason for this is likely multifactorial. A possibility exists that late cases of methemoglobinemia that might occur following the procedure may have gone unnoticed clinically in outpatients and were thereby missed. Although this remains a possibility, we believe that it is unlikely and does not account for the difference observed. Unlike in the hospitalized patients (in whom post-TEE monitoring may be continued in their hospital rooms), outpatients are monitored in the TEE area until they are awake and well and oximetric readings have returned to normal. Moreover, most patients (80.0%) are seen later that same day, with 96.3% seen by a physician within 48 hours. Therefore, it is unlikely that cases of clinically significant methemoglobinemia went unrecognized. More likely, the reason for the preponderance of methemoglobinemia among the hospitalized patients is related to the colocalization of many potential predisposing factors. The difference also did not appear to be technical. Transesophageal echocardiography performed at the Mayo Clinic whether as an outpatient or as an inpatient was performed in the same manner by the same group of physicians and specialized support staff. Although the use of higher doses of benzocaine in patients who developed methemoglobinemia cannot be excluded, distribution across many cardiologists and similarities in the use of sedative medications argue against a pattern of different peri-TEE styles as a major factor.

Patients developing methemoglobinemia had a greater proportion of concomitant states of high oxidative stress, including active systemic infection or sepsis and cancer. Indeed, mild elevations in methemoglobin levels noted in patients with sepsis indicate a situation in which the endogenous protector against methemoglobinemia, cytochrome b5 reductase, may already be almost saturated, enhancing the predisposition for benzocaine to cause methemoglobinemia. In addition, most patients who develop methemoglobinemia had at least a mild degree of anemia. Although the hemoglobin level does not directly affect the production of methemoglobin, it greatly controls the effect of the functional anemia. For example, in a patient with a hemoglobin level of 14.0 g/dL, a methemoglobin level of 30% results in functional anemia of 9.8 g/dL, potentially of little symptomatic consequence; in contrast, in an anemic patient with a baseline hemoglobin level of 9.0 g/dL, a methemoglobin level of 30% results in functional anemia of 6.3 g/dL, likely highly symptomatic. Another factor associated with hospitalized patients is a potential higher prevalence of pharyngeal mucosa injury such as thrush that may affect the degree and rate of benzocaine absorption. Furthermore, there seemed to be a higher prevalence of acid suppression among patients in our study who developed methemo-
globinemia. Our study has insufficient power to differentiate whether this factor is independent of hospitalization status, a potential confounder because hospitalized patients are commonly prescribed proton pump inhibitors for ulcer prophylaxis. However, there is some biologic plausibility because a higher intestinal pH mediated by acid suppression would promote the growth of gram-negative organisms that convert dietary nitrates to nitrites, predisposing to the development of methemoglobin. In addition, many other medications are associated with the development of methemoglobinemia. Herein, 1 patient was receiving ifosfamide chemotherapy, and 5 patients were receiving standard doses of acetaminophen; both drugs are rarely linked to the development of methemoglobinemia. No patient was receiving concomitant nitrate-based therapy or any other medications linked to methemoglobinemia. Although all 19 patients received benzocaine, the contribution of concomitant lidocaine, which has been less strongly linked to methemoglobinemia. Although all 19 patients received benzocaine, the contribution of concomitant lidocaine, which has been less strongly linked to methemoglobinemia, cannot be excluded. Based on our data, the incidence of clinical methemoglobinemia among hospitalized anemic patients with active systemic infection undergoing TEE may be in the range of 1 case per 250 compared with the healthy outpatient, in whom the risk may be less than 1 case per 3200. Whether transient cases of milder elevations in methemoglobin occur more frequently can only be hypothesized in the absence of prospective data.

Management of suspected methemoglobinemia during or following TEE is coordinated in the Mayo Clinic Echocardiography Laboratory through adherence to a formal protocol. Supervising nurses are instructed to consider the diagnosis of methemoglobinemia in patients in whom oxygen saturation continues to be less than 90% in the absence of oxygen administration. This prompts the acquisition of immediate arterial blood gas sampling, with measurement of methemoglobin level. In the presence of an elevated methemoglobin level or a high clinical suspicion of methemoglobinemia (including the presence of coma, seizures, dizziness, confusion, anxiety, tachycardia, arrhythmias, and chocolate-brown blood when drawing arterial blood gases), administration of 100 mg of 1% methylene blue intravenously is prescribed. Arterial blood gas analysis for methemoglobin levels is performed for confirmation of the diagnosis, but administration of methylene blue is warranted if sufficient clinical suspicion is present, without necessarily waiting for the test result.

Reflecting the demographics of the upper Midwest population, all 19 patients in this study were of white race/ethnicity and were subject to a low expected incidence of acquired methemoglobinemia. Most individuals with acute acquired methemoglobinemia are not heterozygous for cytochrome b5 reductase deficiency. High nitrate exposure from well water has been associated with cases of acquired methemoglobinemia. Environmental exposure contributing to the development of methemoglobinemia in our patients cannot be excluded. However, beyond the inciting benzocaine exposure, it is likely in the study patients herein that conditions of high oxidative stress such as sepsis or cancer, reduced hemoglobin reserve secondary to anemia, and potentially the contribution of acid suppression were contributing factors in the development of acquired methemoglobinemia. Based on these findings, we recommend awareness of the increased potential for methemoglobinemia and avoidance (or at least minimization) of the use of benzocaine in these patient populations.

In conclusion, our study demonstrates among a large number of procedures that clinical manifestations of methemoglobinemia in the course of TEE is a rare event, making the use of benzocaine-derived products for local anesthesia a safe procedure except perhaps in a defined higher-risk cohort as identified herein. It is unclear if transient clinically unrecognized methemoglobinemia occurs, and a prospective quantitative periprocedural assessment would be necessary to evaluate this.

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Author Contributions: Dr Kane had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kane and Mulvagh.

Acquisition of data: Kane. Analysis and interpretation of data: Kane, Hoehn, Behrenbeck, and Mulvagh. Drafting of the manuscript: Kane. Critical revision of the manuscript for important intellectual content: Kane, Hoehn, Behrenbeck, and Mulvagh. Statistical analysis: Kane. Study supervision: Hoehn, Behrenbeck, and Mulvagh.

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REFERENCES


