This case report describes a preterm newborn infant who was treated with a single dose of rasburicase for an increase in uric acid level. He died on the third day as a result of complications of hemolysis, which appeared to be precipitated by rasburicase. The patient’s death was preceded by progressive respiratory insufficiency, lactic acidosis, and hyperbilirubinemia, culminating in refractory hypoxia and hypotension. A postmortem assay for glucose-6-phosphate dehydrogenase showed deficiency and the glucose-6-phosphate dehydrogenase Mediterranean genotype. *Pediatrics* 2013;131:e309–e312
Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked disorder and its most common clinical manifestations are neonatal jaundice and acute hemolytic anemia, triggered by an exogenous agent. Most individuals remain asymptomatic throughout their lives, but if they develop neonatal jaundice or hemolytic anemia, then death or permanent neurologic damage may occur. This report concerns the lethal effect of an oxidative drug (rasburicase) administered to reduce the uric acid level in a preterm newborn with G6PD deficiency. This case report shows that caution is needed when considering the risk-benefit ratio of exposing patients to this drug.

**PATIENT PRESENTATION**

A newborn male infant was born at 30 weeks’ gestational age, 2012 g birth weight, by cesarean delivery because of placental abruption in a 29-year-old white female. Umbilical artery blood gas analysis showed normal values. The Apgar score was 3 at 1 minute and 7 at 5 minutes. The infant presented with hypotonia, cyanosis, apnea, and bradycardia. He was dried, his airway was suctioned, and he was stimulated and ventilated after 30 seconds with a laryngeal mask for ~3 minutes. Free-flow 0₂ was administered. Oxygen saturation was 95% to 96%, heart rate was 120 beats per minute, and grunt ing and tachypnea were reported. He was moved to a tertiary-level NICU with a diagnosis of worsening respiratory distress in a preterm infant. Physical examination on admission to the NICU (first hour of life) revealed spontaneous breathing with 0₂ supplementation, flaring of the ala nasi, thoraco-abdominal asynchrony, and poor perfusion. The infant was intubated, administered surfactant intratracheally, and ventilated mechanically; antibiotics were started (gentamicin 10 mg every 24 hrs and ampicillin, 100 mg every 12 hrs intravenously), although blood culture remained negative. Urine output was 0.9 mL/kg/h and a single dose of rasburicase (Fasturtec) was administered in the 33rd hour of life because of a uric acid level of 6.67 mg/dL and a brief period of oliguria. By the 84th hour, the boy’s bilirubin suddenly increased, so phototherapy was begun and intravenous immunoglobulin was administered; nonetheless the bilirubin level remained at 18.3 mg% for 7 hours. Hematocrit dropped to 28% in the 79th hour; and 22% in the 83rd hour. Nurses reported 84% 0₂ transcutaneous saturation in the 77th hour; and capillary blood gases showed mixed acidosis and low 0₂ saturation. In the 80th hour, vecuronium was administered and high-frequency ventilation was started with a fraction of inspired oxygen of 1. On admission, fraction of inspired oxygen was 0.6 and it had stabilized at 0.3. Dopamine, which was stopped at 48 hours, was resumed and dobutamine was added. Blood electrolytes and gases were urgently conducted and a unit of packed red blood cells was ordered but the patient died before it could be administered. The nursing diaries recorded a bronze skin color and dark urine, which may be a sign of urine hemoglobin (Hb) or bilirubin. In the last hour of life, the heart rate gradually decreased (80 beats per minute) and transcutaneous 0₂ saturation dropped to 0%, remaining so until death. Blood drawn postmortem (intracardiac puncture) revealed G6PD: 1.5 IU/g Hb (normal value: 9.0–18.0). Molecular analysis of the G6PD gene on genomic DNA (National Center for Biotechnology Information reference sequence NC_000023.10) revealed hemizygosis for the G6PD Mediterranean variant. The mother’s G6PD level was 6.7 U/g Hb, and the father’s was 13.2 U/g Hb (normal value: 9.4–30.5). Autopsy revealed no evidence of bleeding or other findings that informed the cause of death.

**DISCUSSION**

The main cause of the clinical picture described appears to be hemolytic anemia in conjunction with hyperbilirubinemia, as bleeding and immune-mediated, maternal-fetal incompatibility were ruled out. Among the potential causes of hemolytic anemia, rasburicase was the drug administered to the child that is capable of causing hemolysis. Because hyperuricemia may exacerbate preexisting nephropathy, rasburicase has also been used as a novel treatment of hyperuricemia associated with acute kidney disease in infancy. Rasburicase is an enzyme that catalyzes the conversion of uric acid into the more soluble allantoin, thereby decreasing the risk of renal damage. Ghirardello et al described “The article by Hobbs and coworkers provides scientific evidence for what we believe is a common clinical practice: the use of rasburicase in hyperuricemic newborns with acute kidney injury (AKI).” This report prompted the administration of rasburicase to our newborn infant. The article by Hobbs et al also specifically mentions the main contraindication to the use of rasburicase, however, which is G6PD deficiency. On day 1, the infant had a normal diuresis (0.9 mL/kg/h), followed by a brief period of oliguria that did not satisfy the criteria for acute kidney injury. The urine flow remained normal after rasburicase was administered. Hobbs et al described a retrospective chart review on 7 infants, including 2 newborns, with uric acid levels higher than 8 mg/dL, and Ghirardello et al considered patients with a mean uric acid level of 14.5 ± 3.6 mg/dL, that is, considerably higher than in our patient (6.67 mg/dL in the 33rd hour of life). Therefore, in our case, the administration of rasburicase was not indicated.
No controlled studies of rasburicase in newborn infants with decreased renal function are published, so the benefit and risk of this medicine remain undefined in neonates.

G6PD deficiency is the most common inherited enzyme deficiency, causing acute and chronic hemolytic anemia, or severe jaundice associated with kernicterus, in response to the consumption of oxidant substances. Blood transfusions may be necessary in the acute hemolytic phase, as in the G6PD Mediterranean genetic variant. More than 300 variants are known, but only a few cause chronic hemolysis even in the absence of any trigger. Although some neonatal cases have been reported, most affected individuals exhibit no hemolysis unless Hb oxidation is induced by oxidative drugs, fava beans, or infections. Sudden episodes of hemolysis associated with G6PD deficiency may result in rapid increases in serum total bilirubin concentrations up to levels sufficient to cause neurologic damage. Hemolysis induced by rasburicase usually begins 24 to 72 hours after the drug's administration, and ends 4 to 7 days later. In G6PD deficiency, the drug prompts the formation of intracellular \( \text{H}_2\text{O}_2 \), resulting in cell death and oxidative membrane injury. Another reported adverse effect of rasburicase, when administered to a G6PD-deficient subject, is methemoglobinemia, in which the heme iron changes from the ferrous to the ferric state, and the Hb is incapable of transporting \( \text{O}_2 \). Methemoglobinemia is reported as a rare cause of persistently low oxygen saturation in newborns and can be associated with G6PD deficiency. Tissue hypoxia and failure to eliminate \( \text{CO}_2 \) lead to mixed acidosis. Concerning the causes of cyanosis and death in our patient, the pathology report ruled out a cardiac cause for cyanosis, ventilation problems, or pulmonary embolism. Although it may not have changed the child’s final outcome, we feel it is important to acknowledge that the sudden decrease in hematocrit and increase in oxygen dependence in the 77th hour should have prompted an urgent red blood cell transfusion.

Our patient clearly died of anemia and the consequent progression of tissue hypoxia in spite of maximal support. Mixed metabolic and respiratory acidosis is considered a late finding in severe hemolytic anemia. Furthermore, hemolysis has the effect of increasing the amount of free Hb in the plasma, with a consequent decline in the nitric oxide bioavailability and hemostasis, which produce endothelial dysfunction, platelet activation, and vasculopathy. Methemoglobin may have contributed to this infant’s ineffective tissue oxygenation, but postmortem concentrations are not valid indicators of ante mortem levels.

A single rasburicase dose can be fatal in the G6PD-deficient neonate. In the future, G6PD testing must be carefully considered before using rasburicase in any context, as its use is entertained only in unstable patients who already have organ compromise. With each decision to start a new medication, we should consider whether it may be better to refrain from certain therapies in compliance with the fundamental imperative: primum non nocere.

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