Phenacetin-induced Methemoglobinemia and Renal Failure

JAMES L. EASLEY, M.D.,* AND BRIAN F. CONDON, M.D.

The incidence of methemoglobinemia in surgical patients is unknown, but it may be more common than suspected. Joseph reported ten cases of methemoglobinemia discovered in a three-year period, either preoperatively or intraoperatively.\(^1\) Nine of these were secondary to phenacetin. We present a case in which phenacetin-induced methemoglobinemia not only caused cyanosis but reached potentially lethal levels.

REPORT OF A CASE

A 43-year-old woman with metastatic cervical carcinoma was scheduled for a colostomy because of bowel obstruction. She had no previous history of cardiac, pulmonary, renal, or hepatic disease. Her medications included dihydrohydroxycodeineone (Percodan), prochlorperazine, and phenazopyridine (Pyridium). Preoperative physical examination revealed that the patient was extremely cachectic. No cyanosis was noted. Laboratory data revealed a hematocrit of 30 per cent, a BUN of 20 mg/100 ml, and a normal chest roentgenogram.

One hour preoperatively the patient received diazepam, 10 mg, intramuscularly. Upon arrival in the operating room, she appeared in no distress. Anesthesia was induced with sodium thiopental, 200 mg, and endotracheal intubation was facilitated with d-tubocurarine, 12 mg. Anesthesia was maintained with enflurane and oxygen, with controlled ventilation. Immediately following incision of the skin, the blood was noted to be extremely dark. However, the patient appeared in no acute distress. The blood pressure was 100/60 mm Hg, pulse rate 80/min, and breath sounds were present bilaterally. An arterial blood sample which appeared extremely desaturated was obtained. Analysis revealed \(P_{\text{aO}_2}\) 450 torr, \(P_{\text{aCO}_2}\) 35 torr, \(pH\) 7.47. A diagnosis of methemoglobinemia was entertained, and a potassium cyanide spot test for methemoglobin was positive.\(^2\) Spectrophotometric studies done within an hour revealed 13 per cent methemoglobin. This percentage does not significantly decrease oxygen-carrying capacity; therefore, no treatment was instituted.

\(\text{\textsuperscript{*} Second-year Resident.}\)
\(\text{\textsuperscript{†} Assistant Chief.}\)
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The etiology of the methemoglobin was investigated postoperatively. Initially, phenazopyridine was thought to be the offending agent. However, the blood level of methemoglobin increased to 30 per cent four days after this drug was discontinued. It was then realized that the patient was also consuming 2–3 g phenacetin daily, contained in the dihydrohydroxycodeineone tablets, which were also discontinued. Complicating the excretion of phenacetin was the fact that the patient had developed oliguric renal failure secondary to bilateral ureteral obstruction. Four days after phenacetin was discontinued, methemoglobin had increased to 60 per cent. The patient then became confused and cyanotic; pulse rate was 160/min and respiratory rate, 40/min. Treatment with methylene blue, 80 mg, brought relief of symptoms and a reduction of the methemoglobin level to zero.

DISCUSSION

Methemoglobin is hemoglobin in which the normal ferrous ion of heme is in the ferric state. The ferric ion is unable to bind molecular oxygen; thus, oxygen-carrying capacity is directly decreased. The intracellular environment of hemoglobin is such that some oxidation of the heme iron to the ferric state occurs normally. The concentration of the ferric ion, however, does not exceed 2 per cent because of the reducing capacity of the enzyme NADH–methemoglobin reductase. Abnormal levels of methemoglobin occur secondary to both hereditary and acquired disorders. Hereditary causes are rare, and include deficiency of the reducing enzyme, NADH–methemoglobin reductase, and a hemoglobinopathy, HgM. In the homozygous state a severe deficiency of the enzyme NADH–methemoglobin reductase is found, and methemoglobin levels may be as high as 20 to 40 per cent. A moderate reduction of this enzyme occurs in the heterozygous individual and also in normal neonates.\(^3\) In these cases the methemoglobin percentage is not increased without the stress of abnormal exposure to oxidants. Hemoglobin M is caused by alterations in the globulin structure of hemoglobin which change the
CLINICAL WORKSHOP

Acquired methemoglobinemia occurs on exposure to drugs or chemicals which increase the rate of oxidation beyond the reductive capacity of the erythrocyte. Common oxidizing agents include aniline dyes (crayons, shoe polishes), nitrates (well water), higher oxides of nitrogen gases, and nitrobenzene. Commonly used oxidizing medications causing methemoglobin include amyl nitrite, phenacetin, acetaminophen (Tylenol), prilocaine, benzocaine, para-aminosalicylic acid, dapsone, chloroquine, sulfonamides, and phenazopyridine. Unlike most drugs, phenacetin causes methemoglobinemia in therapeutic doses, and is the most frequent cause seen clinically. Phenacetin is metabolized in the liver, and the minor metabolites responsible for producing methemoglobin are then excreted in the urine. Therapeutic doses of phenacetin can produce only 3–5 per cent methemoglobin in the normal person. Levels high enough to produce cyanosis (10 per cent) are seen in persons who have individual variations in the metabolism of phenacetin to form greater amounts of the toxic metabolites. This not-uncommon trait is the primary cause of phenacetin-induced methemoglobinemia. Elevated methemoglobin levels secondary to phenacetin can also be seen in heterozygotes for NADH–methemoglobin reductase. The NADH–methemoglobin reductase level in our patient was normal as measured by the technique described by Hegesh. Initially, the increased methemoglobin level was probably secondary to abnormal metabolism of phenacetin. This resulted in methemoglobin levels that produced cyanosis but did not significantly decrease oxygen transport. With the onset of renal failure, the toxic metabolites accumulated, with resultant lethal levels of methemoglobin.

Although one dose of methylene blue was adequate to reduce this patient's methemoglobin to zero, repeated doses may be necessary in such cases. However, doses of methylene blue should not exceed 7 mg/kg, since in excessive amounts methylene blue will oxidize hemoglobin to methemoglobin.

In summary, methemoglobinemia is uncommon, yet almost every anesthesiologist is likely to encounter it. Phenacetin is usually the causative agent. The affected patient has asymptomatic cyanosis; the disease is rarely associated with serious morbidity. However, when phenacetin ingestion and abnormal metabolism are complicated by renal failure, a life-threatening condition may develop.

REFERENCES