

A Case of Trimebutine-Induced Anaphylaxis

Suh-Young Lee^{1,2}, Mi-Yeong Kim^{1,2}, Sung-Yoon Kang^{1,2}, Woo-Jung Song^{1,2} and Hye-Ryun Kang^{1,2}

ABSTRACT

Trimebutine maleate [2-dimethylamino-2-phenylbutyl 3,4,5-trimethoxybenzoic acid] has been demonstrated to be active for relieving abdominal pain and it is widely used for patients with irritable bowel syndrome. Adverse drug reactions are mostly mild and well-tolerated. To our knowledge, only two cases of trimebutine induced hypersensitivity have been reported, and both were delayed type reactions. Here, we report the first case of trimebutine maleate-induced anaphylaxis.

KEY WORDS

anaphylaxis, drug hypersensitivity, trimebutine

INTRODUCTION

Trimebutine has been commonly used in many countries for a long time since 1969.¹ It is taken orally to relieve gastroesophageal reflux disease, gastric ulcer, and irritable bowel syndrome.²⁻⁶ It is metabolized into nor-trimebutine, and it can regulate colonic motility through both anti-muscarinic and weak opioid agonistic properties.¹ Since it is commonly used as an over-the-counter drug, some adverse drug reactions such as diarrhea, constipation, vomiting, thirst, tachycardia, headache, fatigue, and elevated serum liver transaminase have been reported.² To our knowledge, trimebutine maleate-induced hypersensitivity reactions have not been reported except for two cases of type IV hypersensitivity reaction including allergic dermatitis and delayed-type urticaria by topical use of trimebutine.^{7,8} However, there have been no reported cases of trimebutine maleate-induced anaphylaxis until now.

CASE REPORT

A 65-year-old woman experienced sudden onset of severe generalized erythema and dyspnea after taking trimebutine maleate, cefaclor, and aceclofenac.

She had no history of allergic diseases or other adverse drug reactions. She had been taking telmisartan, hydrochlorothiazide, rosuvastatin calcium, amlodipine, and metformin hydrochloride safely for the

past 10 years.

Routine laboratory tests revealed no remarkable abnormality, and serum total IgE level was within normal range. A skin test was done with the original drug, trimebutine maleate, which did not contain any preservatives. While the skin prick test was negative, the intradermal test was positive at a 1 mg/ml (10 × 9 mm wheal and 24 × 22 mm flare). Serum specific IgE to cefaclor was not detected by the ImmunoCAP system (Uppsala, Sweden).

In order to confirm the culprit drug, oral challenge tests were done. First, we tested trimebutine maleate. Initial blood pressure was 120/80 mmHg. One hour after taking 100 mg of trimebutine maleate, the patient had generalized erythema with pruritus. She complained of dizziness as her blood pressure suddenly dropped to 80/50 mmHg at 90 minutes after trimebutine intake. Her symptoms were relieved with shock positioning and a rapid saline drip. Administration of intravenous dexamethasone and chlorpheniramine followed the drip. Two weeks after the initial oral challenge test with trimebutine maleate, we did oral challenge tests with aspirin up to 750 mg and cefaclor up to 625 mg separately. Neither aspirin nor cefaclor provoked any symptoms in the patient upon oral challenge test. Aceclofenac (100 mg) was also re-administered without any adverse reaction and has been used by the patient as a safe analgesic.

With these provocation tests, we confirmed

¹Department of Internal Medicine, Seoul National University College of Medicine and ²Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul, Korea. Correspondence: Hye-Ryun Kang, MD, Department of Internal Medicine, Seoul National University College of Medicine, 28

Yongon-dong, Chongno-gu, Seoul, 110-744, Korea.

Email: helenmed@snu.ac.kr

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trimebutine-induced anaphylaxis in this case.

DISCUSSION

Trimebutine [2-dimethylamino-2-phenylbutyl 3,4,5-trimethoxybenzoic acid] is an enkephalin analogue and stimulates the enkephalin receptor in the enteric nerve system by modulating visceral sensitivity and normalizing altered bowel movement.^{1,2} The actions of trimebutine on the gastrointestinal tract are mediated through the agonist effect on the peripheral opiate receptors and through the release of gastrointestinal peptides such as motilin and through the modulation of the release of other peptides including vasoactive intestinal peptide, gastrin, and glucagon.² When given orally, trimebutine is metabolized in the liver to nor-trimebutine.¹ In the Korean domestic market, trimebutine maleate is widely distributed with 83 different brand names including 32 multiple-ingredient preparations containing trimebutine as well as 51 single-ingredient preparations. Moreover, 40% of them are sold as over-the-counter drugs.

Drug-induced anaphylaxis has been frequently associated with beta-lactam antibiotics, aspirin, non-steroidal antiinflammatory drugs (NSAIDs), radio-contrast media, muscle relaxants, and chemotherapeutic agents.^{9,10} Since cefaclor and NSAIDs are widely used in practice and frequently reported as causative agents of drug-induced anaphylaxis, these two drugs were initially suspected as the culprit drug inducing the anaphylaxis in this patient. However, against our expectation, trimebutine was confirmed as the causative agent of anaphylaxis by oral provocation test. To prevent anaphylaxis, the patient was educated to avoid trimebutine, but she was allowed to use cefaclor and NSAIDs. This case emphasizes the importance of the provocation test in drug allergies and suggests not to depend upon assumptions when determining causative drugs.

To our knowledge, this is the first case of trimebutine maleate-induced anaphylaxis that has been reported. Although there were two cases of trimebutine-induced allergic skin reactions by topical use, this case is not only the first case of anaphylaxis by trimebutine, but also the first report of an allergic reaction after the oral administration of trimebutine worldwide. We confirmed trimebutine maleate as the

causative agent of anaphylaxis but could not show the existence of a specific IgE to trimebutine since the patient did not return to the clinic.

In conclusion, we report that trimebutine, a commonly used over-the-counter drug, can induce a severe anaphylactic reaction.

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CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

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