Methylene Blue–induced Phototoxicity: An Unrecognized Complication

Rachel Porat, MD‡; Steve Gilbert, RPh§; and David Magilner, MD‡

ABSTRACT. Objective. To describe photosensitization after prenatal exposure to a toxic amount of methylene blue and to alert pediatricians that, in a review of the literature, photosensitization (which this dye is capable of) has not been reported as a complication of prenatal exposure.

Design and Patients. A descriptive report of physical findings and significant laboratory tests in a very low birth weight preterm infant with prenatal exposure to methylene blue and a comparison of this reported case with previously described patients' complications and treatment.

Setting. Neonatal intensive care unit.

Intervention. Monitoring of laboratory tests to assess for methylene blue toxicity: two exchange transfusions for methemoglobinemia, hemolytic anemia, and hyperbilirubinemia; phototherapy for hyperbilirubinemia; and pathologic examination of skin bullae.

Results. Within hours of exposure to phototherapy, redness developed on all exposed areas of the patient's skin (which was initially deep blue), followed by bullae and desquamation of about 35% of the total skin surface area. The desquamation of erythematous areas continued even after discontinuation of phototherapy. Complete re-epithelialization was attained by 3 weeks of age. In addition to this newly observed complication, the patient had other previously described toxic effects.

Conclusion. We have reported a previously unrecognized complication associated with high prenatal exposure to methylene blue and treatment with phototherapy. Methylene blue phototoxicity may be related to the high prenatal dose of the dye relative to the patient's small size and young gestational age. Pediatrics 1996;97:717-721; methylene blue, complication of phototherapy, phototoxicity.

Complications related to prenatal exposure to methylene blue in neonates include Heinz body hemolytic anemia,5-7,10 hyperbilirubinemia,5-10 methemoglobinemia,4,7,9 respiratory distress,5-4,6,9 and varying degrees of skin staining, which may interfere with clinical assessment and pulse oximetry.8 These reports are mostly the result of prenatal exposure to the dye used either to detect an amniotic fluid leak or to differentiate sacs of twins during assessment for lung maturity.1-4,6-9 In addition, few reports have described hemolytic anemia and hyperbilirubinemia after postnatal use of methylene blue.5,10 Phototherapy is used to treat the hyperbilirubinemia,5,4,6-9 and occasionally an exchange transfusion is required.2,4,7 No complications related to the use of phototherapy were noted in previous reports, except for the mention of possible photosensitization or methylene blue–induced necrosis of skin.10 This recent report describes two full-term neonates, exposed postnatally to methylene blue, in whom bullae and desquamation developed; this involved the hands in one infant and the chest in the other. The authors raised the possibility that either methylene blue photosensitization or its necrosing characteristics contributed to the desquamation observed.

This report describes a very low birth weight infant, exposed prenatally to a very large dose of methylene blue, in whom a severe phototoxic reaction, confirmed by biopsy, developed. We also compare the dose administered to and the treatment, complications, and outcome of this infant with those previously described in the literature.

CASE REPORT

A 1090-g girl was born at 27 weeks' gestation to a 34-year-old black mother, gravida 6, para 2, admitted to the hospital with contractions and a history of probable rupture of membranes for 2 to 3 days. The mother had an elevated temperature (38.7°C) and an elevated white blood cell count (16 300). She was treated with antibiotics and tocolytics, but her labor progressed. Nitrazine and ferning tests were inconclusive; therefore, amniocentesis was performed to determine whether the amniotic fluid was infected and whether the membranes were ruptured. Amniotic fluid was drawn for Gram stain, and 10 mL of 1% methylene blue was injected into the amniotic cavity. Blue fluid in the vagina confirmed rupture of membranes. The Gram stain of the amniotic fluid revealed Gram-negative rods (culture results, positive for Escherichia coli), and labor was augmented with pitocin. Nine hours after the dye injection, a cesarean section was performed because of hand presentation of the fetus. At birth, the infant was deeply blue stained except for small areas under the chin and the inguinal folds (Fig 1). These areas gradually became blue by the next day. The urine remained bluish tinged for 6 days. At birth, she required intubation and ventilation and was assigned Apgar scores of 2 and 7 at 1 and 5 minutes, respectively. Her vital signs, perfusion, and activity were normal. The white blood cell count and differential were not indicative of sepsis.

The infant required double-volume exchange transfusion twice; the first was at 9 hours of age for rising levels of methemoglobin (from 4.9% to 7.8%) and severe hemolysis, which caused a rapid drop in hematocrit (from 37.4% to 29.3%; Table 1). The blood type of both mother and infant was O positive. A glucose 6-phosphate dehydrogenase test was normal. The second exchange, at 80 hours of age, was performed because of ongoing hemolysis and rising bilirubin levels. After the first exchange, as bilirubin levels were rising, phototherapy was instituted (16th hour of life). Within a few hours, a gradual change of skin color was noted from dark blue to red and maroon in all phototherapy-exposed areas. Several hours later, vesicles appeared on the wrists, feet, and anterior axillae. Tzanck preparation and viral cultures of the areas were negative. Pathologic examination revealed marked spongiosis of the mid-epidermis with degenerative keratinocytes of the basilar to mid-portion of the epidermis, indicating a phototoxic reaction;
Fig 1. Photograph of the infant shortly after birth. Her skin is stained deeply blue except for areas in the inguinal folds and under the chin (see "Case Report").

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* Total and direct.
† E-T indicates double volume-exchange transfusion; Photo, phototherapy.
‡ Percentage of total Hg.

therefore, phototherapy was discontinued (48 hours of life). All areas exposed to phototherapy—parts of the face, chest, abdomen, and anterior surfaces of all extremities, an estimated 35% of total body surface area—eventually blistered and desquamated (Fig 2). Skin sloughing and superficial and partial thickness continued for a few days, followed by re-epithelialization. In addition to management of extreme prematurity, the patient required meticulous skin care, consisting of topical antibiotics and dressing changes twice daily in a sterile environment. By 3 weeks of life, all areas had healed well except for a small area in the center of the chest, which had a deeper slough. This area eventually healed with no scarring. At discharge, several areas of depigmentation were noted on the abdomen and extremities (Fig 3). At that time the infant was 87 days old and weighed 2.86 kg. Follow-up visits reveal an adorable, active, alert female infant with normal neurodevelopmental status at 11 months and no change in skin status.

DISCUSSION

Shortly after delivery, this low birth weight infant developed all the complications that have been previously described after a methylene blue overdose: methemoglobinaemia, hemolytic anemia with a precipitous drop in hematocrit, and rising bilirubin levels requiring exchange transfusion twice. Although maternal E coli chorioamnionitis and possible neonatal sepsis could contribute to hemolysis, it probably was not a major factor in this case, because: (1) sepsis would not cause the methemoglobinemia; and (2) the infant was not clinically septic, and cultures were negative for bacterial growth.

Our patient presented with respiratory distress and required ventilator support. It is difficult to determine whether the respiratory distress was related to the methylene blue, as has been suggested by some reports. In our patient, it is more likely that the respiratory problem was related to prematurity and respiratory distress syndrome. Most infants with methylene blue-induced toxicity have been described as having various intensities of bluish stained skin, thought to be a result of systemic absorption of the dye. However, because the areas under the chin and inside the inguinal folds were not stained at birth in our patient (Fig 1), we think that some or most of the initial deep blue skin staining was caused by direct absorption of the dye into the epidermis. These areas were not in contact with the intra-amniotic dye because of the marked body flexion of the fetal position. However, by the next day, these areas gradually became blue (Fig 2), probably because of systemic distribution of methylene blue absorbed enterically.

The early onset and the severity of this infant's toxic reaction were likely caused by the relatively high dose per kilogram of methylene blue to which this infant was exposed. Our patient continued to...
Fig 2. Photograph of the infant at 5 days of age. Extensive redness, bullae, and excoriation of skin in the areas exposed to phototherapy are shown. [Note that areas in the inguinal folds and under the chin gradually became blue (see “Case Report”).]

Fig 3. Photograph of the infant before discharge. Her skin healed well, with several areas of depigmentation on her abdomen and legs.

have bluish tinged urine for 6 days, indicating a very large amount of dye swallowed from the amniotic fluid and absorbed systemically via the gastrointestinal tract. Most reports describe the drop in hematocrit occurring usually at 3 to 7 days and bilirubin levels peaking at 2 to 5 days. In our case, the hematocrit dropped from 37.4% to 29.3% in the first 8 hours of life (Table 1).

In the original communication regarding the use of dye as an amniotic fluid leak marker, Atlay and Sutherst\textsuperscript{11} suggested using Evans blue, which is probably innocuous in the newborn, because it has been used for measurement of blood volume.\textsuperscript{2} However, its use was brief, and instead, physicians used methylene blue, which was readily available.\textsuperscript{1,2} Methylene blue is visible at very low concentrations. Thus, it was suggested that using 5 mL of a dilute solution made by 1.0 mL of the 1% methylene blue in 30 mL of saline (to contain 1.6 mg only) was satisfactory for confirming the presence of rupture of membranes without causing hemolysis.\textsuperscript{1}

Table 2 summarizes all reported cases of methylene blue toxicity as a result of both prenatal\textsuperscript{1,4-9} and postnatal\textsuperscript{5,10} administration. As noted, the infant in this report is the second smallest survivor in terms of birth weight and gestational age. However, she was exposed to the largest amount of methylene blue per weight when compared with all previous cases.

Methylene blue, a tetramethylthionine chloride dye, is used in small doses (1 to 2 mg/kg) to treat methemoglobinemia by hastening the conversion of methemoglobin to hemoglobin.\textsuperscript{12} In a large dose it has the opposite effect and oxidizes hemoglobin, which results in methemoglobinemia.\textsuperscript{4,7,9,12}

Methylene blue is a photosensitizing compound.\textsuperscript{13} It is polycyclic, with a planar ring structure.\textsuperscript{12} A compound with this structure has the capacity to absorb a tremendous amount of energy. The amount of energy absorbed is directly proportional to the concentration of the substance.\textsuperscript{14} The wavelength of light needed to photoactivate a compound is dependent on the absorption spectrum of the compound, with the greatest amount of energy absorbed at the peak absorbance wavelength. The peak absorption of methylene blue is at 665 nm, which is within the light spectrum emitted by the phototherapy units, (radiance up to 700 nm).
Photosensitivity reactions involve the absorption of light energy by a compound, followed by the release of energy into the surrounding tissues. These photon-absorbing compounds are termed chromophores. After a photon is absorbed, a chromophore will go from its normal energy state (ground state) to an elevated (excited) energy state, which is unstable and short lived. While the energy source is present, the chromophore molecules are in a continuous loop of being raised to an excited state, with a subsequent return to the ground state and release of the absorbed energy. On removal of the energy source, the chromophore returns to its ground state. The energy can be released as heat, or it can be transferred, as a free electron, to a bystander molecule or molecular oxygen to form superoxide $\text{O}_2^{-}$. The formation of this highly reactive species results in significant local tissue destruction. 

Cell damage induced by photo-activated methylene blue seems to be related to three distinct mechanisms, depending on its location. First, the dye can cause structural damage to the cell membrane by superoxide formation, which will further enhance entrance of the dye into the cell. Once inside the cell, methylene blue can localize in subcellular structures such as lysosomes and result in their damage. Finally, the dye associates with nuclear DNA. Locally produced superoxide ions damage DNA and interfere with its functions.

The clinical presentation is manifested initially as edema and erythema of the skin, which resemble a sunburn, followed by the formation of bullae, which eventually will desquamate over several days.

In addition to its photoactivated epidermal effects, methylene blue is also known to cause tissue necrosis in adults, involving direct damage to both connective and vascular tissue. It seems that tissue necrosis did not contribute to our patient’s skin changes, because only the phototherapy-exposed areas were involved, and the rest of the blue skin remained intact and gradually achieved a normal appearance.

Additional tissue complications resulting from the use of methylene blue involve the gastrointestinal tract, which may be particularly sensitive in fetuses and neonates. A high incidence of multiple jejunal and ileal atresia was reported as a result of intraamniotic methylene blue injected as a marker during genetic amniocentesis in twins. We have added photosensitivity to the list of reported complications of methylene blue toxicity.

In light of a recent report describing significant complications and fatalities related to postnatal methylene blue overdose, we think it is important not only to alert obstetricians but to caution pediatricians and pediatric surgeons of the proper dosing and potential toxicity of methylene blue.
ACKNOWLEDGMENTS

We thank Frederick M. Henretig, MD, Laura Gealt, RN, MSN, CPNP, and the staff of the Philadelphia Center of Poison Control for providing helpful information and their continued interest and support in this case.

REFERENCES


A MARKETING TOOL

...the spread of extracorporeal membrane oxygenation (ECMO) is not entirely in the hands of the physicians. For example, the May 1990 issue of America West Airlines Magazine contained an ad by the Board of City Development of a Southwest city with the headline: 'Our ability to save struggling newborns with an ECMO Unit makes [our city] one of the healthiest medical communities in the nation.'

Use of ECMO as a marketing tool in a highly competitive health-care system makes its proper diffusion a much more complex problem.


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