CASE REPORT

Pyrazinamide Induced Polyarthralgia and Myalgia in a Case of Pulmonary Tuberculosis – A Case Report

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Abstract:

Pyrazinamide Induced polyarthralgia is common but myalgia is an uncommon adverse drug reaction. Understanding a case with estimated peak plasma concentration correlation is very rarely performed. We describe a case of 45 year old female patient with pulmonary tuberculosis who developed polyarthralgia and myalgia with the standard dose of pyrazinamide in a fixed-dose antitubercular regimen. She had an estimated peak plasma concentration of 48.2 µg/ml which was in the upper limit of the normal range of proposed therapeutic range for pyrazinamide. She had increased levels of serum uric acid and creatine kinase. Resolution of polyarthralgia was observed within 14 days of pyrazinamide dechallenge. However, resolution of myalgia was delayed.

Keywords: Pulmonary Tuberculosis, Pyrazinamide, Polyarthralgia, Myalgia

Introduction

Tuberculosis (TB) is a curable infectious disease that impacted 10 million individuals worldwide and 1.4 million died in the year 2019 [1]. Pyrazinamide (Z) is a bactericidal agent used with other first-line antitubercular drugs in Antitubercular Therapy (ATT) with a fixed-dose regimen to treat tuberculosis. This agent is used in the intensive phase of treatment to reduce the duration of treatment required. However, Pyrazinamide (Z) is a pro-drug that needs to be converted into its active form Pyrazinoic Acid (POA) by a bacterial enzyme. Pyrazinoic Acid, a major metabolite of Pyrazinamide (Z) can inhibit the renal tubular secretion of uric acid, resulting in increased urate production and subsequent hyperuricemia. Hyperuricemia with or without arthralgia is the main adverse effect of Z [2-4].

Drug-induced myalgia is among the most common causes of muscle disease and the spectrum can range from mild myalgia to chronic myopathy, with severe weakness, or massive rhabdomyolysis with acute renal failure [5]. Pyrazinamide with polyarthralgia and myalgia is a rarely observed phenomenon. A pilot study [6] conducted by our institute found all the pulmonary TB patients receiving National Tuberculosis Elimination Program (NTEP) Fixed Dose Combination (FDC) antituberular regimens achieved 2 hour plasma concentration of pyrazinamide in reported normal range but near to the Upper Limit of Normal (ULN) contrary to other studies [7]. According to a study,

the percentage of time when the concentration (C_{max}) exceeded 20 µg/ml for pyrazinamide, rate of adverse event particularly arthralgia is observed in daily regimens [8]. The dose of pyrazinamide that optimizes efficacy while remaining safe is not established with Pharmacokinetic (PK)-toxicity analysis in Indian patients. So, we report a case of 45 y/o female patient with pulmonary tuberculosis who developed polyarthralgia and myalgia with the weight based dose of pyrazinamide therapy in a fixed-dose antitubercular regimen, attempting to correlate with the pharmacokinetics of pyrazinamide.

Case Report:

A 45-year-old woman weighing 42 kg with no known co-morbidities presented to the Pulmonary Outpatient Department (OPD) of Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital, Pune with pain (arthralgia) in the left lower limb and interscapular area with complaint of generalized muscle aches for a day. Physical examination revealed stiffness in popliteal regions, calves, and arches of feet on standing. Her drug history revealed quadruple ATT according to bodyweight with 3 tablets per day of Akurit-4® containing Isoniazid (H) 75 mg, Rifampicin (R) 150 mg, Ethambutol (E) 275 mg, pyrazinamide 400 mg. She had already completed 6 weeks and 3 days of the anti-TB regimen. Her baseline investigations (pre-anti-TB treatment) prior to reporting in this OPD showed Serum Uric Acid (SUA: 386.62 µmol/L) (normal range: 160.6 - 432.2 µmol/L) and Creatine Kinase (CK: 106 U/L) (normal range: 0-170 U/L) within normal limits. Suspecting pyrazinamide-induced hyperuricemia, her SUA and CK were measured. On the same day after admission to the hospital, she was asked to take her usual dose of ATT regimen. Her venous blood (3 ml) was withdrawn at 0, 1, 2, 3, 4, and 6 hours for estimating pharmacokinetic parameters of all the first-line antitubercular drugs. The plasma concentrations were quantified six times to identify intraday variation using a simple and validated Liquid Chromatography-Tandem Mass Spectrometry (LCMS/MS) developed in collaboration with the Department of Pharmaceutical Chemistry, Poona College of Pharmacy, Pune, Maharashtra, India for simultaneous measurement of all the first-line antitubercular drugs [9]. Pharmacokinetic evaluations (area under the curve AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, and C_{max}) and the recording of plasma concentration vs. time profiles of all four analytes were performed using PK solver by non-compartmental extravascular analysis [10].

Fig. 1(a) Plasma concentration curves vs. time profiles of pyrazinamide (Z) and Fig. 1(b) Representative chromatograms pyrazinamide (Z, 1200 mg) in a patient plasma sample obtained 2 hours after an oral dose of weight-based NTEP FDC regimen. The reference ranges for Cmax were 3 to 5 µg/ml for isoniazid, 8 to 24 µg/ml for rifampicin, 20 to 50 µg/ml for pyrazinamide, and 2 to 6 µg/ml for ethambutol. This range represents the expected (average) concentrations (C_{max} in µg/ml) in adults with standard daily doses of ATT used to treat tuberculosis [11]. The method adopted for the estimation of pyrazinamide (Z) was selective, precise, and accurate as per USFDA norms [12].

SUA and CK to 624.54 µmol/L and 376 U/L respectively were increased. Her estimated peak plasma concentration (C_{max}) for pyrazinamide was found to be 48.2 µg/ml (Table 2). Her sodium, potassium, urea, and creatinine levels were all normal as were her transaminases, bilirubin, and

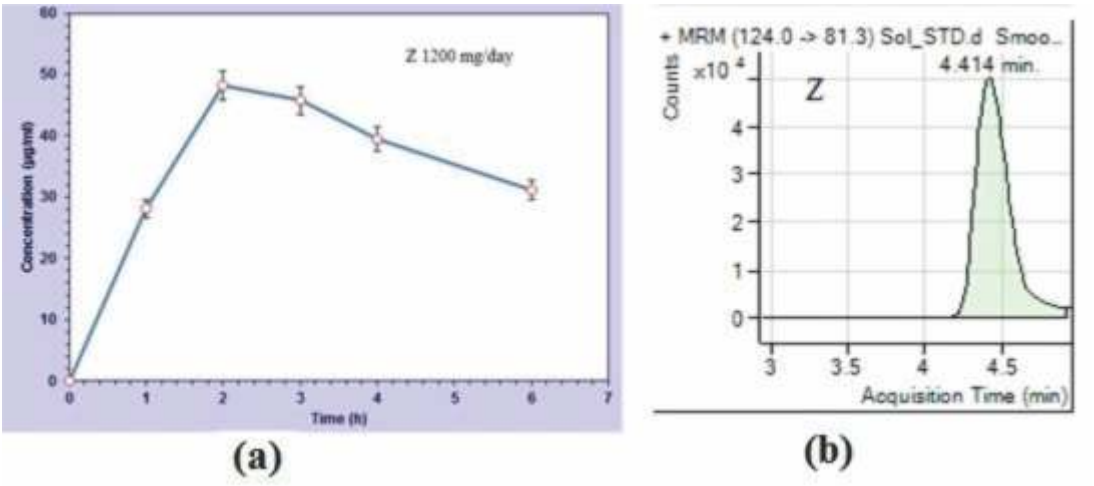

Fig. 1(a): Plasma Concentration Curves vs. Time Profiles of Pyrazinamide (Z)

Fig. 1(b): Representative Chromatograms Pyrazinamide (Z, 1200 mg) in a Patient Plasma Sample Obtained 2 hour after an Oral Dose of Weight Based NTEP FDC Regimen [13]

albumin. Febuxostat 40 mg/d was added to her medication chart for the management of increased SUA. For the next few days, SUA and CPK were measured regularly and found to be in increasing trend (684.02→ 725.66 µmol/L) and (452→ 557 U/L) as shown in Table 1. At this time her joint pain and stiffness evolved at multiple sites. On examination, she had symmetrical polyarthralgia of predominantly large joints without synovitis and joint effusion. As no improvement was observed so Akurit-4® was de-challenged. She was prescribed with Rifampicin/Isoniazid: 450/300 mg/day, Ethambutol: 800 mg/day. Instead of pyrazinamide, Levofloxacin: 500 mg/day was started according to Revised National Tuberculosis Control Program (RNTCP) now renamed as NTEP Guidelines [13]. She was discharged after 18 days of stay in the hospital as her symptoms started resolving. She was advised to continue with febuxostat 40 mg/day for 12 days and ibuprofen 400 mg twice daily for 7 days. Her polyarthralgia subsided completely, however, she still had complaints of generalized muscle aches, feeling weak while walking and standing. On examination, there was no focal muscle tenderness and her reflexes were normal. When SUA and CK tests were repeated, were found to be 423.50 µmol/L and 212 U/L respectively. As her SUA was at the upper limit of the normal range, she was asked to continue febuxostat for 10-more days.

Advised for follow-up after 14-days. Upon follow-up examination, she had no complaints and her weight improved. She was asked to continue with the ATT.

Table 1: Laboratory Monitoring Workup of Serum Uric Acid, Creatine Kinase and Plasma Level of Pyrazinamide

Parameters	Case	
Pre-treatment	SUA – 386.62 µmol/L	CK - 106 U/L
During the treatment	SUA – 624.54 µmol/L SUA – 684.02 µmol/L SUA – 725.66 µmol/L	CK – 376 U/L CK – 452 U/L CK – 557 U/L
Post-discontinuation (18 days)	SUA – 423.50 µmol/L	CK – 212 U/L
Plasma levels of Pyrazinamide (estimated)	**48.2 µg/ml** (Reference therapeutic range: 20-50 µg/ml)	

SUA – serum uric acid, CK – creatine kinase

Table 2: Summary of Pharmacokinetic Parameters Derived from Extravascular Non-compartmental Analysis

Parameter	Results (mean) for:			
	Rifampin (R)	**Isoniazid (H)**	**Pyrazinamide (Z)**	**Ethambutol (E)**
C_{max} (µg/ml)	5.6	4.2	**48.2**	4.2
T_{max} (h)	2.0	2.0	2.0	3.0
AUC_{0-6} (µg/ml · h)	18.1	13.1	212.5	15.65
$AUC_{0-\infty}$ (µg/ml · h)	21.49	15.39	**459.14**	18.96
$t_{1/2}$ (h)	1.80	1.77	**5.47**	1.76
CL/F (liters/h)	20.93	14.61	2.61	43.50
Vz/F (liters)	54.66	37.33	20.65	110.87

Discussion:

Pyrazinamide is responsible for shortening the duration of ATT of rifampin-containing regimens to the current 6-month standard for drug-susceptible TB. Currently, 15 to 30 mg/kg of body weight/day of pyrazinamide is used in standard ATT regimen; however, antimicrobial pharmaco-kinetic-pharmacodynamic studies suggested that higher doses would be more efficacious [14]. But the main limitation has been a high rate of adverse reactions [15]. Frequently described Adverse Events (AEs) are arthralgia and hepatotoxicity. The most frequent AE associated with pyrazinamide

was arthralgia, which occurred late (after 1 month) and was non-severe. In our case, the patient had polyarthralgia with unbearable pain while walking and standing. Polyarthralgia occurred more frequently in pyrazinamide-based regimens, consistent with data from previous reports [16]. Arthralgia secondary to pyrazinamide is caused by hyperuricemia due to the competitive inhibition of xanthine oxidase by POA, a hydrolyzed product) which correlated closely with plasma pyrazinamide concentration. So, we estimated plasma concentrations of pyrazinamide [8].

Estimated peak plasma concentrations (C_{max}) were 4.2 μg/ml for H, 6.6 μg/ml for R, 48.2 μg/ml for Z and 4.2 μg/ml for E. AUC_{0-6} (h μg/ml) was 8.9, 19.5, 212.5 and 13.5 for H, R, Z and E respectively. Similarly, $AUC_{0-\infty}$ (h μg/ml) was 13.1, 18.1, 212.5, 15.7, and $t_{1/2}$ was 1.7 h, 1.8 h, 5.5 h, and 1.8 h for H, R, Z, and E respectively (Table 2). These results are in accordance with previously reported studies [7]. All the antitubercular first-line drugs (H, Z, and E) achieved estimated peak plasma therapeutic concentration (C_{max}) within the proposed range within 2 hours except rifampicin. Pyrazinamide had C_{max} in the ULN range. As per PK-PD studies, the AUC and C_{max} were least associated with either all AEs or arthralgia, however, since the percentage of time when the concentration exceeds 10 μg/ml with increased dose and more frequent dosing, these two parameters better explained the pattern of the higher rates of AE and arthralgia encountered more often with the daily therapy regimens. Meta-analysis performed in the same study also revealed that intermittent dosing reduced the frequency of arthralgia compared to the frequency of arthralgia for daily therapy. So it was proposed longer the concentration persist for pyrazinamide, even low POA levels can saturate xanthine oxidase leading to prolonged urate deposition in joints [8, 17]. Once therapy stops, the concentrations (pyrazinamide/POA) fall and urate deposition stops, and the patients feel better after a few days. In our patient the C_{max} has exceeded 10 μg/ml with 1200mg dose and was probably staying for a long time period due to daily regimen. This necessitates a future study of interest to identify PK association of pyrazinamide and arthralgia association with FDC daily regimens in Indian patients. Pharmacokinetics of other first-line ATT drugs were well within limits and do not associate with polyarthralgia.

In our patient, polyarthralgia occurred within the estimated therapeutic plasma concentration (C_{max}) of pyrazinamide. Her polyarthralgia improved on cessation of pyrazinamide, but the improvement in her myalgia and creatine kinase was delayed. One case report [18] of pyrazinamide-induced polyarthralgia and myopathy was published where even ethambutol was also discontinued, as the patient in this case report had very high CK levels (4786 U/L) and struggled to stand unaided.

However, ethambutol was continued in our patient and responded well on pyrazinamide dechallenge. Other two case reports of myopathy associated with pyrazinamide had myoglobinuric renal failure [19] and mild renal failure on cyclosporine [20]. Our patient did not have such aggravating risk factors to contribute to myopathy/ myalgia.

Conclusion:

Polyarthralgia secondary to pyrazinamide is well recognized and resolves early compared to myalgia upon discontinuation. Polyarthralgia and myalgia can be experienced within the plasma therapeutic range of pyrazinamide.

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How to cite this article:

Panda BK, Suryawanshi VR, Thomas A, Bargaje M, Sathiyanarayanan L. Pyrazinamide Induced Polyarthralgia and Myalgia in a Case of Pulmonary Tuberculosis – A Case Report. *J Krishna Inst Med Sci Univ* 2021; 10(3): 82-87.

Submitted: *28-Feb-2021* ***Accepted:*** *22-May-2021* ***Published:*** *01-Jul-2021*