Methemoglobinemia in a renal transplant patient: case report

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Methemoglobinemia is a condition in which cyanosis develops in the absence of any cardiac or respiratory abnormalities.[1] Cyanosis is a result of the accumulation of methemoglobin, which imparts a bluish color to the blood. This condition has two forms: a hereditary and an acquired form. Hereditary methemoglobinemia is an extremely rare inborn error of metabolism resulting in the accumulation of methemoglobin.[2] The *acquired* form results from exposure to various environmental toxins or administration of certain medications. Cohen and Bovasso[3] include aniline derivatives (found in crayons, inks, shoe polish, dyes, and drugs), benzene derivatives, nitrates, certain local anesthetics, and sulfonamides as compounds known to produce methemoglobinemia. Exposure may be through transdermal absorption, inhalation, ingestion, or parental administration.

Hemoglobin normally contains iron in its ferrous (Fe^{+3}) or reduced state. Methemoglobin contains the oxidized form, ferric (Fe^{+2}), significantly altering the tertiary structure of the heme moiety making it incapable of releasing oxygen. The ferrous cation is inherently unstable and, in the normal biological system, oxidizes to the ferric form.[4] Methemoglobin reductase, normally present in erythrocytes, is absent or decreased in hereditary methemoglobinemia. This enzyme system ensures that 99% of the hemoglobin is maintained in the more functional ferrous state. An absence or decreased level of the enzyme alters homeostasis to favor accumulation of the ferric cation. Agents that cause acquired methemoglobinemia may increase production of methemoglobin or may inhibit the methemoglobin reductase system or both, resulting in a preponderance of ferric iron and thus the nonfunctional methemoglobin.

Clinical signs and symptoms

As methemoglobin levels increase, clinical signs and symptoms develop (Table). As the earliest sign of methemoglobinemia, significant cyanosis, especially involving the nail beds and mucous membranes, develops when methemoglobin levels reach 1.5 g/dl.[4] The cyanotic appearance will not be improved significantly with oxygen administration. This should lead the clinician to consider the diagnosis of methemoglobinemia. When drawn, the blood appears chocolate brown and does not turn red when exposed to oxygen. Headache, malaise, lightheadedness, and lethargy are symptoms of increasing levels of methemoglobin. Severe cases can progress to unconsciousness and death.[4] In patients with underlying cardiac or pulmonary pathology, clinical symptoms may appear at significantly lower levels of methemoglobin.

Management

Treatment is aimed at preventing additional formation of methemoglobin through decontamination of the patient. For most patients with mild symptoms (10–20% level of methemoglobin), supportive oxygen and withdrawal of the offending agent is sufficient treatment. Assuming no ongoing formation of methemoglobin, the normal biological system converts Fe^{+2} to Fe^{+3} at a rate of approximately 15% per hour.[4] Clinically continued absorption, prolonged half-life, and toxic intermediated metabolites may prolong methemoglobinemia, and patients should be closely followed for worsening symptoms.[4]

Clinically severe cases—such as patients showing signs of clinical hypoxia, impairment of mental status, and ischemic

TABLE. ELEVATED METHEMOGLOBIN LEVELS: SIGNS AND SYMPTOMS

Blood Level (g/dl)	*Signs and Symptoms*
< 0.15	None – within normal limits
0.75–2.25	Persistent slate gray cyanosis, diminished cerebral function
4.5–6.0	Exertional dyspnea, headache, weakness, dizziness
7.5–9.0	Stupor, respiratory depression
10.5–12.0	Unconsciousness, death

From Warren RE, Van de Mark TB, and Weinberg S: Methemoglobinemia induced by high doses of prilocaine, Oral Surg 37:866, 1974.

cardiac changes or even more subtle changes such as decreased attentiveness—should be treated aggressively. Administration of 1% methylene blue (1.5 mg/kg over 5 min)[1,4] intravenously is the mainstay of treatment in clinically symptomatic cases. Clinical improvement should be evident within 1 hr post administration. This dose can be repeated every 4 hr until the cyanosis resolves.

The enzyme responsible for the majority of conversion of methemoglobin to hemoglobin in the biological system is methemoglobin reductase. NADH serves as the electron donor in reduction of Fe^{+3} to Fe^{+2} in this enzymatic system.[4] A second enzyme system present in erythrocytes requires the electron donor NADPH, and accounts for a small percentage of methemoglobin reduction under normal conditions.[4] It is this latter biologically less active system that is accelerated by the exogenous electron carrier, methylene blue. Specifically, leukomethylene blue, which is the byproduct of the reduction of methylene blue by NADPH-dependent methylene blue reductase, directly reduces ferric to ferrous iron.[4,8] This significant enhancement of the NADPH methemoglobin reductase pathway by methylene blue is the basis on which methylene blue has become the gold standard in treating symptomatic methemoglobinemia.[4,10,11]

Several other adjunctive therapies have been proposed. These include hyperbaric oxygen therapy and exchange transfusion. Supersaturation of oxygen in the serum through hyperbaric therapy may have a protective effect while the body clears methemoglobin. Theoretically, exchange transfusion should be beneficial, but it takes considerable time and is not without inherent risks. Neither therapy has any proven benefit. Ascorbic acid also has been suggested since it nonenzymatically converts methemoglobin to hemoglobin in the normal biological system. However, it has little place in the treatment of methemoglobinemia since ascorbic acid-related reduction of the heme iron is extremely slow.[4,9]

Relevance to dentistry

Two commonly used local anesthetic agents, articaine (Ultracaine™, Hoechst-Roussel Canada Inc, Montreal, Quebec) and prilocaine hydrochloride (Citanest™, Astra Pharmaceutical, Westboro, MA), are known to cause acquired methemoglobinemia.[3,5,6] The production of methemoglobin by these agents is dose-related and has never been reported to occur within the therapeutic range. Peak levels of methemoglobin are reached 3 to 4 hr post local anesthetic administration and persist for 12 to 14 hr. Toluene, present in the local anesthetic molecule, is converted to *o*-toluidine during biotransformation in the liver and lungs.[1] This compound is an oxidizing agent and converts ferrous iron to ferric iron. It is also an inhibitor of the methemoglobin reductase pathway resulting in methemoglobin accumulation.[1]

One case of acquired methemoglobinemia has been reported by Daly et al.,[7] but a review of the literature has revealed no reported cases in children. This case report is a result of an increasing number of medically challenged children presenting for dental treatment in private offices and, in particular, emphasizes the need for discretion in the amounts of local anesthetics used in children. This child, while medically challenged, would have responded in a similar way to an overdose of prilocaine had he been healthy. This emphasizes that methemoglobinemia is an additional factor to consider in staying within local anesthetic dose safety ranges.

Case report

A 15-year-old white male, 5 years after living related donor renal transplant, was referred to a periodontist for maxillary gingivectomy for cyclosporine-related gingival overgrowth. Prior to his renal transplant, he was dialyzed three times weekly over a 2-year period secondary to nephrotic syndrome. Post-transplant immunosuppressive therapy consisted of cyclosporine and prednisone. The patient also was maintained on verapamil hydrochloride and propanolol for hypertension management. Subsequently, he has maintained normal renal function with no evidence of transplant rejection. Excessive gingival tissue necessitated extraction of several retained primary teeth (soft tissue only), compromised oral hygiene, and impeded recently instituted orthodontic treatment of a class II malocclusion. Due to the patient's general state of good health, good renal function, and excellent cooperation, a gingivectomy with a flap procedure was carried out under local anesthesia using 2 carpules of Marcaine™ (Sanofi Winthrop Pharmaceuticals, New York, NY), 0.5% (1:200,000 epinephrine) and 6 carpules of Citanest 4% (1:200,000 epinephrine). The procedure was completed without complication and the patient was dismissed with standard postoperative instructions.

Approximately 4 hr postoperatively, the patient's mother noticed that the patient's lips and fingernails were blue. The patient also complained of generalized malaise and lightheadedness. On presentation in the emergency department, the patient appeared lethargic with cyanotic lips and nail beds. Following a complete history, evaluation, and consultation with the poison center, a diagnosis of methemoglobinemia was made. Blood levels of methemoglobin were 2.25 g/dl, a level of approximately 15%. His oxygen saturation was 75%. The patient's blood urea nitrogen and creatinine were normal. The patient had a borderline low hemoglobin of 12.3 and hematocrit of 34.7. These normal values suggest the patient's underlying good health.

The patient was admitted for supportive oxygen therapy and observation. The following morning the patient had symptomatically improved with methemoglobin level of 0.15 g/dl (1%) and oxygen saturation at 99%. Followup with the patient's nephrologist revealed no further problems. A 10-day periodontal followup showed excellent healing of the gingival tissue.

Discussion

This case emphasizes the need for a greater appreciation of potential adverse reactions of the various medications commonly used in dental practice. With increasing numbers of medically challenged patients—especially children—presenting for dental treatment, it is even more important to recognize potential hazardous side effects and drug interactions. Specifically, it is essential to know the maximum dosages and adverse side effects of commonly used local anesthetic agents.

As a matter of review, most potential side effects from local anaesthetics commonly used in dentistry result from an administration of a higher-than-recommended dose or from intravascular injection of an appropriate dose resulting in serum levels above the toxic limit. The injectable anesthetic agents used commonly in dentistry are all of the amide class, including longer-acting bupivacaine hydrochloride. Overdose with any of these agents is dose dependent and results in a similar constellation of symptoms. These include psychomotor agitation, palpitations, apprehension, and euphoria, progressing to central nervous system depression, unconsciousness, coma, and seizures.[5,10] Of the amide local anesthetics, prilocaine alone has been reported to cause methemoglobinemia due to accumulation of its metabolite orthotoludine. Benzocaine (Topicaine™, Hoechst-Roussel Pharmaceuticals), a commonly used topical anesthetic of the ester class, may be systemically absorbed from mucous membrane and when used in high enough quantities has been previously reported to result in significant methemoglobinemia.[12-14]

Most amide anesthetic agents are metabolized by amidase in the liver and lungs and excreted by the kidney. Approximately 6% is excreted unchanged in the urine. Thus, in the absence of significant liver disease or abnormal renal function, elimination of amide anesthetic agents should be normal. In this case the patient's renal function had remained normal since transplant. Many of the immunosuppressive regimens, such as the cyclosporine the patient was maintained on, can result in liver disease, yet no liver dysfunction was evident. Thus, one would expect normal metabolism and elimination of the metabolites of local anesthetics in this patient.

Since the patient is also on several medications, the possibility of drug interaction must be considered. Cyclosporine used as an immunosuppressive agent has no specific reported adverse interaction with any of the amide anesthetics. While verapamil and propanolol may adversely affect the myocardial conduction system when administered concurrently, they also have no reported interactions with any of the local amide anesthetics.

The recommended maximum dose of bupivacaine hydrochloride is 1.3 mg/kg. In this case 2 carpules of bupivacaine hydrochloride (9 mg/carpule) were administered. This is equivalent to 0.35 mg/kg (patient's weight = 50.1 kg). This dosage falls well within the therapeutic ranges.

Prilocaine was chosen due to its shorter duration of action, and 6 carpules were required (72 mg/carpule = 8.6 mg/kg). This exceeds the recommended maximum dose of 6 mg/kg.[5] Large doses of prilocaine are a known cause of methemoglobinemia. Doses in excess of 400 mg are necessary to produce significant levels of methemoglobin. The patient in this case received a total of 432 mg of prilocaine. In conferring with the patient's nephrologist, as suspected, the history of successful renal transplant was not thought to affect the therapeutic range of these anesthetic agents. Thus, if the prilocaine dose had been kept within the recommended limits, this incident may have been avoided.

Though no formal testing was undertaken to eliminate hereditary methemoglobinemia, it would be very unusual for a patient with an abnormally low level of NADH-dependent methemoglobin reductase to have remained asymptomatic for so many years. We believe the history of renal failure and subsequent transplant were not complicating factors in this case. The borderline hemoglobin and hematocrit, and thus a less-than-optimal oxygen carrying capacity, may have made the patient more susceptible to the affects of methemoglobinemia, but we felt that this episode of methemoglobinemia was a result of prilocaine overdose.

Finally, as stressed by Malamed,[5] it is important to consider a patient's age and medical history when administering local anesthetics. This case stresses not only that, but more specifically, the importance of knowing the recommended maximum dose of commonly used local anesthetics and being careful not to exceed this therapeutic threshold.

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Public has mixed feelings about welfare

REFORM DEBATE MAY HAVE TO BE DECIDED AT STATE, RATHER THAN NATIONAL LEVEL

As Congress does battle over welfare reform, a new study shows Americans want major reforms, but are reluctant to cut people from the welfare roles without some means of basic support. The study appears in the October issue of the AMA's *Archives of Pediatrics and Adolescent Medicine.*

Robert J. Blendon, ScD, from the Harvard School of Public Health in Boston, Massachusetts, and colleagues conducted a comprehensive review of American attitudes toward the welfare system by analyzing data from 19 surveys taken between 1937 and 1995.

The researchers write: "The jury is still out on what the public will support on welfare reform. At the moment, they favor four things that may be incompatible: "1) get people off welfare within two years; 2) get them jobs that provide a minimum standard of living; 3) do not let children suffer undue hardship; and 4) do not raise taxes or cut government programs to accomplish these things."

Americans traditionally have had different attitudes about welfare than residents of other countries. One survey, cited in the article, shows that only 23% of Americans believe the government should be responsible for taking care of very poor people who can not take care of themselves. That compares to 50–71% in Germany, Poland, the United Kingdom, France, Italy, and Spain.

The researchers found that Americans' opinions about welfare policies and reforms are related to five core values about welfare and poverty: "1) welfare causes more harm than good because it discourages work and causes families to break up; 2) welfare should be a temporary transition to work, not a long-term subsidy; 3) the country spends too much on welfare programs; 4) lack of economic opportunity as well as personal responsibility is the reason people need welfare; and 5) both government and people themselves have a shared responsibility for ensuring that people have a minimum standard of living."

The authors write: "The outcome of the welfare reform debate will have a substantial impact on the 21% of the nation's children who now live in poverty. Given the public's uncertainty about the consequences of many of these welfare decisions, it is a good time for health professionals to get involved in the welfare reform debate ... As the debate continues to focus on the implications of particular proposals — whether there will be severe negative consequences for individuals of families or increased taxes or cuts in other government programs — the public is likely to become more cautious.

"The Medicaid program is caught in the middle of the welfare reform debate. On the one hand, it suffers from being identified as a welfare program (by 60% of Americans).... On the other hand, as a health program Medicaid has substantial popular support. Thus, the public is likely to accept some cuts in Medicaid spending, while, at the same time, it may not want to cut back on needed services to children. How this conflict will be resolved is likely to await much more focused debate at the state level rather than being decided in the broader welfare debate that is now going on at the national level."