FLU LIKE FEBRILE ILLNESS WHILE ON ANTI-TUBERCULAR THERAPY

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ABSTRACT
Pyrazinamide is one of the most commonly used anti tubercular drug. Adverse drug reactions such as gastritis, hyperuricemia and elevated liver enzyme levels are common with pyrazinamide. However, dermatological/skin reactions to pyrazinamide are rare/uncommon. This article finds out a dermatological manifestation/adverse drug reaction (ADR) due to pyrazinamide. Here we present a case report of male patient who developed acute onset exanthematous febrile illness caused by pyrazinamide following treatment with DOTS (Direct Observation Treatment Short course) Category -1 Anti-tubercular therapy for tubercular cervical lymphadenopathy. The patient developed fever with chills, headache, myalgia, arthralgia and itchy rash on the head, chest, trunk and thighs during the first week of DOTS Category -1 anti-tubercular regimen. The rashes and elevated enzyme levels disappeared after 3 days of stopping the anti-tubercular drugs. He was re-challenged with sequential daily dosing of isoniazid followed by rifampicin and ethambutol. Patient tolerated medications well without any fever or rashes. When he was re-challenged with pyrazinamide, rashes reappeared with febrile illness. The causality, preventability and severity were assessed using the Naranjo algorithm and Hartwig scale. Since pyrazinamide is one of the most common drug used in the treatment of tuberculosis, with the similar reports early detection and withdrawing the drug from the regimen helps in decreasing the prolonged hospital stay and healthcare cost significantly.
KEYWORDS: Tuberculosis, Pyrazinamide, Flu like febrile illness, rechallenge, Naranjo and hartwig scales.

INTRODUCTION
Tuberculosis (TB) is an infectious disease caused by a bacterium called Mycobacterium tuberculosis which mainly affects the lungs, but it can also affect the central nervous system, lymphatic system gastro intestinal tract, genitourinary tract and bones. The therapeutic management is primarily with first line anti-tubercular agents. First line drugs isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin have proved successful in treating tuberculosis. However untoward adverse reactions to drugs in general have been associated with non-compliance leading to therapeutic failure. It can also lead to prolonged hospital stay and increased healthcare cost. Anti-tuberculosis drugs are no exception to this. Understanding the nature and severity and early identification of these adverse drug reactions allows for appropriate management. Here we present a case report of male patient who developed acute onset exanthematous febrile illness following treatment with DOTS (Direct Observation Treatment Short course) Category -1 Anti-tubercular therapy for tubercular cervical lymphadenopathy.

CASE REPORT
A 55 year old male, of low socioeconomic status from Mangalore diagnosed in a peripheral clinic with tubercular cervical lymphadenopathy reported to the hospital with acute onset of fever with chills, headache, myalgia, arthralgia and itchy rash on the head, chest, trunk and thighs during the first week of DOTS Category -1 regimen. He was provisionally treated with paracetamol and etoricoxib for flu like febrile illness by a primary care physician. However fever continued to occur every time when he took the DOTS Category -1 drugs. In view of persistent fever, patient requested to be admitted for further evaluation. His white blood cell count was 7900 cells/mm. erythrocyte sedimentation rate 74mm/hr and liver enzyme levels were SGOT- 459 mg/dl and SGPT-159 mg/dl. A similar febrile reaction with maculopapular rashes occurred within 30 minutes following intake of DOTS Category-1 in the hospital. In view of temporal relationship between the drugs and occurrence of febrile illness, DOTS Category-1 was stopped. Patient was treated for his symptoms with antihistamines (oral tablet and lotion for topical application). The rashes and elevated enzyme levels disappeared after 3 days of stopping the anti-tubercular drugs. He was re-challenged with sequential daily dosing of isoniazid followed by rifampicin and ethambutol. Patient tolerated medications well.
without any fever or rashes. When he was re-challenged with pyrazinamide, rashes reappeared with febrile illness. Pyrazinamide, identified as the culprit drug, was stopped. The rash and fever subsided and was discharged from the hospital with isoniazid, rifampicin, ethambutol and pyridoxine. Patient is maintaining well without any symptoms during the follow up period.

DISCUSSION

Adverse drug reactions are considered to be one of the leading causes for increased morbidity and mortality. Around 5-6% of hospital admissions are estimated to be due to adverse drug reactions and about 6-16% of hospitalized patients experience adverse drug reactions. Incidence of adverse drug reactions is higher in elderly patients receiving poly pharmacy for multiple ailments.\textsuperscript{[3,5]} Inclusion of Pyrazinamide in the first line anti-tubercular regimen has significantly reduced the course of therapy to six months. Gastric effects, liver injury and hyperuricemia are common adverse reactions with pyrazinamide. However the incidence of cutaneous reaction to pyrazinamide is very rare and exanthematous febrile reaction mimicking flu like illness is not much reported in medical literature. In a case report by Ribi and Hauser.\textsuperscript{[4]} cutaneous skin reaction has been reported following pyrazinamide administration in a patient with active pulmonary tuberculosis. Patient was initiated with a single dose of isoniazid and rifampicin. The other three drugs (pyrazinamide, ethambutol and pyridoxine) were added on the next day. Within minutes, patient developed nausea, dyspnoea and abdominal discomfort, cutaneous flush followed by an itchy rash. The skin eruption disappeared within 24 hours and didn’t recur after sequential re-challenge initially with reduced dose and later by full doses of isoniazid and rifampicin. Patient developed an identical rash within half an hour after administration of 500mg pyrazinamide. Re-challenge with ethambutol was well tolerated and no further reactions were observed with other anti-tubercular drugs. In our case, the patient developed the rash, fever with chills, myalgia, arthralgia and elevated liver enzyme levels after starting first line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) and disappeared once the regimen was stopped. The SGOT and SGPT levels decreased to 69mg/dl and 93mg/dl on the 3rd day of the hospital stay. The sequential reintroduction with normal dose of isoniazid, rifampicin and ethambutol was well tolerated without any untoward reaction. However patient experienced febrile reaction with rashes when the pyrazinamide was reintroduced. Pyrazinamide was withdrawn from the regimen and the patient was continued with three anti-tubercular drugs and was discharged from the hospital.
The management of suspected adverse drug reaction needs immediate withdrawal of the offending drug and treatment of the symptoms. In our case, the suspected drug was stopped promptly and antihistamines (oral tablet and topical lotion) were added to manage symptoms. We carried out the causality assessments as per the Naranjo algorithm and severity and preventability assessments as per the Hart wig scale and according to Schumock and Thornton scale. The causality assessment revealed a “definite” association (Naranjo score 9) between the adverse drug reaction and pyrazinamide. The severity assessment scale revealed adverse drug reaction to be of moderate (level 4), suggesting that the suspected drug be withheld, discontinued, otherwise changed, and/or an antidote or other treatment was required. There was significant increase in the length of hospital stay. Since this patient did not have any past history of exposure to skin reaction due to pyrazinamide or any other drugs, preventability assessment revealed this adverse drug reaction to be ‘not preventable’.

CONCLUSION

Tuberculosis is one of the most common diseases in India. Pyrazinamide along with isoniazid, rifampicin and ethambutol has been used as first line drug in the management of tuberculosis. Pyrazinamide induced dermatological reactions are rare and an exanthematous flu like illness is still rarer and not much reported in the medical literature. This may mislead the doctor for a nonspecific viral illness. Hence such cutaneous reactions with anti-tubercular drugs should prompt the physician to consider pyrazinamide as the offending drug and it should be withdrawn from the regimen promptly rather than stopping all the four drugs. This will help in decreasing the prolonged hospital stay and healthcare cost significantly. All patients who are on tuberculosis treatment should be advised about the possibility of cutaneous adverse drug reactions with anti-tubercular drugs and to seek medical advice at the earliest.

REFERENCE