

Drug Induced Maculopapular Rash With The Commonly Used First Line Antitubercular Drug, Pyrazinamide

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Citation

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Abstract

Pyrazinamide is a commonly used first line antitubercular drug. Gastric related adverse drug reactions are common with pyrazinamide. Dermatological manifestations due to pyrazinamide are rare. We report a case of erythematous maculopapular rash caused by pyrazinamide in a patient treated for tuberculosis. The rashes disappeared after stopping the drug. The patient was rechallenged with pyrazinamide, which led to occurrence of similar type of rash. The causality, severity and preventability were assessed using the Naranjo, Hartwig scale and Modified Schumock and Thornton scales respectively. Since pyrazinamide is a commonly used drug in tuberculosis and tuberculosis is a common problem in developing countries, this ADR due to pyrazinamide gains importance.

INTRODUCTION

Pyrazinamide is used in the management of Tuberculosis (TB) in combination with other drugs. The common side effects due to pyrazinamide are hyperuricemia (gout) hepatotoxicity, nausea, vomiting, flushing, dysuria, arthralgia, sideroblastic anemia.¹ Rarely skin rashes and photosensitivity are reported during the treatment of pyrazinamide.^{1,2} We could not locate any report regarding maculopapular rashes due to pyrazinamide. We here by report a case of maculopapular rash due to pyrazinamide in a patient undergoing antitubercular treatment. We also establish the causality, severity and preventability of the suspected ADR.

CASE REPORT

A 57 year old lady, a chronic smoker with the history of Chronic Obstructive Pulmonary Disease (COPD) on regular bronchodilators, presented to our hospital with complaints of cough, fever, increased dyspnoea, associated with loss of appetite and weight for the past 4 months. She was evaluated for prolonged pyrexia. Her routine investigations were unremarkable but for raised ESR of 80 mm in the first hour. Chest radiograph was taken, which revealed a cavity in the right upper zone and infiltrates in the right para-hilar region and lower zones. Routine gram staining of the sputum, along with three early morning sputi for Zeihl-Nelson (ZN) staining for Acid Fast Bacillus (AFB) was done. All the three samples sent for ZN staining showed AFB. She was

referred to the local Directly Observed Treatment Short course (DOTS) centre for initiation of category 1 anti tuberculosis therapy as per national protocol according to her weight (45 kilograms). She tolerated the drugs and was discharged on day 6 of starting of therapy along with her usual bronchodilators.

After 11 days of therapy, she presented to our out patient department with symptomatic improvement in respiratory condition but with pruritic erythematous maculopapular lesions all over the body, upper and lower limbs and few papules on both arms. A diagnosis of antitubercular drug induced maculopapular rash was made. Antitubercular treatment (ATT) was stopped, oral antihistaminics were given, and she was admitted for the evaluation of the skin rash. After 3 days of stopping the therapy, her lesions improved and she was started on escalating doses of individual anti TB drugs one after the other according to the WHO guidelines, looking for any recurrence of skin reactions.³ She tolerated Isoniazid, Rifampicin and Ethambutol till the full doses but on inclusion of pyrazinamide 200 mg, she developed the rash again. Pyrazinamide was withheld and she was started on the second line drug Ofloxacin 400 mg twice a day. There was no recurrence of rash anywhere in the body. She was given a challenge dose of pyrazinamide after taking consent, since it is a good bactericidal drug effective in tuberculosis. But she developed the skin rash again (Fig 1 and 2). So pyrazinamide was again withdrawn and she was discharged

on rest of the drugs and ofloxacin. She is on regular follow up with good improvement in her clinical condition.

Figure 1

Figure 1 & 2: Pruritic erythematous maculopapular lesions over the abdomen



We carried out the causality, severity and the preventability assessments as per the Naranjo algorithm,⁴ Hatrwig scale,⁵ and Modified Schumock and Thornton scales,⁶ respectively. The causality assessment revealed a 'probable' association (Naranjo score 7) between the ADR and pyrazinamide. The severity was found to be Moderate (Level 3). The preventability analysis revealed the ADR to be 'not preventable'.

DISCUSSION

Maculopapular eruption is a fairly common adverse cutaneous drug reaction. Maculopapular rashes consist of macules (distinct flat areas) and papules (raised lesions). The rash is usually bright red in colour and the skin may feel it hot with burning sensation or itch. The whole of the skin surface may be involved; though the face is often spared.⁷ Up to 5% of the patients receiving penicillins, sulfonamides, phenytoin, or gold will develop a maculopapular eruption.⁸

Dermatological reactions due to pyrazinamide are rare. In a case report, erythema multiforme has been reported in one patient following pyrazinamide administration for cutaneous tuberculosis related to a pleural fistula. Daily ATT was initiated in this patient with isoniazid, rifampin, ethambutol, and pyrazinamide. After 26 days of therapy, maculopapular erythematous lesions appeared, and biopsy results confirmed the diagnosis of erythema multiforme. The rash disappeared with discontinuation of all drugs, but reappeared when rifampin and pyrazinamide were reintroduced 5 days later. A few days later, urticaria was observed following a single dose of pyrazinamide. No further reactions were observed with other antituberculosis agents.⁹ In our case, the patient developed the rash 11 days after initiating ATT. Upon

occurrence of the rash, the drug was stopped and the rash disappeared. The rash again reappeared when pyrazinamide was restarted. The causal relationship between the drug and the ADR found to be 'probable'.⁴ We could not locate any similar reports of maculopapular rash due to pyrazinamide. Rarely, manufacturer leaflets also reports the occurrence of maculopapular rashes due to pyrazinamide. In one investigational trial of ofloxacin (800 mg a day) and pyrazinamide (1500 mg a day), ADRs occurred very common. Of the 16 subjects, 13 had one or more adverse effects. Generalized maculopapular skin rash was seen in 3 subjects. However, these subjects were also on ofloxacin treatment and hence could not be attributable to pyrazinamide.¹⁰

The treatment of these reactions involves withdrawal of the suspected drug and treatment for any associated itching.⁸ In our patient, the drug was stopped immediately following the ADR. The associated itch was managed with antihistamines for which the patient responded well. The severity assessment revealed the ADR to be Moderate (Level 3) suggesting that the suspected drug be withheld, discontinued, otherwise changed, and/or on antidote or other treatment is required. There was no increase in length of stay. Since this patient did not have a history of skin reaction due to pyrazinamide, this reaction was unpreventable. Our observation is supported by the Modified Schumock and Thornton scale.⁶

CONCLUSION

Since pyrazinamide is a common drug used in TB management, and TB is also a common problem in countries like Nepal, and an increasing problem in the developed world, the dermatological manifestations of pyrazinamide gains attention. Upon occurrence of dermatological manifestations, the patients may become non-compliant, which is one of the common causes with other anti TB drugs for treatment failure in TB therapy. Although skin reactions due to pyrazinamide are not well reported, one should be suspicious of maculopapular rashes due to pyrazinamide also. Upon occurrence, the suspected drug (s) drug should be stopped immediately and the patient should be managed symptomatically. The patients undergoing treatment on outpatient basis should be counseled for the early recognition of dermatological manifestations.

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