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Prilocaine-induced Methemoglobinemia in a Newborn Infant

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The differential diagnosis of cyanosis in the postoperative period includes all causes of reduced hemoglobin, usually focusing on causes of a reduced Pa_{O_2}. Disorders of hemoglobin as a cause of cyanosis are relatively rare, are usually limited to defined abnormalities of the hemoglobin molecule or the metabolic pathways of the erythrocyte, and are usually known to exist in a given patient before surgery. The following case report illustrates a physiologic abnormality occurring in the newborn that may have implications to administration of anesthetic drugs.

REPORT OF A CASE

A 4.8-kg, 6-week-old girl presented for an elective repair of a unilateral cleft lip and anterior palate. She was the product of a normal pregnancy with delivery at 41 weeks and no other abnormalities noted at birth. The infant's mother was totally healthy, but her single status prohibited historic investigation of the father. Because the child was being placed for adoption, she remained institutionalized pending repair of the facial defect. Diet was by standard cow's milk formula, and the only medication she was given was a multivitamin preparation (vitamins A, D, and C).

On day 43 after delivery, an elective repair of the lip and palate was performed. Preoperative cultures were normal, and the preoperative hemoglobin was 15.3 g/dl. After a 6-hr fast and preoperative atropine 0.10 mg i.m., anesthesia was induced with halothane with 50% N_2O via a mask. The trachea then was intubated with a 3.5-mm oral tracheal tube after the administration of 10 mg iv succinylcholine. Anesthesia was maintained with halothane and 50% N_2O delivered from a Jackson-Reese T piece. To reduce bleeding, the surgeon infiltrated the surgical site with 0.8 ml 4% prilocaine (Citanest®) with 1:200,000 epinephrine, then placed a throat pack after the gag was positioned. The surgical procedure was uneventful, with a total blood loss of 5 ml. Replacement of intravascular volume with 0.3% saline in 5% dextrose restored the fasting deficit. After the procedure was completed and laryngoscopy revealed adequate hemostasis, the trachea was extubated while the child was awake. Postoperative rectal temperature was 37.2° C. The total anesthetic exposure was 90 min.

The initial recovery period was stable, the child having normal skin color. After approximately 1 hr, the infant was pale and progressively more cyanotic. Resting respiratory rate was 35 min^{-1}, with no evidence of distress. Results of a chest roentgenogram were normal, while analysis of arterial blood gases revealed a Pa_{O_2} 74 mmHg, Pa_{CO_2} 40 mmHg, pHa 7.35, and HCO_3^- of 21.5 mEq/dl (F_iO_2 = 0.21). Systolic blood pressure was 90 mmHg, heart rate 176 beats/min, and no evidence of further bleeding was noted. Repeat hemoglobin was 13.1 g/dl. As the cyanosis progressed and did not improve with increasing the F_iO_2, a methemoglobin level was found to be 35.7% (6 hours after prilocaine administration). Because the infant was stable with no demonstrable acidosis, no specific therapy was administered. The methemoglobin level 22 h after surgery was 8.3%. The subsequent course of the child was uneventful, and she was discharged in satisfactory condition 10 days postoperatively.

Blood subsequently was obtained from the baby at 4 months of age for red blood cell enzyme analysis and hemoglobin electrophoresis. All values were normal for the child's age, including NADH diaphorase levels, 6-phosphogluconate dehydrogenase, glucose-6-phosphate dehydrogenase, and glutathione reductase levels.

DISCUSSION

Methemoglobinemia from administration of prilocaine is not a new phenomenon—indeed, the side effect is reported in the product monograph. The oxidation of normal hemoglobin to methemoglobinemia is the result of 0-Toluidine, a hepatic-derived metabolite of the drug. This dose-related phenomenon has been reported to give detectable methemoglobin levels (greater than 5%) only following doses of prilocaine greater than 8 mg/kg. While the time course of the appearance of cyanosis in our patient corresponded to the expected appearance of this metabolic product, the level of methemoglobin achieved is far in excess of that anticipated after 32 mg (6.7 mg/kg) of prilocaine.

Methemoglobin is produced by oxidation of hemoglobin during the process of erythrocyte aging and is present normally in a constant amount in the blood. The stable equilibrium between hemoglobin and methemoglobin is maintained by the action of enzymatic reducing systems within the erythrocyte. The major portion of methemoglobin reduction depends upon the action of the NADH-dependent diaphorase, the concentration of which is determined genetically. Patients homozygous for congenital methemoglobinemia demonstrate an elevated concentration of methemoglobin and compensatory polycythemia, while asymptomatic carriers have an intermediate deficiency of the enzyme but a propensity to develop methemoglobinemia upon exposure to oxidants. Congenital predisposition to hemoglobin oxidation also may exist as a consequence of erythrocyte NADH deficiency, or because of congenital

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abnormalities of the hemoglobin itself (hemoglobin M disease). Erythrocytes of individuals with primaquine sensitivity, or hereditary deficiency of glucose 6-phosphate dehydrogenase (G6PD), exhibit a decrease of NADH. However, the normal measured level of diaphorase, normal G-6-PD levels, and normal hemoglobin characterization in our patient excludes a hereditary predisposition to hemoglobin oxidation. While the normal level of NADH diaphorase measured at 4 months of age excludes a familial tendency to methemoglobinemia, it does not rule out a transient deficiency present at the time of surgery but recovered by 4 months of life.

The erythrocyte of the newborn infant metabolically is very different from that of the adult. The glycolytic rate appears to be increased, and the activity of the enzymes, such as glucose-6-phosphate dehydrogenase, 6-phosphogluconic dehydrogenase, aldolase, hexokinase, phosphoglyceric acid kinase, and pyruvate kinase, may be elevated. The activity of certain other erythrocyte enzymes is decreased, including cholinesterase, carbonic anhydrase, and catalase. Umbilical cord blood shows a reduction of NADH methemoglobin reductase to levels of 40–60% of normal, with slow return to normal values in the first 3 months of life.[2] The blood of premature infants generally has a higher methemoglobin concentration than that of term infants, and they are more susceptible to the development of methemoglobinemia upon exposure to aniline dyes[3] and other oxidants.[4] In addition to the documented deficiency of NADH diaphorase activity, fetal hemoglobin may have an increased susceptibility to oxidation.[5]

The diagnosis of methemoglobinemia rests upon exclusion of other cardiac or pulmonary diseases, then directly measuring the methemoglobin concentration. Often the slate-gray cyanosis in methemoglobinemia is entirely out of proportion to the severity of the hypoxic symptoms. The sequelae of methemoglobinemia result from the reduced oxygen-carrying capacity and tissue hypoxia. Clinical cyanosis occurs with methemoglobin concentration below 5%, but concentrations of 25–30% often are tolerated well. Early symptoms of hypoxia (headache, exercise intolerance, irritability) occur as concentrations approach 35–40% and depression of consciousness occurs at 50–60%. Fatalities resulting from toxic drug reactions have been reported.[6] Because symptoms result from reduced oxygen delivery, the clinical manifestations at a given percentage of methemoglobin concentration will vary, depending on other factors present in a given patient (anemia, reduced cardiac output, hypoxemia, *etc.*). Because many of these factors affecting oxygen delivery are impaired postoperatively, the concentration ranges above must be extrapolated to the surgical patient with caution.

The management of methemoglobinemia depends upon identifying and removing possible oxidants and defining the patient's susceptibility to hypoxia (clinical symptoms, presence of acidosis, and presence of confounding anemia or cardiopulmonary disease). In most cases no treatment is required. However, in the presence of any indication of tissue hypoxia, 1–2 mg/kg of methylene blue can be administered iv as a 1% solution in saline. This usually reduces the methemoglobin concentration to less than 1% within an hour. The only side effect of 1% methylene blue is blue urine. Higher concentrations of methylene blue may produce an oxidant-mediated hemolytic anemia directly and should be avoided. Failure of methylene blue treatment of methemoglobinemia should suggest the presence of G6PD deficiency and may require exchange transfusion.

In conclusion, a case of methemeglobinemia occurring postoperatively in a newborn infant after an "acceptable" dose of prilocaine has prompted an evaluation of the infant's physiologic susceptibility to hemoglobin oxidation. Physicians administering known oxidants should be familiar with the reduced methemoglobin reductase (diaphorase) concentration of the newborn.

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