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Incidence of Pyrazinamide Induced Hepatic Transaminitis in Elderly Patients

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ABSTRACT

Objectives: The objective of this study was to determine the incidence of transaminitis in elderly patients treated with pyrazinamide and identify risk factors associated with the development of transaminitis.

Material and Methods: This was a retrospective clinical and epidemiological study of hepatotoxicity in patients of MDR tuberculosis. Two patient groups with and without occurrence of transaminitis were compared in this retrospective risk factor analysis, which was detected by an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >100 mg/dL.

Results: Total 92 patients were initially selected as per inclusion criteria, but 27 patients were excluded as all study details were not available with those. 65 patients were selected for the final analysis. 71.2±11.6 were the mean age of the total population and in which 40% were above 60 years of age. At initiation of pyrazinamide, measurements of both groups had AST and ALT that were within normal laboratory ranges (Table 2). The mean peak AST/ALT in the transaminitis group was 142± 42 mg/dL, with patients who did not develop transaminitis remaining within normal laboratory ranges which was 37±12 mg/dl. As compared to those with no transaminitis group, in the transaminitis group the overall percentage change in AST/ALT from start of pyrazinamide to peak was significantly higher.

Conclusion: We conclude that patients who are older and have concurrent pyrazinamide use have the highest risk of developing pyrazinamide induced transaminitis and should be monitored closely.

Keywords: Transaminitis, hepatotoxicity, elderly patients, pyrazinamide

INTRODUCTION

With an estimated prevalence of 256 per 100,000 population, TB is a major public health issue in India, and 26 per 100,000 population dying of TB [1,2]. Despite the high success rate which is as high as 85% with available antituberculous treatment (ATT), treatment-related adverse events including gastrointestinal and neurological disorders, skin reactions, hepatotoxicity etc reduced effectiveness of therapy and also account for significant morbidity [3].

2–28% of patients who were on antituberculous treatment (ATT) is reported to have Drug-induced liver injury (DILI) and this varying with the treatment regimen and study population [4,5]. Among patients receiving isoniazid monotherapy for latent TB, 20% of patients may represent hepatic adaptation by transaminitis with ATT [6-8]. By compromising treatment regimens anti-TB medications may reduce treatment effectiveness as most frequent and serious adverse effects is hepatotoxicity [9,10].

Transaminase synonymously used with the word aminotransferase, is usually used in reference to the alanine transaminase (ALT) or aspartate transaminase (AST), which are typically grouped among the “liver function tests” or “LFTs”.

Pyrazinamide, is an anti-tuberculous agent, the pyrazine analogue of nicotinamide [11,12]. When combined with other antituberculous agents, Pyrazinamide is indicated for the initial treatment of active tuberculosis in adults and children. Pyrazinamide frequently is an important

drug for a six-month regimen for initial treatment of active tuberculosis [13]. Patients treated with combination of isoniazid, rifampicin and pyrazinamide, 11 % patients discontinued the therapy because of hepatotoxicity and are the commonest of all adverse effect leading to drug discontinuation [14]. Hepatotoxicity with pyrazinamide is dose dependent, doses used in current regimens (25–35 mg/kg) has less frequency of hepatotoxicity than the higher dose at 40–50 mg/kg [15].

The objective of this study was to determine the incidence of transaminitis in elderly patients treated with pyrazinamide and identify risk factors associated with the development of transaminitis.

MATERIALS AND METHOD

This was a retrospective clinical and epidemiological study of hepatotoxicity in patients of MDR tuberculosis. The main inclusion criteria were patients who are on treatment with second line antitubercular drug. Patients who were having records of clinical evaluation, complete history and investigation were included. Patient not suffering from tuberculosis, non consenting individuals, patients with pre-existing hepatic derangements due to some other systemic illnesses and patient not on second line antitubercular therapy were excluded from the study.

Two patient groups with and without occurrence of transaminitis were compared in this retrospective risk factor analysis, which was detected by an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >100 mg/dL. During pyrazinamide treatment if at any point transaminitis develops, is held until the patient's ALT or AST normalise. As per definition 14–40 mg/dL and 9-48 mg/dL were defined as normal ranges. Secondary outcomes included the percent AST/ ALT elevation from baseline and development of liver dysfunction.

A pre-designed proforma were used to record relevant information for the analysis of the result. Statistical analyses were performed using SPSS version 12.0 software (SPSS Inc., Chicago, IL, USA).

RESULT

Total 92 patients were initially selected as per inclusion criteria, but 27 patients were excluded as all study details were not available with those. 65 patients were selected for the final analysis. Demographic details were illustrated in table 1. 71.2±11.6 years were the mean age of the total population and in which 40% were above 60 years of age.

Table 1: Demographic and clinical characteristics of patients (n = 65)

Characteristics	Findings
Age (Years)	71.2±11.6
Age > 60 years	26 (40%)
Men (N%)	39 (60%)
Body weight (Kg)	51.6±9.4
BMI (Kg/m^2)	22.7±2.6
Past history pf pulmonary tuberculosis (N%)	7 (10.8%)
Medical history, n (%)	
Liver disease	0 (0%)
Overweight (BMI>25 kg/m^2)	5 (8%)
Diabetes	9 (13.8%)

At initiation of pyrazinamide, measurements of both groups had AST and ALT that were within normal laboratory ranges (Table 2). The mean peak AST/ALT in the transaminitis group was 142± 42 mg/dL, with patients who did not develop transaminitis remaining within normal laboratory ranges which was 37±12 mg/dl. As compared to those with no transaminitis group, in the transaminitis group the overall percentage change in AST/ALT from start of pyrazinamide to peak was significantly higher.

Table 2: Baseline, peak, and percentage change in AST/ALT measurements during pyrazinamide therapy for the transaminitis and no transaminitis groups.

Characteristics	Transaminitis (n=8)	No transaminitis (n=57)
AST at pyrazinamide initiation (mg/dL)	42±12	31±11
Peak AST (mg/dL)	142± 42	37±12
Change start to peak AST (%)	271±160	25±35
ALT at pyrazinamide initiation (mg/dL)	27±12	22± 5
Peak ALT (mg/dL)	176±48	35±14
Change start to peak ALT (%)	643±268	94±79

DISCUSSION

Current study was conducted among those patients who are on treatment with second line antitubercular drugs. Relevant investigations for the diagnosis of hepatotoxicity were conducted for all the participants from a trusted local clinical pathology laboratory. In the present study, out of 65 patients 60% were male which quite correlates with a previous study conducted by SAARC [16] namely "Gender Differences among Tuberculosis Cases in National TB Control Programmes within SAARC Countries". Even in few studies it has been observed that female sex has been associated with development of drug-induced hepatitis [17,18]. The inclusion criteria of this retrospective analysis were similar to previous studies of complete cohorts of patients with TB and also comparable outcome definition to previous series [16, 19-21].

Between current studies pyrazinamide induced transaminitis reported incidence varies significantly, however the incidence of transaminitis found in this study was 13%, which is significantly higher than previously published literature [22-25]. Like results demonstrated in present study previous studies also established the fact that incidence of PZA-induced hepatotoxicity and rash was significantly higher than for the other first-line anti-TB drugs [26]. Risk factors that may contribute to the development of hepatic dysfunction, transaminitis or pyrazinamide induced transaminitis, little is known.

There are several limitation of this study, like serological test were not performed to evaluate positive hepatitis B or C serology statue and history of alcohol abuse were not recorded or considered. To further identify and evaluate during pyrazinamide use the level of LFT elevation that would raise concern for harmful liver effects and high risk for developing transaminitis, further research is warranted using a larger sample size. If more consistent hepatic monitoring is indicated, pyrazinamide induced transaminitis could then help determine risk factors, to determine if altering concomitant medications or the need for possible dose adjustments of pyrazinamide could reduce the risk of transaminitis in patients receiving pyrazinamide.

CONCLUSION

We conclude that patients who are older and have concurrent pyrazinamide use have the highest risk of developing pyrazinamide induced transaminitis and should be monitored closely.

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