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Intravenous Nitroglycerin, Methemoglobinemia, and Respiratory Distress in a Postoperative Cardiac Surgical Patient

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The use of nitrates for vasodilator therapy is a recognized method of therapy for angina pectoris and congestive heart failure.[1,2] Nitrates, especially iv nitroglycerin, are also used intraoperatively for patients with coronary artery disease requiring surgery.[2] The World Health Organization has defined the acceptable daily intake of nitrates at 5 mg/kg and of nitrites at 0.4 mg/kg.[3] Methemoglobinemia is a well-recognized result of exposure to nitrates; however, methemoglobinemia in levels of up to 20% is thought to be asymptomatic, not requiring specific therapy. Toleration of these levels requires an adequate hemoglobin level, cardiac output, and extraction of oxygen at the tissue level. The current practices in surgery utilizing hemodilution to avoid exposure to homologous blood products may impose additional risk in patients requiring treatment with nitrates for coronary artery disease, since there will be a loss of functioning hemoglobin associated with a limited ability to increase cardiac output. Additionally, nitroglycerin therapy has been associated with hypoxemia as a result of alteration in V/Q relationships within the lung with generation of more areas of low V/Q.[4]

We recently observed a case of methemoglobinemia that was associated with pulmonary congestion and respiratory distress in a postoperative cardiac surgical patient treated with iv nitroglycerin.

Report of a Case

A 55-year-old man, weighing 95 kg, had a diagnosis of severe atherosclerotic heart disease. He had suffered three prior myocardial infarctions during the period of 1978–1980 associated with congestive heart failure. His medications were nifedipine, 10 mg qid; isosorbide dinitrate, 10 mg qid; digoxin, 0.25 mg qd; and furosemide, 40 mg qd. He had a smoking history of 60 pack/years. Significant physical findings included an S-4 and a grade 2/6 systolic ejection murmur at the left sternal border. Cardiac catheterization revealed diffuse coronary artery disease with increased end-diastolic and end-systolic volumes associated with akinesia of the posterolateral, inferior, and apical portions of the left ventricle with an intraventricular clot. The left ventricular end-diastolic pressure (LVEDP) was 20–36 mmHg during the catheterization. For anesthesia he received fentanyl, 4 mg; diazepam, 10 mg; pancuronium, 20 mg, and O_2. The surgery included vein grafts constructed to the left anterior descending, right coronary, high lateral circumflex, and posteriolateral circumflex arteries. A left ventriculotomy was done to remove the ventricular clot. The patient received iv nitroglycerin throughout the procedure at a rate of 33–67 μg/min. Initial pulmonary capillary wedge pressure (PCWP) preinduction of anesthesia was 21 mmHg with a cardiac index of 1.56 $l \cdot min^{-1} \cdot m^2$. Following treatment with iv nitroglycerin, the PCWP decreased to 15 mmHg, and cardiac index increased to 2.7 $l \cdot min^{-1} \cdot m^2$. Following cardiopulmonary bypass, nitroprusside was required at 16–45 μg/min to maintain mean arterial pressure (MAP) 80–100 mmHg. These medications were continued for 25 h following surgery. Cardiopulmonary bypass was terminated with a left atrial pressure of 10–13 mmHg and a cardiac index (thermodilution) 2.2–2.7 $l \cdot min^{-1} \cdot m^2$. Ventilation was controlled the first postoperative night and the trachea extubated the next morning. His weight increased 5 kg from his preoperative weight. He then was given furosemide iv. He was hemodynamically stable, with left atrial pressure 20 mmHg, cardiac index 3.24 $l \cdot min^{-1} \cdot m^2$, mean arterial pressure 86 mmHg. Pa_{O_2} was 80 mmHg with an FI_{O_2} of 0.45.

The vasodilators were weaned slowly over the first postoperative day. By the evening of the first postoperative day, the patient had developed both rales and rhonchi in both bases of the lung and required an increase in FI_{O_2} to 0.6 in order to maintain a Pa_{O_2} of 65–74 mmHg. On the morning of the second postoperative day, the chest roentgenogram revealed bilateral areas of atelectasis and in-

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creased pulmonary vascular markings. He received additional doses of furosemide iv. His pulmonary artery catheter had been removed because of his continued hemodynamic stability. By midday, work of breathing was increasing and respiratory rate increased to more than 30 breaths/min. During this period (table 1), the FI_{O_2} was increased to 1.0, and continuous positive airway pressure (CPAP) (15 cmH_2O) via a mask was applied periodically then continuously at the patient's request. He felt it made his breathing easier. Despite a Pa_{O_2} of 72 mmHg, the patient had a dusky appearance peripherally. The chest roentgenogram revealed diffuse pulmonary congestion. The patient became diaphoretic, and after topical anesthesia the trachea was intubated. An intermittent mandatory ventilation (IMV) at a rate of 10 breaths/min with 15 cmH_2O PEEP and an FI_{O_2} of 1.0 was instituted. Despite a Pa_{O_2} of more than 200 mmHg, he remained peripherally cyanotic, and the diagnosis of decreased cardiac output state was considered. After reinsertion of a pulmonary artery catheter, the cardiac index was 2.85 $l \cdot min^{-1} \cdot m^2$ with a wedge pressure measured during controlled ventilation 24 mmHg. The arterial blood despite a high Pa_{O_2}, looked dark, and a sample was sent for co-oximetry (table 1). The methemoglobin level was 28%. The patient was treated with methylene blue, 100 mg iv, and the methemoglobin level decreased to 17%. An additional 100 mg of methylene blue was administered, and the methemoglobin level decreased to 1–2% (table 1). The clinical condition seemed to improve rapidly following treatment of the methemoglobinemia. The cardiac index increased from 2.8 to 3.5 $l \cdot min^{-1} \cdot m^2$. The pulmonary congestion and atelectasis resolved over the next 30 h. The trachea was extubated, and he was discharged from the cardiovascular intensive care unit.

TABLE 1. Respiratory Variables, Blood Gas Tensions, O_2 Saturation, and Per Cent Methemoglobin Immediately Prior to Endotracheal Intubation, prior to, and following Treatment with Methylene blue

	Before Intubation		After Intubation Before Methylene Blue	After Intubation After Methylene Blue
	Mask	Mask CPAP		
FI_{O_2}	1.0	1.0	1.0	1.0
CPAP/PEEP (cmH_2O)	0	15	15	15
Resp. rate (breaths/min)	34	34	10	10
pH_a	7.43	7.42	7.49	7.52
Pa_{CO_2} (mmHg)	41	41	36	35
Pa_{O_2} (mmHg)	50	72	205	113
% O_2 saturation (calculated)	89	95	100	96
% O_2 saturation (co-oximeter)	—	—	69	96
Per cent MetHgb	—	—	28.2	1.9
Per cent COHgb	—	—	2.1	1.9
Hgb (g/dl)	—	—	11	11

DISCUSSION

Although the clinical picture presented by this patient in the postoperative period is not unusual, it was associated with methemoglobinemia in a patient who had been treated with iv nitroglycerin. This was surprising for several reasons. First, this patient had taken isosorbide dinitrate, 10 mg qid, for at least 2 years without problems or history of cyanosis. Second, the total dose of nitroglycerin infused over the course of his 25-h period of exposure was 112 mg, well below the 5 mg/kg level defined as the maximally acceptable exposure to nitrates by the World Helth Organization. Third, he had not received the iv nitroglycerin for almost 16 h at the time the initial methemoglobin level was measured.

Methemoglobin (hemoglobin in which the iron of heme is oxidized to the ferric form) is produced as a side reaction in the normal course of hemoglobin oxygenation. This autooxidation of red blood cell hemoglobin produces 1–2% methemoglobin daily. This process is kept in balance by the action of methemoglobin reductase, which catalyzes the reduction of methemoglobin to hemoglobin. Methemoglobinemia may be the result of hereditary deficiency of this enzyme or the presence of hemoglobin M (a variant that when oxidized is not a suitable substrate for enzymatic reduction by methemoglobin reductase).[2,3,5] Although we were not able to test for either of these hereditary conditions, the patient had no history of persistent cyanosis preoperatively or postoperatively following his discharge from the Cardiovascular Intensive Care Unit. A number of chemicals and drugs can produce methemoglobin in excess of what the enzymatic reductive capacities are within the erythrocyte. Substances that can act as oxidizing agents include aniline dyes, nitrates, nitrites, nitrobenzene, amyl nitrate, phenacetin, acetaminophen, prilocaine, benzocaine, para-amino-salicylic acid, and sulfonamides.[3,6,7] Nitrates, in particular, nitroglycerin, are metabolized in the liver by nitrate reductase (glutathione dependent) to glyceral dinitrate and nitrite. The nitrite is thought to convert hemoglobin to methemoglobin. Glutathione is thought to protect against methemoglobin formation, provided that the pentose monophosphate metabolic pathways are functioning.[2,3]

Did the methemoglbinemia contribute to the generation of this patient's respiratory distress? Since methemoglobin cannot effectively transport O_2, it is "lost" hemoglobin. For example, in this case, the hemoglobin was 11 g%, and the methemoglobin concentration of 30% would result in a loss of 3.3 g%, leaving an effective circulating level of hemoglobin available for O_2 transport of 7.7 g%. This level of anemia would require an increase in cardiac index to ensure oxygen delivery in a compromised heart that would require higher filling pressures with higher pulmonary capillary hydrostatic pressures that would favor loss of fluid into the pulmonary interstitium.

Did the congestive failure cause the methemoglobinemia? With congestive heart failure, both hepatic and renal blood flow can be reduced. Since nitroglycerin is metabolized in the liver, metabolism would be reduced, and since nitroglycerin is lipid soluble, it would accu-

mulate in body fat. The metabolites of nitroglycerin are glyceral dinitrate and nitrite, both water soluble and excretable in urine.[2] However, with decreased urine production both metabolites would remain in the body for a longer period of time. This may explain the high level of methemoglobin found despite discontinuation of the nitroglycerin almost 16 hours earlier.

This patient's clinical condition seemed to respond and improve with the treatment of the methemoglobinemia with methylene blue. Methylene blue is 3,9-bisdimethylaminophenazothionium chloride. In low concentrations, the reduced form of methylene blue speeds the conversion of methemoglobin to hemoglobin, and the NADP-dependent methemoglobin reductase can regenerate reduced methylene blue from oxidized methylene blue.[3,8] The increase in O_2 transport associated with the increase in functional hemoglobin following treatment with methylene blue may have been responsible for the improvement in the patient's clinical condition.

In conclusion, we present a case of methemoglobinemia complicating the postoperative period of a patient following cardiac surgery who was exposed to iv nitroglycerin therapy. The methemoglobinemia occurred in association with respiratory distress secondary to pulmonary congestion. Whether the methemoglobinemia was a causal factor in the generation of the respiratory distress is unknown; however, treatment of the methemoglobinemia seemed to enhance recovery.

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Clinical Advantages of Fentanyl Given Epidurally for Postoperative Analgesia

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The analgesic effect of epidurally administered narcotics is well documented.[1–4] The various possible mechanisms of action include systemic absorption, medullary fixation, and cephalad diffusion via the cerebral spinal fluid. These factors may be a determining factor in the relative importance of side effects, in particular, respiratory depression.[5] The action of fentanyl given epidurally is rapid, intense, and of short duration.[6,7] However, the role played by systemic absorption on the respiratory effect from this analgesic technique, is unknown. The present study was designed to examine the analgesic effects, plasma concentrations, and ventilatory consequences of an injection of the same dose of fentanyl given epidurally or intramuscularly in random sequence and in the same subjects for postoperative pain relief.

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Materials and Methods

This study was conducted with the informed consent of 11 patients who had undergone an abdominal or thoracic surgery. In these subjects, the indication for analgesia was determined by the presence of pulmonary disease sufficient to require intense and rapid respiratory physiotherapy. All patients were anesthetized with flunitrazepam, fentanyl, and pancuronium iv. All patients had radial artery and epidural catheters inserted, the latter at the end of surgical intervention. The day after