Case Report of Methemoglobinemia in a Toddler Secondary to Topical Dapsone Exposure

Danielle M. Graff, MD, FAAP,a George M. Bosse, MD,b, c Janice Sullivan, MD, FAAPa,c

Departments of aPediatrics and bEmergency Medicine, University of Louisville School of Medicine, Louisville, Kentucky; and cKentucky Regional Poison Center of Kosair Children’s Hospital, Louisville, Kentucky

Dr. Graff drafted the initial manuscript; Drs Bosse and Sullivan revised the manuscript; and all authors reviewed and approved the final manuscript as submitted.

DOI: 10.1542/peds.2015-3186

Accepted for publication May 3, 2016

Address correspondence to Danielle M. Graff, MD, FAAP, Department of Pediatrics, University of Louisville, 571 South Floyd St, Suite 300 Louisville, KY 40202. E-mail: dmgraf02@louisville.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Oral dapsone effectively treats acne vulgaris, but systemic adverse events may occur. To limit absorption and potential adverse events or side effects, a topical version has been constituted. Aczone gel 5% contains dapsone and is constituted into an aqueous gel base. Pharmacological and safety studies conclude that topical dapsone results in a 100-fold lower plasma concentration than oral dapsone and has a limited adverse event profile, making it a favorable formulation for the treatment of acne vulgaris in both adults and adolescents.

We report a case of methemoglobinemia in a child after a single application of an unknown amount of topical dapsone.

CASE PRESENTATION

A 19-month-old girl presented to an emergency department with acute onset of blue discoloration of skin, lips, and nails. The patient's mother stated the toddler, previously healthy, was in her normal state of health before going to bed the evening before. Throughout the night the patient was described as fussy and irritable. When the child awoke in the morning, her mother noted the bluish discoloration of her skin. At that time, the patient's brother stated that the patient had applied an unknown amount of Aczone gel 5% (older sibling’s acne medication) to both of her arms just before going to bed. He did not see any oral ingestion but could not confirm that she did not place her hands in her mouth. Her mother initially attempted to wash the medication off, but there was no improvement in the child’s coloration. The patient had 2 episodes of nonbloody, nonbilious emesis at that time and appeared drowsy, but no respiratory distress was noted. The regional poison control center was contacted by the child’s mother, and they presumed the child had methemoglobinemia based on signs and symptoms of exposure to dapsone. The patient was referred immediately to the local emergency department.

On initial presentation the patient was alert but crying. Her physical examination was consistent with her mother’s description: blue lips, hands, and nailbeds. She was afebrile with tachycardia at 160 beats per minute.
respiratory rate of 30 breaths per minute, and digital pulse oximetry saturations fluctuating in high 70s and low 80s on room air. Her hemoglobin was 12.2 g/dL, with no hemolysis noted. Because of her clinical signs and symptoms and presumed methemoglobinemia, the patient was given 0.8 mg/kg of intravenous methylene blue. It is unknown why the outside hospital chose this pediatric dosing. Her methemoglobin level before administration of methylene blue was reported at 9.6%. Her color rapidly improved, and oxygen saturations were 92% on room air. She was then transferred to a tertiary pediatric hospital for management.

Ten hours after the initial dose of methylene blue was given, the patient developed perioral cyanosis and nailbed dusky. Pulse oximetry was 93% on 2 liters per minute of oxygen by nasal cannula. The repeat methemoglobin level was 20.6%, so the patient was given 2 mg/kg of methylene blue intravenously, with improvement in skin and mucous membrane color. Her subsequent methemoglobin level was 5%. The patient had complete resolution of all symptoms, and oxygen saturations were 98% on room air. The patient was discharged from the hospital on hospital day 2.

**DISCUSSION**

To our knowledge, this is the first, if not the only, case in pediatrics of topical dapsone exposure resulting in methemoglobinemia. It should be noted that a component of oral ingestion could not be ruled out.

With its lipid solubility, dapsone may be easily absorbed into the skin. It is known that a plasma level of dapsone can be detected 2 hours (time of maximum concentration of 6 hours) after application and is associated with a half-life of 48 hours. With its rapid peak concentration, in conjunction with the mechanism of action and metabolism of dapsone through cytochrome P450 2C, the systemic exposure from the topical medication can lead to adverse complications, including hemolytic anemia and methemoglobinemia. The potent metabolites of dapsone cause oxidative stress in the red blood cells, which leads to free radical production. The end result is the production of methemoglobin, which increases the affinity of the unaltered hemoglobin for oxygen. As a result, the hemoglobin dissociation curve is shifted to the left, which impairs oxygen delivery. Patients usually present with a wide spectrum of signs and symptoms ranging from peripheral and central cyanosis to cardiac dysrhythmia and seizures, with the most extreme being death. Pulse oximetry is often affected, and pulse oxygen saturation can overestimate the actual oxygen saturation level, thus providing false reassurance to the provider. Previous studies demonstrated the higher the methemoglobin levels, the greater the degree of overestimation of arterial oxygen saturation.

In all previous clinical trials, adverse events related to topical dapsone were limited to superficial application site irritation, including pruritus and erythema. There were no significant adverse events, including hemolysis or methemoglobinemia, in the clinical trials evaluating safety in both the adult and adolescent populations. Patients with glucose-6-phosphate dehydrogenase were included in the clinical trials, and no significant hemolysis was noted, also adding to its favorable profile. This finding is in contrast to our patient’s presentation after a single application. However, there have been no clinical trials in patients <12 years old. The only previously published report with a similar presentation is a case in a 19-year-old woman using topical dapsone for acne treatment. However, she was also taking citalopram, a serotonin selective reuptake inhibitor, which can inhibit the cytochrome P450 system and lead to increased systemic levels of other medications. Our patient was taking no other medications.

**CONCLUSIONS**

This patient demonstrates the complications of systemic absorption of dapsone in the young pediatric population, resulting in clinically significant methemoglobinemia from a reported single topical application. Institution of the appropriate therapy and ongoing monitoring resulted in effective treatment and complete recovery.

It is imperative that health care providers educate patients and families about safe medication storage practices. Early intervention and guidance by toxicology specialists are important for providing the best care to the patient, with the goal of an uncomplicated and full recovery.

**REFERENCES**

Case Report of Methemoglobinemia in a Toddler Secondary to Topical Dapsone Exposure
Danielle M. Graff, George M. Bosse and Janice Sullivan
*Pediatrics* 2016;138;
DOI: 10.1542/peds.2015-3186 originally published online July 8, 2016;
Case Report of Methemoglobinemia in a Toddler Secondary to Topical Dapsone Exposure
Danielle M. Graff, George M. Bosse and Janice Sullivan
*Pediatrics* 2016;138;
DOI: 10.1542/peds.2015-3186 originally published online July 8, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/138/2/e20153186