Urticaria and asthma exacerbation after ingestion of menthol-containing lozenges

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Menthol, an ingredient in a wide variety of pharmaceutical and nonpharmaceutical products, has been associated with urticaria and dermatitis, as well as bronchospasm.\(^1\)\(^-\)\(^6\) Case reports have focused on exposures from cigarettes, ointments, and toothpaste. We detail a case report of a patient who experienced urticaria and a subjective increase in asthma symptoms after ingestion of mentholated cough lozenges.

Case report. A 30-year-old female with a weight of 80 kg and whose only significant medical condition was mild persistent asthma visited her physician’s office in November 2001 complaining of two separate episodes of generalized urticaria. She reported that on two occasions she had experienced upper-respiratory-tract symptoms, including nasal congestion, rhinorrhea, and cough. She treated her symptoms on both occasions with nonprescription cough lozenges, each containing 10 mg of menthol, blue dye #2, cherry flavoring, sucrose, and red dye #40 (Halls Cough Suppressant Drops, Cherry, Warner-Lambert Company).

The patient directions on the lozenge packaging indicated that one drop could be used every hour as needed. On the first occasion, she ingested 64 lozenges over a four-day period. Beginning on the second day of the initial ingestion of the lozenges, she experienced generalized hives and urticaria, which worsened until she discontinued use of the lozenges on day 4. She described an even distribution of wheals over her trunk, face, and extremities. During that time, there was a subjective increase in her asthma symptoms, which she managed by increasing the use of albuterol metered aerosol inhalation from her normal 2–4 puffs each day to more than 10 puffs each day. She treated her urticaria with diphenhydramine 50 mg p.o. every six hours on days 4 and 5, and her urticarial symptoms improved. Two months later she had the same urticarial symptoms after taking five of the same lozenges during a 12-hour period for persistent cough. The patient's wheezing subjectively increased after ingesting the lozenges. She stopped taking the lozenges and treated her symptoms with diphenhydramine and albuterol. Two days after the second episode she visited her physician’s office requesting treatment for her upper-respiratory-tract symptoms. She also inquired about the possibility of a hypersensitivity to cough lozenges.

She had never been hospitalized for her asthma but had been treated for several mild exacerbations as an outpatient. Her asthma had not been triggered by any medications in the past. She did not monitor peak expiratory flow rates, and her only current medications were inhaled fluticasone propionate metered aerosol inhalation 110 \(\mu g\) twice daily and albuterol 90 \(\mu g\) as needed for wheezing. She did not take any other medications during either episode and denied the use of alternative medications. She did not report any allergies to drugs or environmental substances or previous reactions to mentholated substances such as toothpaste and mouthwash. She denied the use of any other mentholated substances, and she did not smoke cigarettes.
Discussion. According to Naranjo et al.'s probability scale, the strength of association between this patient’s urticaria and menthol is probable. The lack of objective evidence for bronchoconstriction in this patient results in a possible rating for the association between menthol and her subjective complaints of asthma symptoms.

A MEDLINE search including available literature from 1960 to the present revealed several case reports and small-scaled case series documenting urticaria after exposure to mentholated products. However, this reaction has not been previously reported with cough lozenges. The first case of urticaria attributed to menthol was reported in 1964. In this case, the patient was exposed to a number of mentholated products, including cigarettes, room spray, and topical ointments. The patient experienced urticaria during an oral rechallenge with menthol. Laboratory test results showed a decrease in the patient’s circulating basophils. A similar case was reported in 1966. In both cases, skin tests for menthol hypersensitivity were negative. McGowan suggested that menthol-induced urticaria might be difficult to diagnose because of the ingredient’s prevalence in different products. Two other reports related cases of chronic dermatitis of the lip to smoking mentholated cigarettes.

In 2001, dos Santos et al. reported a case of possible menthol-induced asthma. A 40-year-old patient with no history of asthma experienced dyspnea and wheezing when exposed to toothpaste or candy products containing menthol. Her symptoms occurred minutes after ingestion. The patient’s sensitivity to menthol was confirmed through skin testing and a bronchial challenge. Her forced expiratory volume at one second (FEV1) decreased by more than 20% after using mentholated toothpaste. The skin test was completed with both saline and histamine controls. She developed a similar wheal and itching when exposed to both histamine and menthol and a negative response to saline. Another report described five asthma patients with concomitant aspirin sensitivity whose asthma was exacerbated after exposure to mentholated toothpaste and gum. This report did not provide specific details on the patients’ asthma history but revealed that one patient’s FEV1 decreased 10% with menthol exposure. Tamaoki et al. evaluated the effects of menthol vapor on the airway in patients with asthma. Patients received nebulized menthol or placebo twice a day for four weeks. Peak expiratory flow rates were measured daily, and FEV1 was determined at the beginning and end of the trial. Although the sample size was small, the authors concluded that menthol may decrease airway hyperresponsiveness. The patients had a decrease in the peak variation in the peak expiratory flow rate but no change in FEV1. Of significance, two patients were withdrawn from the study because of increased chest tightness after inhaling menthol vapor. The laboratory test values from these two patients were not included in the evaluation. A study of the action of continuously administered menthol vapor in guinea pigs concluded that menthol may have bronchodilating effects.

Menthol is a monocyclic alcohol that is rapidly absorbed from the small intestine when ingested, metabolized by glucuronidation to its main metabolite, and excreted in the urine. It undergoes significant enterohepatic recirculation. Although the plasma half-life is between 40 and 60 minutes, the drug appears to have multicompartment pharmacokinetics, possibly due to its lipophilic nature. Thorup et al. suggested that, based on animal data, adverse effects are more common when menthol dosages exceed 2 mg/kg/day.

The patient described here ingested approximately 2 mg/kg/day of menthol over the initial four-day period; however, she had ingested only 1.25 mg/kg/day during the second period of exposure. This suggests the possibility of a sensitization effect, which is consistent with other case reports. Although no objective measurements were taken of this patient’s asthma symptomatology, her albuterol requirements returned to baseline after resolution of her urticarial symptoms. The confounding variable in evaluation of her bronchial symptoms is the presence of upper-respiratory-tract symptoms. It is possible that her viral illness was responsible for her symptoms. However, her upper-respiratory-tract symptoms preceded the onset of urticaria by several days without significant asthma exacerbation. Although menthol is the only active ingredient in these lozenges, they also contain several dyes and a flavoring agent. It is possible that she had an adverse reaction to one of these constituents; however, she had no history of reactions to food dyes or flavorings.

The possibility of menthol-induced urticaria and bronchoconstriction is very concerning and deserves further review. Based on available information, the current labeling for some menthol-containing cough lozenges exceeds the dosage that may cause adverse reactions. The labeling for the lozenges does not mention the possibility of dermatologic or pulmonary symptoms from their use. These reactions may go unrecognized or be attributed to other causes or concomitant medications. Because of the widespread use of menthol, patients and health care providers should be aware that this ingredient may cause dermatologic and airway adverse reactions.

Conclusion. Urticaria and exacerbation of asthma developed in a patient taking menthol-containing cough lozenges.

References
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