CASE REPORT

Methemoglobinemia Associated with Metoclopramide Therapy in a Neonate

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With the removal of cisapride from the U.S. market, practitioners have increasingly used other medications, such as metoclopramide, to treat gastroesophageal reflux in pediatric patients. We describe the case of a neonate who developed methemoglobinemia after receiving metoclopramide at doses slightly above the recommended age-appropriate dosage. Health care providers should be aware of this potentially serious side effect in young infants who receive this medication.

KEYWORDS: methemoglobinemia, metoclopramide, neonate

J Pediatr Pharmacol Ther 2003;9:49-54

INTRODUCTION

Cisapride (Prepulsid, Janssen Pharmaceutica, Titusville, NJ) was removed from the U.S. market in July of 2000 following continuing reports of heart rhythm disorders and deaths. Although it is still available for patients with unusual, debilitating problems for whom there is no alternative therapy, the majority of pediatric patients must use alternative medications for the treatment of gastroesophageal reflux disease. One such drug that is frequently being prescribed is metoclopramide (Reglan, Wyeth Pharmaceuticals, Collegeville, PA). Like many medications used in the pediatric arena, metoclopramide is not approved by the Food and Drug Administration for use in those <18 years of age. Although pharmacokinetic and pharmacodynamic studies of metoclopramide have been performed in the pediatric population,[1] particularly in neonates,[2,3] the available information is limited. Therefore, neonates may be at increased risk for the development of adverse effects associated with metoclopramide, including lethargy, irritability, diarrhea, extrapyramidal symptoms, and seizures.[2-4]

An increased risk of methemoglobinemia in metoclopramide-exposed infants has been reported.[5-7] Case reports have been limited to patients receiving large doses, to those given the parenteral formulations of the drug, or to patients with concomitant diarrheal illness.[5-7] We describe the case of a neonate who developed methemoglobinemia after receiving metoclopramide at 0.33 mg/kg/dose orally every 6 hours.

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CASE REPORT

A 10-day-old 3 kg neonate was seen by her pediatrician for the complaint of excessive crying for 5–10 minutes after breastfeeding. Feeds were not associated with emesis. The pregnancy history was remarkable for two previous maternal spontaneous abortions and vaginal bleeding during the first trimester with this pregnancy. The full-term newborn was delivered at a birth weight of 2.98 kg by spontaneous vaginal delivery. No problems were noted after birth, and the infant was discharged home at two days of age. The social history was significant for tobacco exposure in the home, and the family history was negative.

Based on the above history, the 11-day-old was prescribed ranitidine 15 mg by mouth twice daily (10 mg/kg/day) and metoclopramide 0.6 mg by mouth every 6 hours (0.2 mg/kg/dose) for presumed esophagitis with gastroesophageal reflux. One day after beginning the medication, the mother noticed that the baby appeared "dusky" despite feeding well. She also had

several loose stools but did not have an increased frequency of stools. The mother noted that the baby had a brief period of apnea during a feed; however, the apnea responded to stimulation. The baby continued to breastfeed well for a minimum of 30 minutes every three hours. Over the following 24 hours, the mother and grandmother noted a worsening "dusky" color and an increasing frequency of apneic episodes; these episodes were of several seconds duration and occurred 2 to 3 times. The apnea responded to stimulation and at times was associated with emesis.

At 13 days of age, the infant was evaluated in the emergency department of the referring hospital where she was noted to have blue-grey discoloration of the skin and lips. She also had 5 to 6 episodes of brief "apnea" of 5 to 10 seconds each, but an otherwise normal physical examination. The respiratory rate was 35 breaths per minute, and the SpO_2 on room air was 90%. An arterial blood gas was pH 7.51, pCO_2 23, pO_2 141, HCO_3 18 and the calculated saturation was 99%. She was placed on nasal cannula oxygen and transported to Arkansas Children's Hospital.

On admission, the history was also notable for mother's report that the infant had been receiving ranitidine 15 mg twice daily. Instead of receiving the prescribed 0.6 mg every 6 hours of metoclopramide, the newborn had been given 1 mg every 6 hours (0.33 mg/kg/dose). Due to an error in administration, the baby had received a larger-than-prescribed dose of metoclopramide since starting the medication for a total of 10 doses. The physical examination revealed a 3 kg baby (20 grams above the birth weight) who was alert, fussy but consolable, with a'"dusky" grey color on nasal cannula oxygen. The vital signs were as follows: temperature 36.5 °C, pulse 136 beats per minute, respiratory rate 28 breaths per minute, and blood pressure 103/72 mm Hg. The oxygen saturation by pulse oximetry was 91% on 1.5 L/min of oxygen by nasal cannula (100% FiO_2). The remainder of the physical examination was normal. The infant had normal skin turgor, moist mucous membranes, and no respiratory distress.

The laboratory evaluation included cultures of blood, urine, and spinal fluid. Electrolytes and complete blood count were normal. There was a discrepancy between the calculated saturation by the arterial blood gas (99%) and the oxygen saturation by pulse oximetry (90%) from the referral hospital. The patient also continued to be cyanotic despite a normal PaO_2, hence, an arterial blood gas with co-oximetry and methemoglobin level was obtained: pH 7.43, pCO_2 29, pO_2 140, HCO_3 19, and base excess –2.9. The initial methemoglobin level was 16%, and measured oxygen saturation was 52.6%.

Metoclopramide and ranitidine were discontinued. The infant was treated empirically with ampicillin and cefuroxime for potential infection. Approximately four hours after admission, the patient had a brief apneic episode that responded to gentle stimulation. Five hours later, she had prolonged apnea (>20 sec), which responded to positive pressure ventilation. A repeat methemoglobin level at this time was 27.5%. She received 5 mg of methylene blue (1.67 mg/kg) intravenously over 5 minutes. The methemoglobin level one hour later was 1.1%. She had no apnea for the subsequent 24 hours, but apneic events recurred and were associated with oxygen desaturation by pulse oximetry. A repeat methemoglobin level at this time was again 1.1%. The patient was transferred to the Pediatric Intensive Care Unit for observation.

Further evaluation the following day included an electroencephalogram and a head ultrasound, which were both normal. An upper GI was significant for reflux to the thoracic inlet. A simultaneous sleep evaluation (including thermistry, chest wall impedance, SpO_2, and heart rate recordings) and pH probe were completed on the fifth day of hospitalization. The pH probe revealed increased frequency as well as prolonged duration of reflux episodes. The sleep evaluation revealed excessive episodes of periodic breathing, which did not correlate with the reflux episodes. The blood, urine, and spinal fluid cultures were negative at 72 hours, and antibiotics were discontinued. The hemoglobin electrophoresis was normal.

Therapy for gastroesophageal reflux was initiated with oral ranitidine (2 mg/kg/dose twice daily) and bethanechol (0.2 mg/kg/dose three times daily). Oxygen was weaned to 1/8 lpm (100% FiO_2) with feeding and sleeping only. On this regimen, the patient had no further apneic events for 48 hours and was discharged home on oxygen, an apnea monitor, and a pulse oximeter. The patient's primary care physician weaned the oxygen over the next few weeks. No further episodes of cyanosis were reported.

DISCUSSION

Methemoglobinemia has been described as an adverse effect of metoclopramide.[7,8] A limited number of case reports have addressed the occurrence of methemoglobinemia in infants exposed to metoclopramide.[5-7] Due to the increased frequency of metoclopramide use in recent years, it is important for health care providers to be aware of this potential adverse effect. The patient described here presented with clinical cyanosis and apnea in the absence of respiratory distress. The cyanosis resolved after treatment with methylene blue and discontinuation of metoclopramide. Although diarrheal illness with acidosis has been associated with methemoglobinemia in infants,[9,10] the neonate in the current report did not experience significant diarrhea or acidosis.

Methemoglobin is formed when the hemoglobin molecule is oxidized from the normal ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. In normal individuals, the level of methemoglobin is maintained at less than 0.6% by cytochrome b_5 reductase (NADH-dependent methemoglobin reductase).[10] If low levels of this enzyme are present, or if the red blood cells are under excessive oxidative stress, methemoglobin levels may rise.[10, 11-12] Metoclopramide or its metabolites have been postulated to have a direct oxidizing effect on erythrocytes.

Neonatal methemoglobinemia may be congenital or acquired. Congenital methemoglobinemia is due either to a defect in the cytochrome b5 reductase system (autosomal recessive form) or to inheritance of one of the M hemoglobins that binds ferric iron preferentially (autosomal dominant form).[10] Our patient's hemoglobin electrophoresis was normal, thus eliminating abnormal hemoglobin (hemoglobin M) as a potential cause of the methemoglobinemia. After discharge, a NADH-methemoglobin reductase level was to be obtained by the primary care physician, but the infant was lost to follow-up.

The acquired form of methemoglobinemia may be due to exposure to agents such nitrate-contaminated water,[12] nitrate-contaminated foods (e.g. vegetables),[13,14] inhaled nitric oxide,[15] metoclopramide,[5,6] topical anesthetics (benzocaine, prilocaine, and lidocaine/prilocaine cream (EMLA),[16] and other medications or environmental exposures.[16] The infant did not have exposure to other drugs associated with methemoglobinemia.[11] Transient methemoglobinemia associated with acute diarrheal illness and acidosis has also been reported, although the mechanism for this association is not clear.[9]

Metoclopramide, a derivative of orthoprocainamide, is primarily metabolized (at the first pass through the gut wall or liver) to metoclopramide N-4-sulfate, but as much as 25–40% of the parent compound may undergo renal clearance.[17] In addition, CYP2D6 may also be involved in the metabolism of metoclopramide.[18] In neonates, developmentally determined changes in hepatic metabolism and renal clearance may significantly alter the pharmacokinetics of metoclopramide, thereby increasing the risk of side effects.

Two pharmacokinetic studies have been performed in infants, with a total of 16 infants included.[2,3] The first study included 6 full-term infants (0.9–5.4 months).[2] One dose of metoclopramide in this populationcleared at a mean of 0.66 L/hr/kg (range: 0.15 to 1.29 L/hr/kg). The youngest subject was 3.5 weeks of age. Based on a first-dose pharmacokinetics study, this infant had a markedly prolonged elimination half-life (23.1 hours), which decreased to 10.3 hours at steady state. A wide variation in the clearance of a single dose of oral metoclopramide was reported (Cl=0.15 to 2.43 L/hr/kg) in a follow-up study involving premature infants with a mean gestational age of 31.2±3.2 weeks.[3] Three of ten infants had elimination half-lives in excess of 10 hours.[3]

Previously reported values for the clearance of metoclopramide in adults were 0.53±0.19 L/hr/kg[19] and 0.55±0.12 L/hr/kg.[20] In a pharmacokinetic study of 9 older children (7–14 years of age) receiving metoclopramide for cytotoxic drug induced vomiting, clearance values appeared to be more comparable to adults with less variability than that reported in infants (0.56±0.1 L/kg/hr).[21] In addition, normal pharmacogenetic variability in sulfotransferase isoforms and CYP2D6 may also contribute to variability in metabolism between individuals.[2,22]

Two other mechanisms may account for the increased rate of methemoglobinemia in young infants exposed to metoclopramide. First, the erythrocyte activity of cytochrome b_5 reductase, which is responsible for reducing methemoglobin, is age-dependent; therefore, newborns and

premature infants may have transient enzymatic deficiency resulting in lower enzyme levels.[10,23] Secondly, neonates have increased levels of fetal hemoglobin, which may be more readily oxidized than the adult form.[10]

Previous reports of methemoglobinemia in infants associated with metoclopramide have primarily included infants who were receiving larger doses of metoclopramide or were receiving the drug by the parenteral route. For example, one case report described an 18-day-old who developed methemoglobinemia after receiving metoclopramide 0.7 mg/kg/day intravenously (including 0.2 mg/kg every 4 hours for three doses).[6] This patient became dusky and was noted to have a dark arterial blood sample despite a high pO2. The methemoglobin level was 23.2%. He fully recovered after discontinuation of metoclopramide. Methemoglobinemia has also been reported in a 3-week-old infant who received metoclopramide 1 mg/kg/dose orally every 6 hours over a 36-hour period for gastroesophageal reflux. He became cyanotic, lethargic, irritable, with poor feeding, diarrhea and respiratory distress. The methemoglobin level in this newborn was 20.5%. The methemoglobinemia and associated symptoms resolved quickly after one dose of methylene blue.[5] Both of these patients had normal methemoglobin reductase levels and no measurable hemoglobin M.

The recommended dose for metoclopramide is 0.4–0.8 mg/kg/day in four divided doses.[11,24] The present case represents a very young neonate who received a metoclopramide dose slightly above what is age-appropriate for the recommended dose. The etiology of this patient's apnea is unknown. The apneic spells persisted greater than 24 hours after resolution of the methemoglobinemia but resolved prior to hospital discharge. Respiratory depression has been described in the continuum of symptoms associated with methemoglobinemia. In this case, the sleep study showed no association between the apneic episodes and gastroesophageal reflux.

Clinical symptoms associated with methemoglobinemia are influenced by the concentration of methemoglobin. Although cyanosis is generally present at methomoglobinen levels above 15%, they may occur at lower levels in infants.[13] At concentrations of 30 to 40%, symptoms are usually generalized (e.g., poor feeding, lethargy, and irritability). Levels greater than 55% are usually associated with more severe symptoms such as respiratory depression, cardiac arrhythmias, seizures, coma, and death. It is possible that infants may have respiratory depression and apnea at lower methemoglobin levels than are typically described for older patients.

For patients who have drug-induced methemoglobinemia, the first treatment is the removal of the causative agent. Methylene blue may be used, particularly if the methemoglobin levels are markedly elevated or if there are signs of hypoxia. The dose is 1–2 mg/kg of a 1% solution, delivered by slow intravenous infusion, and may be repeated if needed. Methylene blue is an effective electron acceptor from NADPH-dependent methemoglobin reductase and is converted to leucomethylene blue, which then reduces methemoglobin to hemoglobin. Methylene blue is contraindicated in patients with G6PD deficiency because it is ineffective and may cause a severe hemolytic anemia.[25]

G6PD deficiency is an X-linked disorder that affects primarily males, but also homozygous females. Clinically, these patients develop hemolysis after receiving oxidizing substances, including a long list of medications (e.g., fava beans, acetaminophen, methylene blue). Certain ethnic groups have a high incidence of the disease, including Italians, Greeks, and other persons of Mediterranean, Middle Eastern, African, and Asian descent.[26] Our Caucasian female patient was not tested prior to treatment with methylene blue, but was unlikely to have this disease since she had an excellent response to the drug. With the removal of cisapride from the market and the subsequent increased use of metoclopramide, particularly in the intensive care nursery, an increased incidence of methemoglobinemia and other metoclopramide-associated side effects can be anticipated.

Despite its common use in infants, metoclopramide is one of the many drugs prescribed for children with minimal pediatric pharmacokinetic/pharmacodynamic data available. Methemoglobinemia should be suspected in infants with clinical cyanosis and discordance between the calculated oxygen saturation (based on PaO_2) and SpO_2. A measured methemoglobin concentration by co-oximetry is diagnostic. Based on the available pharmacokinetic data, a starting dose of metoclopramide of 0.1 mg/kg/dose four times daily is recommended in young

infants. Larger doses may be used in a step-wise approach in infants who do not respond to lower doses. Use of dosing syringes and parent education about drug dispensing are needed to minimize dosing errors and subsequent morbidity.

DISCLOSURES The authors declare no conflicts of interest or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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