

Acebrophylline-induced angioedema

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» Abstract

A 53-year-old woman visited her physician complaining of acute breathlessness and productive cough. Her medications included budesonide and formoterol for asthma, fixed-dose combination aspirin 150 mg + clopidogrel 75 mg + atorvastatin 20 mg for ischemic heart disease. History revealed that she had allergic rhinitis and was hypersensitive to penicillins. The patient was prescribed acebrophylline (ABP). Six hours after ABP therapy she presented with generalized urticarial lesions, swelling of hands, feet, lips and face, suggestive of angioedema. ABP was stopped immediately, and the patient was treated symptomatically. This case was categorized as probable as per standard causality assessment scale.

Keywords: Allergic, de-challenge, Naranjo's scale, urticarial lesions

» Introduction

Angioedema is defined as a deep dermal, subcutaneous and/or mucous swelling, which usually lasts for 1 to 3 days, whereas urticaria usually represents a more acute, superficial dermal swelling due to plasma leakage and vasodilation. [1] Drug-induced angioedema is associated with urticarial lesions in approximately 50% of cases and may be complicated by life-threatening anaphylaxis. It could be due to a wide range of drugs and vaccines including non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors, bupropion, angiotensin II receptor blockers, antibiotics, radio-contrast agents, proton pump inhibitors, statins, fibrinolytic agents, estrogens, diuretics, calcium channel blockers, beta blockers, and anti-depressants (serotonin reuptake inhibitors). [1] Angioedema is one of the most

commonly reported ADRs and is usually seen in women. [2] ACE inhibitors are the leading cause of angioedema wherein, 0.5% of patients develop this reaction and the highest incidence (5.5%) is seen in the black race. NSAIDs can produce the angioedema in about 0.3% of patients; facial edema is the commonest presentation. [2]

The rationale behind using acebrophylline (ABP) in this patient was that the drug is known to be most effective in patients suffering from acute or chronic bronchitis, chronic obstructive pulmonary disease, and asthma. It reduces the episodes of bronchial obstruction, dosage of β_2 -agonists, and improves ventilatory functions. [3]

» Case Report

A 53-year-old female patient with a history of asthma and allergic rhinitis since 18 years with a known history of hypersensitivity to penicillins came to the hospital with worsening of breathlessness and productive cough. She was on budesonide and formoterol dry powder inhalers daily prophylaxis for control of asthmatic symptoms. The patient was on fixed-dose combination (FDC) of aspirin 150 mg + clopidogrel 75 mg + atorvastatin 20 mg and Tablet diltiazem 40 mg since 1 year for ischemic heart disease. Patient vitals were stable, and respiratory examination revealed bilateral rhonchi. Chest radiographs were normal, and all the laboratory investigations (including complete blood count, arterial pH, serum electrolytes, thyroid profile, liver function tests and urinalysis) were reported normal. The patient was admitted in view of severity of symptoms and was treated with (ipratropium + salbutamol) nebulization, injection methylprednisolone 40 mg intravenously (IV) 3 times a day, tablet (aspirin 150 mg + clopidogrel 75 mg + atorvastatin 20 mg) FDC and tablet diltiazem 40 mg. FDC containing tablet (montelukast 10 mg + levocetirizine HCl 5 mg) and tablet ABP 100 mg 2 times a day were added, 1 day later due to non-resolution of symptoms. After 6 h of ABP administration, she developed generalized itching, swelling of both hands and feet. On clinical examination, both hands and feet, lips and face were swollen with no signs of laryngeal edema. This could be attributed to the prior administration of systemic corticosteroids. Dermatology consultation was sought, and ABP was stopped. Swelling started regressing 24 h after withdrawal of the drug. However, erythematous lesions overpalms and soles were not resolved completely. Disappearance of lesions within 24 h following ABP discontinuation confirmed drug induced angioedema. However, no rechallenge was done. A detailed past medication history was elicited which revealed patient was treated with doxophylline and ambroxol in the past for acute exacerbations of asthma with no untoward effects. After 2 days of drug discontinuation, all lesions subsided. Methyl prednisolone was tapered and replaced by oral deflazacort 6 mg. Patient was discharged after complete clinical recovery.

» Discussion

Mucoactive agents are very useful for the treatment of respiratory diseases in which mucus hypersecretion is a major clinical complication. ABP (drug molecule containing ambroxol and theophylline-7 acetic acid) is a bronchodilator with mucosecretolytic, anti-reactive and anti-inflammatory activities. The efficacy, cost effectiveness and favorable tolerability profile of ABP are reflected in recommending it as an add-on drug. Numerous trials in adults and children confirm the excellent safety profile of ABP, with a low rate of adverse reactions like mild gastrointestinal upset (2.6%). In a post-marketing survey, ADRs were reported only in 6.5% of subjects. Most of the ADRs were mild and transient, and treatment required discontinuation only in 0.7% of cases. [4] A clinically significant reduction of bronchial hyperresponsiveness was also noted in 7 out of 10 patients after a single dosage of ABP and the effect was seen 24 h after the last dose following 1-month of treatment. [5]

In the present case, symptoms of angioedema were found to be unrelated to food, activity or stress. Aspirin (NSAID) could not be the alternate cause for angioedema as the patient was tolerating the drug well for past 1 year. Moreover, the reaction started six hours after starting ABP, hence proving temporal association. Discontinuation of the drug is the ultimate litmus test to confirm an ADR which was done in this case. Angioedema abated after 2 days of withdrawal. However, no re-challenge was done. According to Naranjo's (score +5) and WHO causality assessment scale, this case was categorized as "Probable." A serious complication like angioedema due to ABP might not be uncommon and should be looked out for.

In the absence of concrete proof regarding mechanism of development of ABP hypersensitivity, we can only speculate that it could be due to IgE-mediated type 1 allergic reaction. Clinicians prescribing ABP should be aware of this potential adverse effect, such that it may be recognized and managed in a timely manner.

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