Banning Benzocaine: Of Bananas, Bureaucrats, and Blue Men

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It is not often one gets to start an editorial with a story about bananas . . . or their odor. A few years back, I took over a case late in the afternoon and noted a very heavy smell on my way into the operating room that reminded me of my favorite childhood candy: spongy and soft, filled with artificial banana flavoring. I gave it no further thought because the case was ending and the residents were concerned about extubating a patient with a difficult airway who required awake, fiberoptic-assisted intubation. My attention was immediately drawn to the patient's bluish hue and the arterial oxygen saturation, which was hovering just below 90%, despite breathing oxygen 100% and use of standard maneuvers to improve lung expansion. I ordered cooximetric arterial blood gas, which indicated 20% methemoglobin. I may not be Sherlock Holmes, but I did figure out that the cyanosis, difficult airway, and requirement for awake intubation pointed to a common source: "pleasantly flavored," banana-scented, 20% benzocaine topical spray. A little methylene blue and the patient was fine. Indeed, it even provided an opportunity for teaching the causes and treatment of methemoglobinemia. However, as Dr. Guay reports in a superb review of the topic published in this issue of *Anesthesia & Analgesia*,[1] not all cases of local anesthetic-induced methemoglobinemia have such a benign outcome.

Methemoglobin, the form of hemoglobin incorporating iron oxidized to the ferric state (Fe^{+3}), is normally kept at levels <1% by the constitutively expressed methemoglobin reductase system in red cells. Tissue hypoxia ensues when methemoglobin reaches sufficiently high levels because, as Dr. Guay so aptly explains, methemoglobin is useless as an oxygen carrier: it is incapable of binding oxygen. Furthermore, the p50 of partially oxidized hemoglobin is abnormally low, impairing oxygen release to the tissues. Methemoglobin can also cause direct tissue damage because oxidized heme is cytotoxic and readily dissociates from the globin molecule. Obviously, this is a condition we definitely want to avoid! There are various scenarios where it complicates clinical care.

Hereditary methemoglobinemia is a genetically heterogeneous disease, most often resulting from a mutation affecting one of the two enzymes that comprise the methemoglobin reductase system, or the cofactor, cytochrome b5. The famous "blue Fugate" family of Troublesome Creek, Kentucky is an example of a pedigree with a high rate of recessive methemoglobinemia. Fortunately, they present with isolated cyanosis and no other significant medical problems. Other variants are associated with developmental delay. A variety of structural mutations in either the α or β globin gene, generically grouped as HbM, can stabilize the ferric form of heme, and also lead to autosomal dominantly inherited methemoglobinemia.

Acquired methemoglobinemia generally results from exposure to a drug that provides a sufficient oxidative stress to overwhelm the endogenous reductive pathways. This phenomenon is of particular importance to anesthesiologists because several local anesthetics can provide that trigger with potentially serious consequences.

Dr. Guay's article focuses specifically on the clinical spectrum of local anesthetic-induced methemoglobinemia and makes clear recommendations for its prevention, detection, and treatment. The basis for these

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recommendations is a careful analysis of 242 cases culled from the English and French literature through a search of the PubMed database. She excluded cases of potential local anesthetic overdose and patients having alternate causes of methemoglobinemia, e.g., hereditary forms, G-6-phosphate dehydrogenase deficiency, and treatment with nitrates. Inherent deficiencies in such retrospective literature reviews limit the conclusions one can draw. Case reports are generally biased in favor of positive outcomes so the spectrum of clinical presentation may be too favorable. There are also no accurate numerators or denominators, so prevalence or incidence cannot be ascertained. Furthermore, we must assume that many occurrences of methemoglobinemia are missed or misdiagnosed. Thus, the frequency of the problem and its severity are likely to be underestimated by this approach. Nevertheless, Dr. Guay makes several key observations that I believe significantly inform our approach to managing this serious iatrogenic condition.

The pulse oximeter is notoriously inaccurate in the presence of methemoglobinemia. Dr. Guay found that 92% of the cases had the simultaneous combination of Spo_2 <90% with Pao_2 >70 mm Hg. This apparent dissonance between pulse oximetry, a spectrophotometric method dependent on Beer's law, and standard blood gas analysis of oxygen tension via Clark electrode, provides a simple but useful diagnostic screening tool with a very high degree of sensitivity. Cooximetry uses multiple wavelengths to distinguish additional hemoglobin species, provides a direct measure of methemoglobin, and adds specificity to the diagnosis. Lacking the additional wavelengths of cooximeters, traditional pulse oximetry will substantially underestimate the degree of hypoxemia. As noted in the case report by Annabi and Barker,[2] a new generation of pulse oximeters incorporates multiple wavelengths, permitting accurate measurement of blood methemoglobin.

Giving supplemental oxygen does not reverse the hypoxemia and tissue hypoxia. This was the case in my patient from the "banana room" and it is not reassuring. Fortunately, methylene blue induces the endogenous reductive system, restores the normal redox status of heme-bound iron, and allows conversion of methemoglobin to hemoglobin. Anecdotal reports indicate that even small doses of oral methylene blue rapidly turned the blue Fugates pink.[3]

Occurrences of reported methemoglobinemia involved use of either benzocaine or prilocaine in more than 90% of cases. More importantly, such events are unpredictable, particularly those related to benzocaine. Several patients developed methemoglobinemia after a single short spray of benzocaine, whereas others seemed resistant to high doses. In several instances, rebound occurred hours after successful treatment of benzocaine-induced methemoglobinemia. Furthermore, severe adverse effects, including coma, myocardial infarction, and death, occurred at even modest degrees of methemoglobinemia. This combination of symptoms reflects the intolerance of the brain and heart to anaerobic metabolism, a direct consequence of the tissue hypoxia caused by methemoglobinemia.

The lack of correlation between dose and adverse reaction is very concerning. Certain patient factors, such as very young age, renal insufficiency, or use of other oxidizing drugs, can increase the likelihood of developing local anesthetic-induced methemoglobinemia. However, there is clearly an extreme interpatient variability in sensitivity, which probably reflects a complex interaction of genetic and epigenetic (environmental) factors leading to the conditional penetrance or largely unpredictable expression of acquired methemoglobinemia. There is no well-defined dose-response or pharmacokinetic relationship on which to base a rational approach to dosing topical benzocaine. This observation is the basis for Dr. Guay's compelling argument for the banning of benzocaine from our practice, a stance I strongly support.

In February 2006, shortly after my experience in the "banana room," the Veterans Affairs Central Pharmacy, Medical Advisory Panel, and the National Center for Patient Safety issued a document entitled "Guidance on the Use of Topical Anesthetics for Naso/Oropharyngeal and Laryngotracheal Procedures" that reviewed reported incidents of anesthetic-related methemoglobinemia. This advisory recommended that "the Veterans Health Administration adopt the use of lidocaine for naso/oropharyngeal, and laryngotracheal procedures, and strongly discourage or prohibit the routine use of topical benzocaine for this purpose." Shortly afterward, the Veterans Affairs Central Office issued a Patient Safety Alert instructing all facility directors to ensure that all benzocaine-containing sprays be removed from inventory no later than April 1, 2006. I recall that, at the time, my reaction to this directive was quite negative. I resented the intrusion and limitation of my practice. In reality, it did not limit my practice at all, because 4% lidocaine is an equally, if not more effective, topical anesthetic. In Dr. Guay's review, only three cases involved use of standard lidocaine doses and, in her words, "If lidocaine does cause methemoglobinemia, it must be quite rare, given the paucity of reports and the huge clinical exposure."

Local anesthetic toxicity clearly encompasses more than direct cardiac and central nervous system toxicity because of overdose or intravascular injection. Oxidative stress leading to methemoglobinemia jeopardizes patient safety. Dr. Guay has done our specialty a tremendous service by pointing out the dangers of this underappreciated and serious iatrogenic complication. Moreover, she has presented a sober and well-reasoned argument for banning the use of benzocaine

from our practice. Our inability to predict potentially fatal events related to use of this drug, particularly when much safer alternatives are available, leaves little weight to the argument against this ban. Anesthesiologists focus on the airway as one part of our role in assuring the adequate delivery of oxygen to tissues. Benzocaine-induced methemoglobinemia is a direct challenge to that mission and presents a real danger to our patients. I will miss the occasional smell of bananas in the operating room, but I will not miss the blue patients.

REFERENCES

1. Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. Anesth Analg 2009;108:837–45
2. Annabi EE, Barker SJ. Severe methemoglobinemia detected by pulse oximetry: a case report. Anesth Analg 2009;108:898–9
3. Cawein M, Behlen CH 2nd, Lappat EJ, Cohn JE. Hereditary diaphorase deficiency and methemoglobinemia. Arch Intern Med 1964;113:578–85