

Erythema Multiforme Secondary to Dimenhydrinate in a Patient With Previous Similar Reactions to Pamabrom

Annals of Pharmacotherapy
2014, Vol. 48(3) 425–428
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DOI: 10.1177/1060028013518728
aop.sagepub.com


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Abstract

Objective: To report a case of erythema multiforme secondary to dimenhydrinate and pamabrom cross-sensitivity.

Case Summary: A 22-year-old Chinese female presented with a complaint of lip mucosal ulceration with necrosis and stomatitis, worsening over the past 24 hours and associated with reduced oral intake and incomplete opening of the mouth. Presentation was accompanied by a generalized rash and genital mucosal involvement. The only new systemically ingested agent was dimenhydrinate approximately 4 days prior to admission. She had no significant medical history, but was labeled to be allergic to acetaminophen. She had a positive history of 2 similar presentations secondary to Panadol Menstrual (acetaminophen and pamabrom), once 3 years ago and again 5 months prior to the current admission. An objective causality assessment revealed that the adverse drug event was “probable” to dimenhydrinate. A detailed history revealed a negative drug challenge to acetaminophen. She had previously taken plain acetaminophen and Beserol (acetaminophen and chlormezanone) with no reaction. **Discussion:** A comprehensive history taking facilitated the diagnosis of erythema multiforme secondary to dimenhydrinate without the need to perform invasive testing, and the removal of erroneous allergy labeling to acetaminophen. Dimenhydrinate and pamabrom both contain theophylline-related structures in their chemical composition. Similar reactions to pamabrom strongly suggested cross-sensitivity to theophylline-related structures. **Conclusions:** To our knowledge, this is the first report of erythema multiforme due to dimenhydrinate with pamabrom cross-sensitivity. We recommend that comprehensive medication-history taking be carried out for all drug-allergy patients to ensure greater informed decision making when choosing medications to use for that patient in the future.

Keywords

dimenhydrinate, theophylline, pamabrom, cross-sensitivity, allergy, erythema multiforme

Dimenhydrinate, an antiemetic, is widely used for motion sickness in travelers. It is classified as a pharmacy-only medication in Singapore and is easily obtainable from any pharmacy from a pharmacist on duty. Dimenhydrinate is a 1:1 salt of diphenhydramine, an ethanolamine, and 8-chlorotheophylline, a xanthine derivative that is intended to counteract the sedative properties of diphenhydramine.¹⁻³ Pamabrom, a diuretic, is found as the second component in the over-the-counter product Panadol Menstrual (acetaminophen 500 mg and pamabrom 25 mg) and is indicated for headaches, back pain, and menstrual pain relief by relieving bloating. It is a 1:1 salt of 2-amino-2-methyl-1-propanol and 8-bromotheophylline.

We present a case of a patient who developed erythema multiforme secondary to use of dimenhydrinate. PubMed and Clin-Alert databases were searched using search terms “dimenhydrinate,” “pamabrom,” “theophylline,” “allergy,” “angioedema,” and “erythema multiforme” in various combinations.

Only English databases were reviewed. Previous reports of allergic reactions to dimenhydrinate and pamabrom have manifest as fixed drug eruptions, with only 1 report each of anaphylaxis to dimenhydrinate and serum sickness to pamabrom.^{2,4,5} To our knowledge, this is the first case of erythema multiforme due to dimenhydrinate in a patient with a history of periorbital and lip swelling secondary to pamabrom.

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Case Report

A 22-year-old Chinese female presented to the emergency department with a complaint of new-onset necrosis of lip mucosal ulcerations, which worsened in the past 24 hours. Lip ulceration and stomatitis had occurred 2 days before and progressed to necrosis. She also reported a generalized rash of 4 days' duration, which was initially itchy, but the itch had resolved.

She had taken dimenhydrinate 50 mg (Dramamine brand) enroute to Thailand 4 days prior to admission for prophylaxis of motion sickness. She developed symptoms of generalized rash and mild periorbital edema while in Bangkok, Thailand, and was seen at a Bangkok hospital where she was given a dose of dexamethasone injection and prescribed chlorpheniramine and hydroxyzine (doses unknown). She was better initially; however, symptoms started to progress 2 days prior to admission with ulceration of the upper and lower lips, swollen oral mucosa, associated with poor oral intake, and inability to open her mouth fully. Progression to necrosis of the lips was observed in the past 24 hours. In addition, she experienced dysuria and slight hematuria.

The patient had no significant past medical history of note, except for a diagnosis of thalassemia minor. She had been labeled as allergic to acetaminophen. She worked as a manicurist for more than 5 years at the same company.

On examination, palms were tender and erythematous bilaterally with swelling and blistering. Lesions were blanchable. There was also genital blistering observed with no active bleeding. The rest of the physical examination findings were unremarkable. She was afebrile and vitals were within normal limits for her age and gender. Laboratory values reported were within normal limits for renal function, liver function, and complete blood count. Herpes simplex virus and syphilis testing were carried out in order to exclude sexually transmitted diseases because she reported an active sexual history. Both tests came out negative. The Dermatology Service was consulted and diagnosed her with erythema multiforme. She was treated with oral prednisolone, a short course of acyclovir, which was discontinued when herpes simplex virus swab was found negative, oral amoxicillin-clavulanate, and topical tetracycline ointment for weepy skin lesions. Her course of stay of 4 days was uneventful and she was discharged well.

To determine if this reaction was drug related, a thorough medication history was obtained from the patient. She described a similar experience of generalized rash and mild periorbital swelling 3 years ago when she self-medicated with Panadol Menstrual for menstrual cramps. She presented to another hospital's emergency department and was given "medications" and sent home. However, her symptoms worsened with increasing periorbital and lip swelling overnight, and concurrent fever and chills. She then presented to our

hospital's emergency department and was given intravenous hydrocortisone 200 mg and diphenhydramine (dose unknown) and was subsequently admitted for observation. Symptoms resolved overnight and she was sent home, only to experience a recurrence of lip mucosal ulceration and stomatitis for which she was admitted again the next day. There was no vulval, perineal, nor eye involvement. She was labeled with an acetaminophen allergy and sent to a nearby clinic for drug challenge. She was given a test dose of acetaminophen 500 mg with no reaction. She was able to reiterate that she had no such reactions when she took plain acetaminophen or Beserol (acetaminophen and chlormezanone). However, her allergy status to acetaminophen was left unchanged from then to the current admission. There were no remarkable events since that time until 5 months prior to the current admission, when she had taken half a tablet of Panadol Menstrual for menstrual cramping and developed periorbital swelling, which resolved without intervention. She had taken Nutrifresh, a nutritional supplement, for 3 months, but had stopped taking it over a month prior to admission. She denied use of any other over-the-counter medications and supplements. There had not been any changes in her dietary habits, and no new chemicals or products used at her workplace. There were no reasons to suspect ingestion of any other chemical or medications other than what was revealed to us.

We researched on structural similarities of pamabrom and dimenhydrinate and discovered the theophylline moiety as a common characteristic (Figure 1).^{1,3,6,7} Given the history of a positive rechallenge with Panadol Menstrual, a negative challenge of acetaminophen, and having received diphenhydramine previously with no reaction, we suspected that the theophylline moiety was responsible for the reactions our patient experienced. The Naranjo algorithm was used to ascertain the probability of causality of the adverse drug reaction.⁸ The total score was 7, making it "probable" that dimenhydrinate was the cause of the erythema multiforme. We did not rechallenge her with dimenhydrinate given the severity of her reaction to it.

Discussion

Our patient presented similarly on 3 separate occasions of exposure to theophylline-related substances. To date, a number of case reports of allergic reactions to theophylline, dimenhydrinate, and pamabrom have been published. The reactions reported were fixed drug eruptions in almost all cases, with only a few exceptions.^{2,4,5,9-11} This is hardly surprising since these drugs are structurally related. No reports of cross-sensitivity have been reported to date. However, given the very different indications of dimenhydrinate and pamabrom, the index of suspicion that our patient had a reaction to theophylline-related structures within dimenhydrinate and pamabrom would have been extremely low.

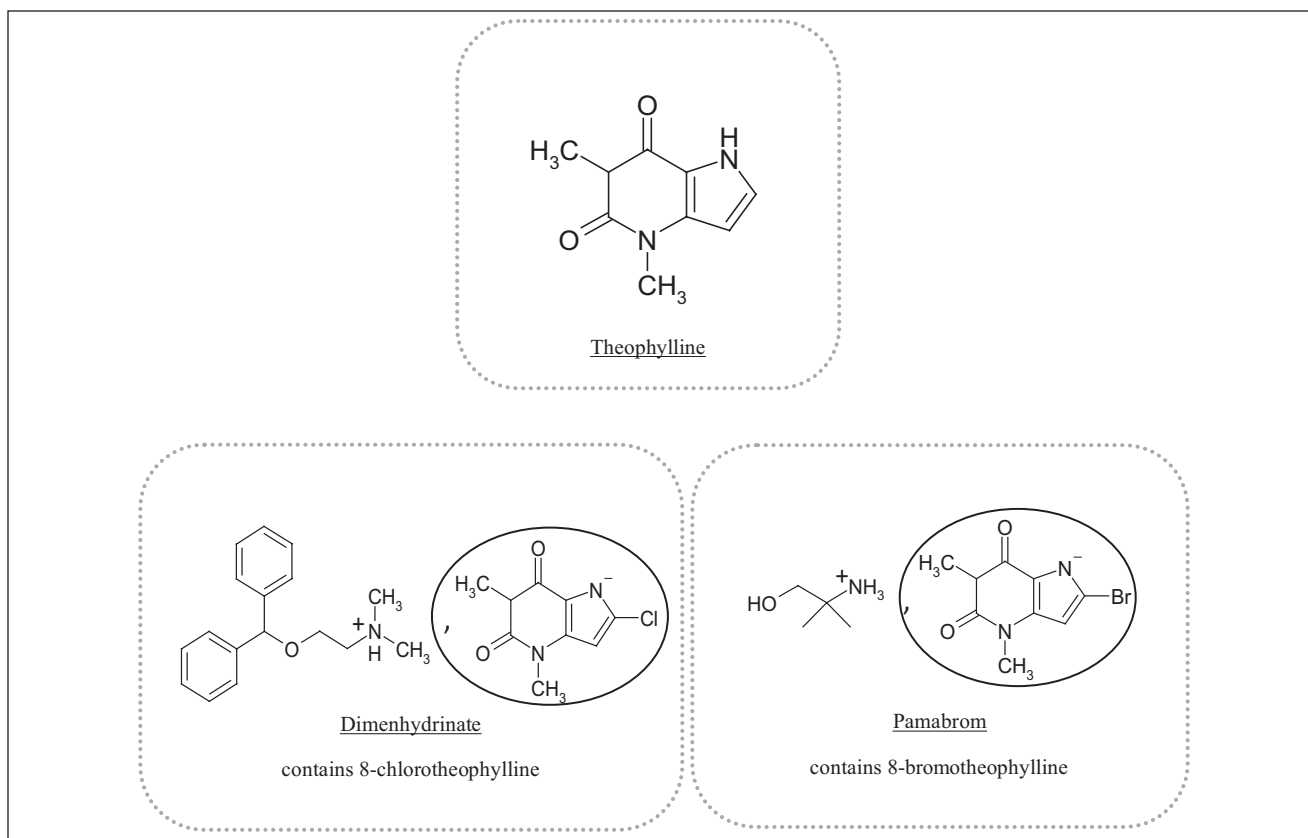


Figure 1. Chemical structures of theophylline, dimenhydrinate and pamabrom.

There were 2 other reports found in the literature that presented similarly to our case.^{2,12} A 27-year-old woman presented with sudden pruritic rash on the palms that rapidly progressed to the soles and the flexural surface of the elbows 10 minutes after she took 50 mg of dimenhydrinate due to a planned car trip. Within 30 minutes of appearance of the rash, she developed emesis, diarrhea, and pain in the lower abdomen. The symptoms resolved without treatment within 1 hour. She reported multiple intakes of dimenhydrinate in the past without any reaction. History was insignificant for other allergic disease, with no reports of atopic dermatitis, urticaria, or food or drug allergy. A skin test was carried out to confirm allergy to the theophylline component of dimenhydrinate.² The second case was a 9-year-old boy who developed Stevens-Johnson syndrome after taking slow-release theophylline for bronchial asthma. He presented to the emergency department with a history of fever and rash. Slow-release theophylline was started 2 weeks prior to the current presentation. Two days before admission, he developed high fever and conjunctivitis, which became purulent the next day. A rash appeared on his face, eyelids, and neck. When his condition worsened, he was given oral penicillin-V and was brought to the hospital. The rash was morbilliform with some vesicles and erythema multiforme was considered. Blood samples sent for migratory inhibition factor test showed

sensitivity to sustained-release theophylline with a migration index of 0.68 (normal values are 0.85-1.00). Migration index for penicillin was found to be 0.71, which is considered only borderline low. The final diagnosis was reached when a bullous eruption with positive Nikolsky's sign appeared and the mucous membranes became affected. The authors concluded that, considering time line, positive migratory inhibition factor test for theophylline and clinical course, theophylline was the causative agent of Stevens-Johnson's in this case.¹²

We recommend that an in-depth and comprehensive history taking should be carried out for all patients presenting with drug allergies before they are labeled as allergic to a particular medication. In our case, the patient was erroneously labeled as allergic to acetaminophen in spite of a negative drug challenge 3 years ago. This may deny her proper use of a very important agent which forms the cornerstone in the management of pain. History taking should include all ingested medications and supplements, dietary changes, and possible chemical and environmental exposures. Any relevant medical history, including previous reactions and when they occurred, severity of reactions, what was done before the resolution of signs and symptoms occurred, and any temporal relationship between exposure and presentation of symptoms should be delineated to ascertain causality and exclude unlikely contributors.^{13,14} In our case, we

extensively questioned the patient about her medical history and all possible drug, chemical, and dietary exposures with respect to presentation of signs and symptoms in order to come to the conclusion that there was a relationship between dimenhydrinate and pamabrom.

Although the gold standard of diagnosis for a true allergic reaction to any drug would be to carry out skin testing, we did not do it because we felt that the clinical history was sufficient. Additionally, because of the severity and nature of her reaction to just half a tablet of Panadol Menstrual, it would not be ethical to subject her to the risks of testing.

Our patient was informed of her allergies to pamabrom and dimenhydrinate. Her allergy to acetaminophen was removed from the national patient database, and allergy status to pamabrom and dimenhydrinate were added to the database. She was educated to inform all health care professionals of her severe adverse reaction to theophylline-related medications, and the importance of strict avoidance of all medications containing the theophylline structure. We reinforced that she was able to take plain acetaminophen, but since many acetaminophen-containing products have other active ingredients, she should always check with a pharmacist or a doctor before consuming them.

This is the first report of erythema multiforme to dimenhydrinate. Our case was unique as the patient experienced cross-reactivity between pamabrom and dimenhydrinate, with the common factor being the theophylline structure. Both are easily accessible medications and could lead to serious complications if consumed unknowingly.

All patients presenting with allergies should be subject to detailed history taking to establish causal and temporal relationships between drug exposure and manifestations of signs and symptoms to ensure accuracy of labeling of drug allergies. Reactions to related medications with similar structures can be predicted, and thus adverse sequelae that could result in disability or prolonged admissions could be avoided.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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