CASE REPORTS

Anesthesiology 82:1065-1067, 1995
© 1995 American Society of Anesthesiologists, Inc.
J. B. Lippincott Company, Philadelphia

Methemoglobinemia in a Patient Receiving Flutamide

Stephen H. Jackson, M.D.,* Steven J. Barker, Ph.D., M.D.†

FLUTAMIDE (Eulexin, Schering) is a nonsteroidal antian- drogenic chemotherapeutic drug commonly employed in the treatment of prostate cancer. Its mechanism of action is to block androgen binding to nuclear androgen receptors. This case report describes the most clinically striking of a series of surgical patients with a flutamide-induced methemoglobinemia.

Case Report

A 74-yr-old, 70-kg man with prostate cancer receiving flutamide (750 mg/day for 2 yr) was scheduled for a coronary artery bypass grafting procedure. Four months before admission, during the last of his three previous myocardial infarctions, pulmonary edema had developed. His ejection fraction at that time was 36%, but it improved to 50% in the interim while receiving medical treatment with nifedipine, metoprolol, furosemide, and aspirin. His 100 pack/year cigarette smoking history had produced a mild degree of obstructive pulmonary impairment (ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) = 72%). He tolerated light exercise well, his lungs were clear to auscultation, and chest x-ray showed mild prominence of his interstitial markings. However, his skin and lips appeared blue on room air, which prompted preoperative arterial blood gas determination that was reported to the anesthesiologist to be within normal limits: arterial oxygen tension (Pao2) 83 mmHg, arterial carbon dioxide tension (Paco2) 39 mmHg, pH 7.40, and hemoglobin 14.4 g/dl. There was no verbal communication from the laboratory that the measured hemoglobin oxygen saturation (SaO2) was 90%, whereas the calculated SpO2 was 96%, and the blood methemoglobin was 5.5% (carboxyhemoglobin was 0%), as measured on a Ciba Corning 2500 co-oximeter (Medfield, MA).

The patient received 4 mg midazolam and 0.2 mg glycopyrrolate intramuscularly, and arrived in the operating room awake and alert. Pulse oximetry (Nellcor, Pleasanton, CA) during supplemental oxygen breathing via nasal prongs revealed pulse oximetry (SpO2) 95–96%, his skin and mucous membrane discoloration persisted. His radial artery was cannulated. He received 1,000 mg cefazolin and 105 mg gentamicin intravenously before induction of anesthesia, which proceeded uneventfully with 30 mg morphine, 500 µg fentanyl, 10 mg midazolam, and 50 mg methohexital intravenously. Intubation was facilitated with succinylcholine, and anesthesia was maintained with oxygen/enfuran/pancuronium. Intravenous nitroglycerin (15 µg/min) was administered. Throughout the anesthetic course, SpO2 remained stable at 94–96%. Cardiopulmonary bypass (CPB) using a Cobe Sotckert heart lung console (Arvada, CO) and a Sarnes Turbo (Hollow Fiber) membrane oxygenator (Ann Arbor, MI) was initiated. The oxygenator had been primed with 1,500 ml Normosol (Abbott, Chicago, IL). Five hundred milliliters of autologous venous blood was removed upon initiating bypass for post-CPB reinfusion. The perfusionist immediately announced that the oxygenator’s arterial (outflow) blood was “dark,” which was confirmed by the surgeon. Rapid evaluation of the perfusion system and its gas supply provided no explanation for the “dark” blood. The in-line mixed venous oxygen saturation (SvO2) measured with a Bentley Oxi-Sat Meter SM-0100 (Irvine, CA) was 65%, a value consistent with early CPB, and it increased to 70% within several minutes (and later to 75%) as the nasopharyngeal temperature drifted from 35.2°C to 32.5°C. Oxygenator arterial blood with a hemoglobin of 7.4 g/dl was analyzed rapidly in the operating room on a Mallincrodt sensor system (GEM Premier, Ann Arbor, MI) blood gas analyzer: Pao2 563 mmHg, Paco2 25 mmHg, pH 7.54, and base deficit = −0.9 mEq. Minutes later, another arterial blood sample was sent to the respiratory laboratory for blood gas analysis and co-oximetry and measured: Pao2 590 mmHg, Paco2 25 mmHg, pH 7.60, base excess 2.2 mEq. measured SaO2 96% and calculated SvaO2 100%, methemoglobin content 5.4%, and carboxyhemoglobin 0%.

This methemoglobin value prompted a review and initial discovery of the preoperative co-oximetry with its methemoglobinemia. However, the etiology of the preexisting methemoglobinemia remained to be determined. On review of all preoperative drugs in the Physicians’ Desk Reference, † flutamide was identified as the most likely culprit.

There was no need to treat the existing methemoglobinemia with methylene blue because serial SvaO2 and arterial blood gas determinations demonstrated adequate oxygen delivery. Sixty and 105 minutes after initiation of CPB, the methemoglobin level had decreased to 4.7% and 3.8%, respectively, and the measured SvaO2 values were 95% and 96%, respectively. The patient was separated uneventfully from CPB and was neurologically intact within 6 h. Nitroglycerin was not employed after CPB. The methemoglobin level 1 day later was 3.2%. The patient received no homologous blood transfusion.

Flumazenil treatment was not restarted postoperatively, and 6 months later, his methemoglobin level was 0.5% and his skin color was normal. At that time, he also had a normal blood methemoglobin.
CASE REPORTS

Bilirubinemia evaluation 4 This included (1) a spectral absorbance scan that revealed normal hemoglobin M ratios at 630/600 nm (1.36, normal range > 1.25) and 500/600 nm (3.15, normal range > 2.5), and (2) a normal erythrocyte reduced nicotinamide adenine dinucleotide (NADH) cytochrome c5 reductase level (15.8 IU/g hemoglobin, normal range 10.1–19.4). His blood glucose-6-phosphate dehydrogenase level also was normal.

Discussion

Methemoglobin is formed when iron of the heme moiety in the hemoglobin molecule becomes oxidized from the ferrous to the ferric state. In this form, the methemoglobin molecule cannot bind oxygen, and moreover, it interferes with the ability of the remaining normal hemoglobin molecules to bind oxygen. The erythrocyte has several metabolic pathways that concomitantly prevent oxidative formation of methemoglobin and reductively reactivate any methemoglobin so formed to hemoglobin. Accumulation of methemoglobin to increased (>1.5%) levels occurs when (1) the rate of heme oxidation is increased by drugs or chemicals; (2) an abnormal globin moiety stabilizes the hemoglobin in the oxidized state, as in inherited hemoglobin M disorders; or (3) methemoglobin reduction is impaired, as in the autosomal recessive inherited absence (homozygous) or deficiency (heterozygous) of NADH-cytochrome c5 reductase. 2

Flutamide is a nonsteroidal antiandrogenic chemotherapeutic drug for prostate cancer. Because of its chemical structure derived from anilide, flutamide can induce a clinical methemoglobinemia. 3,4 The Physicians’ Desk Reference lists flutamide-induced methemoglobinemia as a “spontaneous adverse effect” and reports that overdose in animals caused methemoglobinemia. 5 There is no published information that quantitates the range of levels of methemoglobin that occur in flutamide-treated patients or whether methemoglobinemia is dose-related. However, an asymptomatic increase of the methemoglobin as high as 7.7% had been detected occasionally in clinical trials. 5

One case of clinical methemoglobinemia attributed to flutamide therapy has been reported. 6 An 80-year-old man experienced severe cyanosis and dyspnea with a methemoglobin of 16.2% after receiving flutamide 750 mg/day for 16 months. Treatment included discontinuation of flutamide combined with intravenous ascorbic acid, and clinical improvement occurred within 10 days. Methemoglobin decreased to 12.7% several days after initiation of therapy and was <1% 1 week later. We have detected methemoglobinemia in each of five surgical patients who were receiving flutamide, but only in the case presented above did the methemoglobin level exceed 2%.

In this case report, the methemoglobin was 5.5% and sufficient to visibly alter the color of the patient’s skin, mucous membranes, and arterial blood to an appearance consistent with cyanosis. When the mean capillary concentration of reduced hemoglobin is >5 g/dl, cyanosis usually becomes apparent. This case demonstrated that methemoglobin can discolor the skin and mucous membranes at concentrations as low as 0.8 g/dl. 2

Pulse oximetry failed to correlate with either the clinical signs of “cyanosis” or the calculated hemoglobin saturation. Co-oximetry demonstrated the disparity between the calculated and measured hemoglobin saturations. In this case, pulse oximetry values approximated those measured by co-oximetry. However, a potential danger for the patient with methemoglobinemia is that the pulse oximetry readings can significantly overestimate measured hemoglobin saturation values. 6–8 This was exemplified in a previous case report, in which a methemoglobin level of 26% (caused by benzocaine) resulted in a significant overestimate of saturation by pulse oximetry. 9 At levels of methemoglobinemia greater than 35%, the pulse oximetry readings tend to approach a minimum level of 85%. 6,9 At high methemoglobin levels, the pulse oximeter Spo2 value represents neither fractional nor functional hemoglobin saturation. 9 In the current case, the level of methemoglobinemia was low enough not to cause physiologically significant hemoglobin desaturation.

If a disparity is detected between pulse oximetry and either an oxygen saturation calculated from PaO2 or a clinical “cyanosis,” then methemoglobinemia should be suspected. In such instances, pulse oximetry should be correlated with SaO2 and methemoglobin values measured by co-oximetry. Any clinical diagnosis or therapy should be based on co-oximetry measurements of the several hemoglobin species.

The Bentley Oxi Sat Meter SM-0100 mixed venous oxygen saturation monitor used during CPB is a two wavelength oximeter that operates at 660 and 900 nm. Because these are the same wavelengths used by most pulse oximeters and oximetric pulmonary artery catheters, the SM-0100 will be subject to similar measure-

1066

CASE REPORTS

ent errors. The error cannot be caused by low 

Svo2 by any method of methemoglobin level.

Despite the normal methemoglobin level, a normal 
possibility of methemoglobin in the hemoglobin 
and this was not detected by co-oximeter or 
oligated blood sample. The patient is in a state of

References

82:1067–1077
© 1995 Anesthesiology
J. B. Lippincott Co.

Anesthesiology

THE carci

diarrhea, a

dised valve

1 Assistant

† Associate Professor

Received for publication September 10, 1994
Address correspondence to Dr. Chang, Department of Anesthesiology, Box 6070, The City University of New York, New York, NY 10010
Key words: 

Anesthesiology

† Fairbanks VF, Department of Laboratory Medicine and Pathology, Methemoglobin Evaluation Section, Mayo Clinic, Rochester, Minnesota: Personal communication. 1994.

Anesthesiology, V 82, No 4, Apr 1995

Downloaded From: http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931304/ on 11/24/2018
CASE REPORTS

The complicated case of a patient with carcinoid heart disease is presented. The patient was diagnosed with carcinoid syndrome, characterized by flushing, diarrhea, abdominal pain, bronchospasm, and right-sided valvar disease. Carcinoid tumors develop from enterochromaffin cells and may produce the carcinoid syndrome in the presence of hepatic metastases, via drainage directly into the systemic circulation, or with lung involvement. Carcinoid tumors can secrete serotonin, histamine, kallikrein, bradykinins, prostaglandins, and neuropeptides. Severe hypotension and bronchospasm that is refractory to treatment may occur during a crisis.

There have been a limited number of reports of patients undergoing simultaneous tricuspid and pulmonic valve replacements. Left-sided carcinoid valvar disease is rare and is thought to require pulmonary involvement by carcinoid disease or an intra-atrial commen errors induced by methemoglobin. Although the error caused by a methemoglobin level of 5% would not be large, the SM-1000 would overestimate the \( \text{SvO}_2 \) by an amount directly related to the methemoglobin level. Thus, the return of the patient’s methemoglobin to a normal level after discontinuation of flutamide, the possibility of an inherited basis for the patient’s methemoglobinemia was considered. The absence of a history of congenital cyanosis or skin discoloration mitigated both a hemoglobin M disorder and a homozygous state of NADH-cytochrome c5 reductase deficiency, and this was confirmed by laboratory tests. The carrier or heterozygous state, characterized by an enhanced susceptibility to methemoglobin formation with exposure to oxidant drugs and chemicals also was ruled out by the normal level of NADH-cytochrome c5 reductase activity. Both the normal blood glucose-6-dehydrogenase and the absence of a hemolytic anemia precluded any other inherited basis for a drug-induced methemoglobinemia. Therefore, the conclusion that this patient’s methemoglobinemia was induced by flutamide is incontestable.

References


Anesthesia for Aortic and Mitral Valve Replacement in a Patient with Carcinoid Heart Disease

Steven M. Neustein, M.D., *Edmond Cohen, M.D. †

Anesthesiology, V 82, No 4, Apr 1995

THE carcinoid syndrome is characterized by flushing, diarrhea, abdominal pain, bronchospasm, and right-sided valvar disease. Carcinoid tumors develop from mixed venous blood ( \( \text{SvO}_2 \) ) and arterial blood ( \( \text{SaO}_2 \)) during CPB is a two wavelength method at 660 and 900 nm. The wavelengths used by most coronary artery catheters is similar measure-