An evaluation of 10 percent and 20 percent benzocaine gels in patients with acute toothaches

Efficacy, tolerability and compliance with label dose administration directions

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Topical benzocaine is marketed in 10 percent and 20 percent formulations (regular [10 percent] and maximum [20 percent] strength Orajel [Church & Dwight, Princeton, N.J.] and Anbesol [Pfizer Consumer Healthcare. Madison, N.J.]) for the temporary relief of toothache pain and has been used widely since 1903.[1] The U.S. Food and Drug Administration (FDA) assigned this product category I monograph status (generally recognized as safe and effective) as an external anesthetic or analgesic for the temporary relief of pain due to minor irritation or injury of the mouth and gingivae, minor dental procedures, dentures, orthodontic appliances, canker sores, teething, sore mouth and sore throat.[2] However, the FDA concluded that the available data were not adequate to establish the effectiveness of benzocaine for the temporary relief of toothache pain and assigned category III status (judged to be safe but efficacy data not confirmative) in the over-the-counter (OTC) monograph for this indication, noting that the FDA would consider reclassifying benzocaine as category I if additional data were received from well-controlled studies.[2] We conducted a study with the intention of meeting this requirement.

Investigators in several small

ABSTRACT

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Background. The authors evaluated the efficacy and tolerability of 10 percent and 20 percent benzocaine gels compared with those of a vehicle (placebo) gel for the temporary relief of toothache pain. They also assessed the compliance with the label dose administration directions on the part of participants with toothache pain.

Methods. Under double-masked conditions, 576 participants self-applied study gel to an open tooth cavity and surrounding oral tissues. Participants evaluated their pain intensity and pain relief for 120 minutes. The authors determined the amount of gel the participants applied.

Results. The responders' rates (the primary efficacy parameter), defined as the percentage of participants who had an improvement in pain intensity as exhibited by a pain score reduction of at least one unit on the dental pain scale from baseline for two consecutive assessments any time between the five- and 20-minute points, were 87.3 percent, 80.7 percent and 70.4 percent, respectively, for 20 percent benzocaine gel, 10 percent benzocaine gel and vehicle gel. Both benzocaine gels were significantly ($P \leq .05$) better than vehicle gel; the 20 percent benzocaine gel also was significantly ($P \leq .05$) better than the 10 percent benzocaine gel. The mean amount of gel applied was 235.6 milligrams, with 88.2 percent of participants applying 400 mg or less.

Conclusions. Both 10 percent and 20 percent benzocaine gels were more efficacious than the vehicle gel, and the 20 percent benzocaine gel was more efficacious than the 10 percent benzocaine gel. All treatments were well tolerated by participants.

Practical Implications. Patients can use 10 percent and 20 percent benzocaine gels to temporarily treat toothache pain safely.

Key Words. Benzocaine; toothache; pain; topical anesthetic; methemoglobinemia; double stopwatch.

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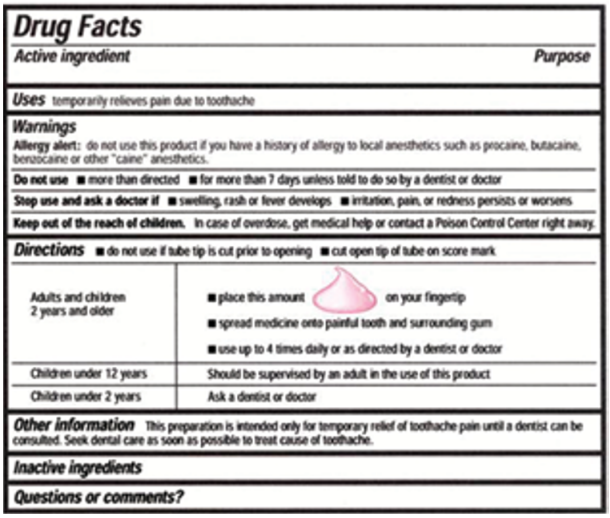

Drug Facts

Active ingredient	Purpose

Uses temporarily relieves pain due to toothache

Warnings

Allergy alert: do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine or other "caine" anesthetics.

Do not use ■ more than directed ■ for more than 7 days unless told to do so by a dentist or doctor

Stop use and ask a doctor if ■ swelling, rash or fever develops ■ irritation, pain, or redness persists or worsens

Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ do not use if tube tip is cut prior to opening ■ cut open tip of tube on score mark

Adults and children 2 years and older	■ place this amount on your fingertip ■ spread medicine onto painful tooth and surrounding gum ■ use up to 4 times daily or as directed by a dentist or doctor
Children under 12 years	Should be supervised by an adult in the use of this product
Children under 2 years	Ask a dentist or doctor

Other information This preparation is intended only for temporary relief of toothache pain until a dentist can be consulted. Seek dental care as soon as possible to treat cause of toothache.

Inactive ingredients

Questions or comments?

Figure 1. Label showing dose administration directions presented to study participants.

vehicle- (placebo-) controlled studies published results supporting the effectiveness of 7.5 to 20.0 percent benzocaine gels in relieving toothache pain.[3-5] In these studies, the benzocaine and polyethylene glycol vehicle gels were applied by the investigators[3,4] or the study participants[5] to both the open tooth cavity and the surrounding soft tissue; significant differences in favor of benzocaine were achieved. In another study, investigators placed a mucoadhesive patch containing 12 milligrams of benzocaine or a vehicle apical to the mucogingival junction of the symptomatic tooth, and a significantly greater percentage ($P < .05$) of participants in the benzocaine group reported meaningful pain relief (PR) than did participants in the vehicle group by the 30-minute point.[6] The results of these studies show that the ability of benzocaine to anesthetize the surrounding soft tissue may contribute to its effectiveness in temporarily relieving toothache pain. Label dose administration directions for one 20 percent benzocaine gel product stated that it should be applied to both the symptomatic open tooth cavity and around the gingivae surrounding the teeth.[7] We designed our study to incorporate application to both the tooth and the soft tissue.

Despite benzocaine's long history of safe use, it has been associated in rare instances with methemoglobinemia, a condition in which the oxygen-carrying capacity of the blood is reduced (ferric state). Although most of the cases of methemoglobinemia in the literature involve benzocaine spray application in a hospital environment for diagnostic procedures such as intubation, endoscopy, bronchoscopy and transesophageal echocardiography,[8-44] case reports of methemoglobinemia associated with OTC use of benzocaine have been published.[11,45-55] Only two of these cases involved benzocaine self-application for toothache, and both of these cases involved significant overdoses.[54,55]

In 2011, the FDA issued a safety communication noting the potential for OTC benzocaine products to cause methemoglobinemia on rare occasions.[56] Most reports of methemoglobinemia involved children. Thus, although cases of methemoglobinemia involving self-application by adult patients with toothache are rare and typically involve significant overdoses of the drug, it is important to evaluate patients' compliance with label dose administration directions in patients as young as 12 years (12 years is the youngest age recommended for benzocaine self-application in patients with an acute toothache[7]).

The FDA has determined that the existing body of evidence supporting the use of topical benzocaine for the temporary relief of toothache pain is lacking.[2] For benzocaine to gain category I status for the treatment of toothache pain under the OTC monograph system, additional data are needed. We conducted a study to evaluate the efficacy and tolerability of 10 percent and 20 percent benzocaine gels compared with those of a vehicle gel in participants with toothache pain, as well as to assess the compliance of these participants with the benzocaine gel dose administration directions in a newly proposed product label developed by the manufacturers of Orajel and Anbesol.

METHODS

The institutional review boards at the participating research centers (University of Pennsylvania, Philadelphia; The State University of New York at Buffalo; University of Pittsburgh; Nationwide Children's Hospital, Columbus, Ohio; The Ohio State University, Columbus; University of Detroit Mercy; New York University, New York City; Tufts University, Boston; and University of Maryland, Baltimore) approved the protocol, informed consent forms and assent forms (for minors), and we listed the trial in ClinicalTrials.gov under the identifier NCT00474175. Male and female patients aged at least 12 years from all ethnic backgrounds were eligible to participate in the study. In the case of minors (those younger than 18 years), both a parental informed consent form and an adolescent assent form had to be

ABBREVIATION KEY. AE: Adverse event. **DPS:** Dental pain scale. **FDA:** Food and Drug Administration. **OTC:** Over the counter. **PID:** Pain intensity difference. **PR:** Pain relief. **PRID:** Pain relief combined with pain intensity difference. **SPRID:** Time-weighted sum of pain relief combined with pain intensity difference.