Case Report

Methylene-blue-induced hemolytic anemia in a neonate

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Transabdominal intra-amniotic injection of dye to diagnose premature rupture of fetal membranes was first reported in 1970.[1] This technique has also been used to stain the amniotic fluid in twin pregnancies in order to identify fluid from two separate amniotic sacs.[2] Of the many dyes available, methylene blue has been widely used, although it has been associated with complications such as Heinz-body anemia and hyperbilirubinemia in the fetus and the newborn infant.[3,4]

We report a case in which a newborn, the first of twins, had Heinz-body anemia and hyperbilirubinemia after an intra-amniotic injection of methylene blue. We also review previously reported cases of neonatal complications of this procedure.

Case report

A healthy 27-year-old woman in her third pregnancy underwent ultrasonography at 10 weeks' gestation and was found to have twins. At 32 weeks' gestation repeat ultrasonography showed that one twin was growing poorly, and delivery before term was therefore believed necessary. Amniocentesis to determine fetal lung maturity was performed at 38 weeks' gestation. The sac of the first twin was entered, amniotic fluid was obtained, and less than 50 mg of methylene blue was injected. The sac of the second twin was then entered, and the withdrawal of colourless fluid confirmed that the sac was separate from that of the first twin. Since the phosphatidylglycerol concentration in the amniotic fluid from both sacs suggested lung maturity, the infants were delivered by means of cesarean section 26 hours later.

At birth the first twin weighed 2440 g, and her skin was stained blue. Her Apgar scores were 7 at 1 minute and 8 at 5 minutes. Mild respiratory distress and two brief spells of bradycardia were noted during the first 36 hours after birth; however, the more serious problems were marked hyperbilirubinemia and Heinz-body anemia.

The total serum level of bilirubin rose to a maximum of 16.1 mg/dl (275 μmol/L) by 58 hours after birth and then gradually decreased over the next 2 weeks. The infant was treated with phototherapy from 2 to 12 days of age, and no exchange transfusion was required. The capillary hemoglobin level decreased from 142 g/L at birth to 102 g/L by day 3; the proportion of reticulocytes was 11.4% at 4 days of age. At 3 and 15 days of age she received packed erythrocyte transfusions for anemia. Investigations ruled out blood-group incompatibilities, infection, erythrocyte enzyme disorders, hemoglobinopathy, spherocytosis and metabolic diseases as causes of the hyperbilirubinemia.

The infant was discharged home at 24 days of age; the hemoglobin level was 109 g/L, and the proportion of reticulocytes was 1.2%.

At birth the second twin weighed 1440 g, and her skin was not stained blue. The peak total serum level of bilirubin was 12.4 mg/dl (212 μmol/L), and the capillary hemoglobin level decreased from 163 g/L at birth to 125 g/L by day 4.

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She did not require exchange transfusion, and a blood smear showed no hemolysis. She had a severe defect of both legs, only femoral stumps being present.

Discussion

We found five reports of complications after the intra-amniotic injection of methylene blue in doses ranging from 3.2 to 58.8 mg/kg.[4-8] Three infants each required two exchange transfusions to correct marked hyperbilirubinemia,[5-7] and in our case the infant required two transfusions to correct anemia. One infant received only 3.6 mg/kg of methylene blue but had marked hyperbilirubinemia and hemolysis.[5]

Jaundice was present in all the infants, peaking an average of 4 days after methylene blue was injected. In our case jaundice was detected within 36 hours of birth and peaked at 3.5 days of age. The hemoglobin level or hematocrit decreased in all the infants in whom it was assessed, and blood smears generally showed hemolysis. The hemolytic process continued in some newborns for as long as 10 days after the injection of methylene blue.[7] The number of Heinz bodies was elevated in our affected infant and in four newborns who had received methylene blue *after* birth.[3,9] The methemoglobin levels were elevated in two infants[7,8] and were normal in one.[4]

Erythrocytes are constantly exposed to oxidizing agents. These agents attack either the cell membranes, causing hemolysis, or the hemoglobin, resulting in the formation of sulfhemoglobin and Heinz bodies, which contribute to hemolysis. To prevent this, superoxide dismutase in erythrocytes produces hydrogen peroxide from activated oxygen; the hydrogen peroxide is then detoxified by reduced glutathione to water and oxidized glutathione.[10]

When methylene blue enters an erythrocyte it is rapidly converted to leukomethylene blue, which produces hydrogen peroxide.[3] When the concentration of methylene blue is high, hydrogen peroxide is produced in quantities that overwhelm the erythrocyte's ability to detoxify it.

Because serious complications have occurred and dangerous procedures like exchange transfusion have been required in newborns who were given as little as 3.6 mg/kg of methylene blue, we recommend that a safer dye, such as Evans blue,[1] be used for diagnosis in obstetric and neonatal practice.

References

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The price to pay

The poorest man would not part with health for money, but the richest would gladly part with all their money for health.

— Charles C. Colton (1780?-1832)