Official Case Reports Journal of the Asian Pacific Society of Respirology
Respirology Case Reports
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Anaphylaxis caused by tipepidine hibenzate, a central antitussive drug

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Keywords
Anaphylaxis, antitussive drug, double-blind placebo-controlled oral challenge, tipepidine hibenzate, urinary leukotriene E4.

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Received: 25 August 2014; Revised: 13 September 2014; Accepted: 8 October 2014

Respirology Case Reports **2015; 3(1): 3–5**

doi: 10.1002/rcr2.85

Abstract

Tipepidine hibenzate, a central antitussive drug, is widely used in the management of cough and is generally safe and well tolerated. We present here a case of anaphylaxis caused by this drug. When the patient had caught a cold over the previous 10 years, she had received medications, including tipepidine hibenzate, from her family doctor. However, this time, she developed dyspnea, skin eruption, and anaphylactic shock after taking a Chinese herbal medicine and this drug. After her conditions improved due to adequate treatment, she was referred to our hospital to confirm the causative drug. Double-blind placebo-controlled oral challenge tests were performed after obtaining informed consent. Oral challenge with one-third tablet dose of tipepidine hibenzate caused a positive reaction. Urinary leukotriene E4 rose during the challenge with tipepidine hibenzate, but not with control. Clinicians should keep in mind that common antitussive drug use can cause anaphylactic reactions in very rare cases and can be harmful.

Introduction

Cough suppressants include mucolytic drugs and peripheral and central cough suppressants. Cough guidelines conclude that suppressant therapy is most effective when used for the short-term reduction of coughing and that relatively few drugs are effective as cough suppressants [1]. In patients with cough due to upper respiratory infection, central cough suppressants have limited efficacy for symptomatic relief and are not recommended for this use.

Tipepidine hibenzate, a central antitussive drug, has been used in Japan since 1959 and also in other Asian countries. This drug is generally safe and well tolerated, so it can sometimes be prescribed without caution. We describe here a case of anaphylaxis in a 43-year-old woman caused by tipepidine hibenzate after long-term and recurrent use. After obtaining informed consent, we performed double-blind placebo-controlled oral challenge tests and measured urinary leukotriene (LT) E4 concentrations during the challenge.

Case Report

The patient was a 43-year-old woman with allergic rhinitis but no history of allergy to food or drugs. Over the previous 10 years, each time she had caught a cold, she had regularly taken several medications, including acetaminophen, carbocysteine, a mucolytic drug, and tipepidine hibenzate prescribed by her family doctor. She had had itchy skin or occasionally slight dyspnea a few hours after taking all these medications during the previous few years. In 2013, when she saw her family doctor with the complaints of cough and fever, she was prescribed the above medications and additionally, fexofenadine, an H1 receptor antagonist, and levofloxacin. Since she developed urticaria and subsequently dyspnea a few hours after taking these drugs, she was taken to a medical emergency center where hypotension was found, and she was treated with adequate therapy, including epinephrine and systemic corticosteroids. Her symptoms resolved within an hour. Soon after this episode, she went to another hospital complaining of cough, and

tipepidine hibenzate and Bakumondoto, a Chinese herbal medicine, were prescribed. After taking these two drugs, she developed identical symptoms within a few hours again, requiring urgent treatment, including epinephrine and systemic corticosteroids. Thus, she was referred to our hospital to clarify the cause of anaphylaxis. The total immunoglobulin (Ig)E level was 71.2 IU/mL and specific IgE to Japanese cedar pollen was positive (5.59 U/mL, class 3). On the basis of this last episode, tipepidine hibenzate or Bakumondoto was most strongly suspected as the causative agent. Skin prick tests with tipepidine hibenzate syrup (0.5% w/v) and Bakumondoto extract (3 g in 150 mL of hot water) were negative. Since she had two episodes of anaphylaxis, we decided to determine the causative drug definitively. After obtaining informed consent, double-blind placebo-controlled oral challenge tests were performed on three different days (for the administration of tipepidine hibenzate, Bakumondoto, or placebo) with a 2-day interval, according to a previously described method with minor modifications [2]. One milliliter of tipepidine hibenzate syrup was diluted with saline at the following ratios: 1:10,000, 1:3000, 1:1000, 1:300, 1:100, 1:30, 1:10, 1:3, and 1:1. Bakumondoto extract was diluted to 1:10, 1:3, and 1:1. Saline was used as a placebo. To achieve double blinding between tipepidine hibenzate and Bakumondoto, additional saline controls were used. One milliliter each was mixed with 20 mL of orange juice and the doses were increased at each 30-min challenge for tipepidine hibenzate and Bakumondoto in a stepwise fashion. In addition, we measured urinary LTE4 concentrations during the challenge as there is evidence that urinary LTE4 levels are elevated soon after episodes of anaphylaxis [3]. After the intake of 1:100 dilution of tipepidine hibenzate, she complained of slight itchy palms with erythema, and after the intake of 1:3 dilution, she developed abdominal pain, vomiting, and urticarial without respiratory or cardiovascular compromise. These symptoms promptly disappeared after treatment with subcutaneous epinephrine and intravenous corticosteroids. In contrast, the challenges with Bakumondoto at all doses and placebo were negative, supporting our theory that tipepidine hibenzate had precipitated her previous episodes of anaphylaxis. The urinary LTE4 levels were elevated in the 2- to 5-h period after starting the oral challenge test with tipepidine hibenzate, but not control or Bakumondoto (Fig. 1). The patient was advised not to take tipepidine hibenzate again.

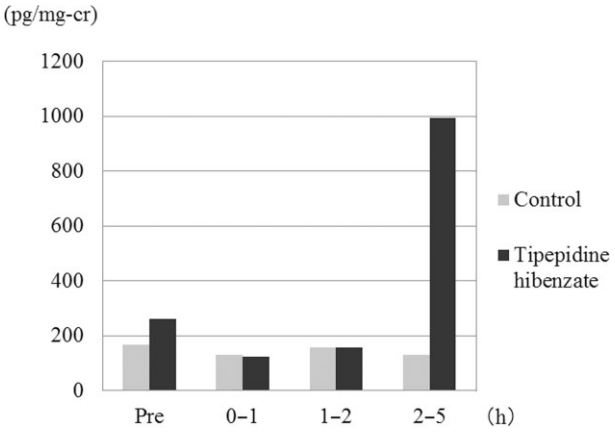

Figure 1. Changes in urinary leukotriene E4 concentrations during oral challenge tests. Fivefold increase was observed in the 2- to 5-h period after starting the oral challenge test with tipepidine hibenzate, but not control or Bakumondoto. Abbreviations: h, hours after starting oral challenge test; pg/mg-cr, picogram per milligram of creatinine.

Discussion

Anaphylaxis caused by antitussive drugs is rare. A recent study analyzed 333 cases with severe drug-induced anaphylaxis reported for 8 years and found that antibiotics (49.6%), muscle relaxants, latex and anesthetics (15.0%), and nonsteroidal anti-inflammatory drugs (10.2%) were the most common [4]. There were only five cases caused by antitussive drugs. To the best of our knowledge, there is only one other case report of anaphylaxis caused by tipepidine hibenzate in an adult [5]. Clinicians may falsely assume that antitussive drugs are always safe to prescribe to patients presenting with cough. In fact, when the present patient had caught a cold, her family doctor had prescribed tipepidine hibenzate for many years and had not identified any adverse events. Even after she developed the first episode of anaphylactic shock, the next doctor prescribed not antibiotics but tipepidine hibenzate and a Chinese herbal medicine for safety reasons. Antitussives are commonly prescribed as they generally regarded as safe, but clinicians should be aware that they can rarely cause severe drug reactions including anaphylaxis. We emphasize again that antitussive drugs have limited roles for symptomatic relief and can be harmful.

As Ono et al. reported previously [3], we also observed an increase in LTE4 concentrations in urine in the 2- to 5-h period following oral challenge test. This time frame would fit with the findings reported by Ono et al. as they found it was in the first 6 h following anaphylaxis (maximal in first 3 h) that patients had elevated urinary LTE4 levels. The findings of elevated urinary LTE4 following the tipepidine oral challenge would also support the theory that this was the culprit medication in this patient, suggesting that mast cells may participate in the generation of cysteinyl LTs in anaphylaxis. If the measurement of urinary LTE4 were to become available in clinical practice, it could prove helpful in supporting the diagnosis of anaphylaxis.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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