ACEBROPHYLLINE INDUCED FIXED DRUG ERUPTIONS: A CASE REPORT

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ABSTRACT
Acebrophylline is used in the treatment of asthma and chronic obstructive pulmonary disorder. Acebrophylline is a widely prescribed oral bronchodilator with mucosecretolytic and anti-inflammatory activity. It works by relaxing the muscles of the airways and also thins and loosens mucus, making it easier to breathe. Side effects include Abdominal discomfort and distension, Flatulence, Nausea or Vomiting, Diarrhea, Heartburn, Gastrointestinal Bleeding, Difficulty in breathing, Skin rash, Increase in white blood cell count, Drowsiness, Swelling of the eyes, ears, and inside of nose, Fever with chills, Headache, Numbness of the hands, Sleeplessness, Increased heartbeat and weakness. A 60year old male visited to hospital with Complaints of worsening breathlessness and productive cough. His past medications include Budesonide and formetrol inhalation for acute exacerbation of COPD and oral phenytoin for Epilepsy. He was prescribed Acebrophylline(ABP) 200mg once daily after 3 days he presented with multiple erythematous wheals seen over back and shoulders associated with itching. ABP was stopped immediately and patient was treated symptomatically. This case is categorized as Probable as per Narinjos causality assessment scale.

KEYWORDS: fixed drug eruptions, pharmacovigilance, Naranjo’s causality assessment scale, Acebrophylline.

INTRODUCTION
Fixed drug eruptions (FDE) are known to arise from a variety of medications such as analgesics, anticonvulsants, sedatives, antifungal medications, and antibiotics. Fixed drug eruptions is a cutaneous reaction to ingested drugs and is not uncommon. Typically, FDE
begins with a sharply demarcated oval or circinate macule. Less commonly, FDE appear as plaques, bullae or erosions and may koebnerize. Although they are usually asymptomatic, there may be associated pruritus, pain, or burning. Each eruption may form solitary or multiple lesions, which typically appear within hours to days after ingestion of the drug. The lesions initially are small and solitary, but may become quite large and numerous. After the initial stage of acute flare, hyperpigmentation of the lesion may follow. Most initial eruptions are localized; recurrent eruptions localize to the same region after re-challenge with the drug (hence, "fixed"). However, the lesions can also be generalized or random. The genitalia, lips, and hands are among the most commonly affected sites, although any site may be affected, including the conjunctivae and oropharynx. Lesions persist as long as the drug challenge exists and tend to resolve with scaling. Upon re-challenge, lesions typically develop more rapidly than in the first exposure and commonly appear in original and additional sites. The healing process may take days to weeks after the drug is discontinued and may leave a hyperpigmented patch. Atypical presentations may include non-pigmented, giant (>20 cm), urticarial, and papular lesions.\textsuperscript{[1]} 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 $\beta_2$-agonists, and improves ventilatory functions.\textsuperscript{[2]}

**CASE REPORT**

A 60 years old male patient with history of Epilepsy and COPD since 3 years with no known history of hypersensitivity to any drug came to hospital with worsening of breathlessness and productive cough. He was on budesonide and formetrol inhalation daily prophylaxis for control of COPD symptoms. The patient was on phenytoin 100mg since 3 years for epilepsy. Patient vitals were stable and respiratory examination revealed bilateral rhonchi, chest radiographs were normal and all other laboratory investigations (include complete blood count, arterial PH, serum electrolytes, thyroid profile, LFT and urine analysis) were reported normal. The patient was admitted in view of severity of symptoms and was treated with Ipratropium and salbutamol nebulisation, tab. Azithromycin 500mg, inj. Methylpresnisolone 40mg I.V. once daily, Tab. Phenytoin 100mg once daily, Tab. Acebrophylline 200mg once a day is added. After 3 days of ABP(Acebrophylline) administration he developed multiple erythematous wheels seen over back and shoulders. Multiple eruptions seen over back associated with rash and itching which was more during night.
Dermatologist consultation was sought, ABP was stopped. Itching started regressing after 24hrs of withdrawal of drug. However erythematous lesions over back, shoulders were not completely resolved.

Disappearance of lesions and itching within 24hrs following ABP discontinuation confirmed drug induced fixed drug eruptions. However no rechallenge was done. A detailed past medication history was elicited which revealed patient was treated with budesonide and formetrol, phenytoin in past for acute exacerbations of COPD and epilepsy with no untoward effects. After 4 days of Drug discontinuation all lesions subsided. 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. 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.

In present case, symptoms of drug eruptions were found to be unrelated to food, activity or stress. Phenytin couldn't be the alternate cause for fixed drug eruptions as the patient is tolerating the drug well for past 3years. Moreover the reaction started 3 days of 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. Lesions abated after 4days of drug withdrawal. However no rechallenge was done. According to Narinjo causality assessment scale, this case was categorized as "Probable". A serious complication like drug eruptions due to ABP might not be uncommon and should be looked out for. In absence of concrete proof regarding mechanism of development of ABP hypersensitivity we can only speculate it could be due to IgE-mediated type 1 allergic reaction.
Management
When taking history it is important to look for evidence implicating a particular offending agent, such as newly initiated drug. A full history of exposure to drugs and other chemicals is essential. The reaction usually occurs in first week after initiating of therapy and sometimes within hours of first dose. As a result it may be clear which drug is most likely cause, in patients taking more than one implicated agent. In severe angioedema, the most critical step is to maintain patient airway, since mortality is related directly to the severity of airway obstructive. If signs of shock are present, Adrenaline (epinephrine) should be administered. Initiation of Antihistamine and steroids may be of value, especially if causative agent is unknown or if the mechanism is thought to be allergic. Patients with mild self limiting urticaria may be reassured that symptoms typically disappear within few hours to days.

REFERENCES
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