U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

Risk of serious and potentially fatal blood disorder prompts FDA action on oral over-the-counter benzocaine products used for teething and mouth pain and prescription local anesthetics

This is an update to two previous FDA Drug Safety Communications, "Reports of a rare, but serious and potentially fatal adverse effect with the use of over-the-counter (OTC) benzocaine gels and liquids applied to the gums or mouth" and "FDA continues to receive reports of a rare, but serious and potentially fatal adverse effect with the use of benzocaine sprays for medical procedures", issued on April 7, 2011.

Safety Announcement

[5-23-2018] The U.S. Food and Drug Administration (FDA) is warning that over-the-counter (OTC) oral drug products containing benzocaine should not be used to treat infants and children younger than 2 years. We are also warning that benzocaine oral drug products should only be used in adults and children 2 years and older if they contain certain warnings on the drug label. These products carry serious risks and provide little to no benefits for treating oral pain, including sore gums in infants due to teething. Benzocaine, a local anesthetic, can cause a condition in which the amount of oxygen carried through the blood is greatly reduced. This condition, called methemoglobinemia, can be life-threatening and result in death.

Due to the significant safety risk of methemoglobinemia, we have urged manufacturers that they should stop marketing OTC oral drug products for treating teething in infants and children younger than 2 years. If companies do not comply, we will take action to remove these products from the market. We have also urged manufacturers of OTC oral drug products containing benzocaine for adults and children 2 years and older to make the following changes to the labels of their products:

- Adding a warning about methemoglobinemia;
- Adding contraindications, FDA's strongest warnings, directing parents and caregivers not to use the product for teething and not to use in infants and children younger than 2 years; and
- Revising the directions to direct parents and caregivers not to use the product in infants and children younger than 2 years.

We continue to monitor the safety and effectiveness of OTC benzocaine products and intend to take additional actions in the future as needed. We will notify the public about any updates. In addition to our recent actions regarding OTC benzocaine products, we

are also requiring a standardized methemoglobinemia warning to be included in the prescribing information of all prescription local anesthetics.

Parents and caregivers should follow the American Academy of Pediatrics' recommendations for treating teething pain:[1]

- Gently rub or massage the child's gums with one of your fingers.
- Use a firm rubber teething ring.

Topical pain relievers and medications that are rubbed on the gums are not useful because they wash out of a baby's mouth within minutes. FDA has previously cautioned parents and caregivers to not give certain homeopathic teething tablets to children.

Alternative treatments for adults who experience mouth pain may include dilute salt water mouth rinse and OTC pain relief medications. Adults should follow the American Dental Association's recommendations for mouth sores and spots:

- Schedule regular oral health checkups
- Keep a diary of what you eat and drink
- Keep a list of oral hygiene products you have been using
- Avoid all tobacco products
- If you drink alcoholic beverages, do so in moderation
- See your dentist if you notice any change in your mouth

Consumers using benzocaine products to treat mouth pain should seek medical attention immediately for signs and symptoms of methemoglobinemia. These include pale, gray or blue-colored skin, lips, and nail beds; shortness of breath; fatigue; confusion; headache; lightheadedness; and fast heart rate. Signs and symptoms of methemoglobinemia may appear within minutes to one to two hours after using benzocaine. Symptoms may occur after using benzocaine for the first time, as well as after prior uses.

Health care professionals should warn patients of the possibility of methemoglobinemia and advise them of the signs and symptoms when recommending or prescribing local anesthetic products. Some patients are at greater risk for complications related to methemoglobinemia. This includes those with breathing problems such as asthma, bronchitis, or emphysema; heart disease, and the elderly. Health care professionals using local anesthetics during medical procedures should take steps to minimize the risk for methemoglobinemia. These include monitoring patients for signs and symptoms suggestive of methemoglobinemia; using co-oximetry when possible; and having resuscitation equipment and medications readily available, including methylene blue.

Benzocaine is a local anesthetic contained in some OTC products for the temporary relief of pain due to minor irritation, soreness, or injury of the mouth and throat. Benzocaine products are marketed as gels, sprays, ointments, solutions, and lozenges under brand names such as Anbesol, Orabase, Orajel, Baby Orajel, Hurricaine, and Topex, as well as store brands and generics. Prescription local anesthetics include articaine, bupivacaine, chloroprocaine, lidocaine, mepivacaine, prilocaine, ropivacaine, and tetracaine.

We have been closely monitoring the risk of methemoglobinemia with the use of OTC and prescription local anesthetics and previously communicated about this risk in 2014, 2011, and 2006. We estimate that more than 400 cases of benzocaine-associated methemoglobinemia have been reported to FDA* or published in the medical literature since 1971. There are likely additional cases about which we are unaware.

As part of our continued monitoring of this safety risk, we recently evaluated 119 cases of benzocaine-associated methemoglobinemia reported to FDA and identified in the medical literature in the 8½ years between February 2009 and October 2017. We have continued to receive cases even after our 2014 communication. Most of the 119 cases were serious and required treatment. Twenty-two cases occurred in patients younger than 18 years, and 11 of these were in children younger than 2 years. Four patients died among the 119 patients, including one infant. We also conducted a study comparing the relative ability of the two local anesthetics benzocaine and lidocaine to make methemoglobin. The study showed that benzocaine generated much more methemoglobin than lidocaine in a red blood cell model.[2]

We urge patients, consumers, and health care professionals to report side effects involving benzocaine, prescription local anesthetics, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS).

Facts about benzocaine and prescription local anesthetics

- Benzocaine is a topical anesthetic contained in some marketed over-the-counter (OTC) oral drug products intended to relieve pain from a variety of conditions such as sore throats, canker sores, and irritation of the mouth and gums.
- Health care professionals often use sprays containing benzocaine to numb the mucous membranes of the mouth and throat during procedures such as inserting instruments down the throat to view internal organs, inserting breathing tubes, and feeding tubes; however, benzocaine products are not FDA-approved for these uses.
- Benzocaine products are available as gels, sprays, ointments, solutions, and lozenges.
- Benzocaine products are marketed under brand names such as Anbesol, Orabase, Orajel, Baby Orajel, Hurricaine, and Topex, as well as store brands and generics.
- Prescription local anesthetics include articaine, bupivacaine, chloroprocaine, lidocaine, mepivacaine, prilocaine, ropivacaine, and tetracaine.
- Prescription local anesthetics are given as an injection into the body area that needs to be numbed for minor procedures or surgeries, or they are applied directly to the skin or mucous membranes.

Additional Information for Parents/Caregivers, Consumers, and Patients

- Do not use benzocaine or other local anesthetics to treat teething pain in infants and children. Any potential benefits of using these products to treat teething pain do not outweigh their risks.
- Benzocaine and other local anesthetics can cause methemoglobinemia, a serious condition in which the amount of oxygen carried through the blood is greatly reduced. This condition is life-threatening and can result in death.
- Follow the American Academy of Pediatrics' recommendations for treating teething pain:[1]
    - Gently rub or massage the child's gums with one of your fingers.
    - Use a firm rubber teething ring.
- Topical pain relievers and medications that are rubbed on a baby's gums to treat teething can pose serious risks and are not useful because they wash out of the baby's mouth within minutes.
- Use over-the-counter (OTC) benzocaine products in adults and children 2 years and older sparingly and only as needed. Do not use the product more than four times a day. Do not use the product in children younger than 2 years.
- Watch for signs and symptoms of methemoglobinemia, including pale, gray or blue-colored skin, lips, and nail beds; shortness of breath; fatigue; confusion; headache; lightheadedness; and rapid heart rate. **If you or someone you are caring for has any of these symptoms, seek medical attention immediately.**
- Patients who have breathing problems such as asthma, bronchitis, or emphysema; heart disease; the elderly; and those who smoke are at greater risk for complications related to methemoglobinemia.
- Signs and symptoms of methemoglobinemia may appear within minutes to one or two hours after using benzocaine. Symptoms may occur after using benzocaine for the first time as well as after several uses.
- When OTC products, always read the OTC Drug Facts Label to see if benzocaine is an active ingredient. If you are unsure if a product contains benzocaine, ask a pharmacist or your health care professional for help.
- Store all local anesthetics out of reach of children.
- Report side effects from benzocaine, prescription local anesthetics, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Advise parents and caregivers not to use benzocaine for teething and to follow the American Academy of Pediatrics' recommendations for treating teething pain.[1]
- Before recommending benzocaine products for other mouth pain, discuss the signs and symptoms of methemoglobinemia with your patients and advise them to seek medical attention immediately if they suspect methemoglobinemia.
- Advise patients to use the smallest amount of benzocaine possible to relieve pain and not to apply the product more frequently than four times daily. Advise patients not to use the product in children younger than 2 years.

- Recognize the signs and symptoms of methemoglobinemia, including pale, gray or blue colored skin, lips, and nail beds; headache; lightheadedness; shortness of breath; fatigue; and tachycardia. These indicate a moderate to severe level of methemoglobin and a marked reduction in the oxygen-carrying capacity of the blood. A characteristic color of the blood (chocolate-brown rather than blood red) may indicate methemoglobinemia, but this change is a late sign of the condition.
- Signs may appear within minutes to one or two hours after using benzocaine.
- Benzocaine sprays are not FDA-approved to numb the mucous membranes of the mouth and throat, or to suppress the gag reflex during minor medical and surgical procedures.
- If lidocaine is used to anesthetize the mucous membranes of the mouth and throat, ensure health care staff are familiar with the appropriate dosing, proper administration techniques, and safety monitoring.
- Be aware that the development of methemoglobinemia after treatment with a benzocaine spray is not dose-related. Methemoglobinemia has been reported to occur following the administration of a single benzocaine spray, or may occur with the first or subsequent applications of topical benzocaine formulations.
- An FDA-cleared multiple wavelength pulse co-oximeter should be used to reliably measure blood oxygen saturation and methemoglobin noninvasively. Methemoglobinemia can cause unreliable oxygen saturation readings on standard two-wavelength pulse oximeters
- Patients who have breathing problems such as asthma, bronchitis, or emphysema, patients with heart disease, and patients who smoke are at greater risk for complications related to methemoglobinemia.
- Elderly patients and patients with certain inborn defects such as glucose-6-phosphodiesterase deficiency, hemoglobin-M disease, NADH-methemoglobin reductase (diaphorase 1) deficiency, and pyruvate-kinase deficiency may also be at greater risk of developing methemoglobinemia.
- Medications, foods, and water containing nitrites and nitrates may also induce methemoglobin formation that will be additive to that formed by benzocaine products.
- Report adverse events involving benzocaine, prescription local anesthetics, or other medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.

Data Summary

We have been closely monitoring this safety risk and estimate that more than 400 cases of benzocaine-associated methemoglobinemia have been reported to the FDA Adverse Event Reporting System (FAERS) or published in the medical literature since 1971. As part of our continued monitoring of this safety risk, we recently evaluated 119 cases of benzocaine-associated methemoglobinemia reported to FAERS and identified in the medical literature between February 26, 2009, and October 6, 2017. The patients' ages were reported in 116 cases and ranged from 1 day to 85 years. Twenty-two cases involved patients younger than 18 years, 11 of which described a patient younger than 2 years. A transesophageal echocardiogram was the reported reason for benzocaine use for

53 cases (45 percent), and other cases commonly cited endoscopy, intubation, oral pain, and feeding tube pain. Among the thirty cases (25 percent) describing oral pain, the specific conditions cited included toothache or dental pain, teething, throat pain, tonsillectomy pain, and mucositis. Approximately two-thirds (n=75) of the 119 cases specified that the benzocaine product used was a topical spray. The second most common dosage form was oral gel (n=20).

Four cases resulted in death, including one infant and three adults. In 36 of the 119 cases (30 percent) the reported methemoglobin level was 30 to 55 percent, with the normal concentration typically around one to two percent. Seventeen cases (14 percent) had a reported methemoglobin level of 55 percent or greater, which may be considered life-threatening. A majority of cases (n=95) stated that the methemoglobinemia was treated with methylene blue. Some patients still died despite receiving methylene blue.

To better characterize the risk of methemoglobinemia with benzocaine, we conducted a study to determine the relative ability of benzocaine and lidocaine to form methemoglobin in vitro.[2] When 500 µM of benzocaine was incubated with whole human blood and pooled human liver postmitochondrial fraction (referred to as "S9") over 5 hours, methemoglobin levels greater than 40 percent of the total hemoglobin were detected. When 500 µM of lidocaine was evaluated under the same conditions, no methemoglobin was formed. Because liver S9 does not readily form lidocaine hydrolytic metabolites based on xylidine, a primary metabolic pathway, 500 µM xylidine was directly incubated with whole blood and S9. Under these conditions, methemoglobin levels of about 5 percent were reached by 5 hours. Thus, we concluded that benzocaine forms substantially more methemoglobin in vitro than lidocaine, and that benzocaine also would be more likely to form methemoglobin in vivo.

References

1. American Academy of Pediatrics. Teething: 4 to 7 Months. https://www.healthychildren.org/English/ages-stages/baby/teething-tooth-care/pages/Teething-4-to-7-Months.aspx. Last Updated October 6, 2016. Accessed May 15, 2018.

2. Hartman NR, Mao JJ, Zhou H, Boyne MT, Wasserman AM, Taylor K, Racoosin JA, Patel V, Colatsky T. More methemoglobin is produced by benzocaine treatment than lidocaine treatment in human in vitro systems. Regul Toxicol Pharmacol 2014; 70:182-8.

Related Information

Benzocaine Information

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

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