BRIEF REPORT

CLINICAL CHARACTERISTICS OF PYRAZINAMIDE-ASSOCIATED HEPATOTOXICITY IN PATIENTS AT A HOSPITAL IN LIMA, PERU

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ABSTRACT

In order to determine the characteristics of drug-induced liver injury (DILI), adult patients diagnosed with tuberculosis and with an anti-tuberculosis treatment scheme including pyrazinamide were studied. The re-exposure process was used for the cause-effect analysis of the DILI. A total of 10 patients were found with pyrazinamide-associated DILI; the median age and hospital stay were 40.5 years (from 22 to 76 years) and 41 days (from 11 to 130 days), respectively. The median time in which the events appeared was 14 days (from 3 to 46 days); jaundice was observed in 4 patients and radiological patterns such as hepatocellular, mixed and cholestatic were found in 5, 3 and 2 patients, respectively. Mild presentation of DILI was observed in 6 cases (60%) and moderate in 3 (30%). In conclusion, pyrazinamide-associated DILI required prolonged hospital stay, presented jaundice in little more than a third of the cases, and radiologically, the hepatocellular pattern predominated.

Keywords: Tuberculosis; Drug Induced Liver Injury; Antituberculosis Drugs; Pyrazinamide; Adverse Drug Reaction; Length of Stay. (Source: MeSH NLM).

INTRODUCTION

Tuberculosis is a public health problem in Peru, and the total morbidity incidence rate is 99.5 per 100 000 inhabitants [1]. The two major difficulties regarding treatment are drug resistance and adverse drug reactions (ADRs). The frequency of ADRs to first-line drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) is 3.4%, the most serious one is drug-induced liver injury (DILI), which has an incidence of 2 to 28% depending on the therapeutic regimen and the characteristics of the patients (age, race, and sex) [2]

Four antibiotics are used in the treatment of tuberculosis, three of which are administered simultaneously and are potentially hepatotoxic: isoniazid (H), rifampicin (R) and pyrazinamide (Z). When the causality relationship between the antitubercular drugs administered and the DILI is analyzed, it is generally established that the three drugs are associated, since the administration was simultaneous. The most commonly used instrument to establish the cause effect relationship of a drug and DILI is the Roussel Uclaf Causality Assessment Method (RUCAM) [3], an algorithmic scorecard that allows us to determine whether the injury is hepatocellular, cholestatic, or mixed. However, when a patient receives more than one potentially hepatotoxic drug, as in the treatment of tuberculosis, RUCAM recommends considering these three drugs as one [4], so it is difficult to establish whether the DILI was associated exclusively with pyrazinamide.

There is no information available about about the characteristics or phenotypic models of DILI associated with pyrazinamide. The cases reported in Peru tend to relate the three drugs (H, R, and

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Z) to DILI without specifying whether it was possible to identify pyrazinamide [5]. The objective of this study is to describe the clinical and laboratory characteristics of pyrazinamide-induced DILI using RUCAM criteria.

KEY MESSAGES

Motivation for the study: Hepatotoxicity induced by antitubercular drugs represents a problem during treatment; adverse reactions related to rifampicin and isoniazid are well known, however, studies on pyrazinamide specifically are scarce.

Main findings: This study shows that pyrazinamide-induced hepatotoxicity begins at the third week of exposure, jaundice occurs in one-third of cases, and the predominant pattern is hepatocellular

Implications: The study and adequate phenotyping of pyrazinamide-induced hepatotoxicity would allow its prevention through future pharmacogenetic studies.

THE STUDY

Design and site research

This is an observational and retrospective study. We reviewed the medical records of hospitalized patients diagnosed with DILI by antitubercular drugs, from January 2014 to January 2019, at Almenara Hospital, in Lima, Peru, a high-complexity referral national hospital.

Inclusion criteria

The inclusion criteria were age >18 years, diagnosis of tuberculosis by baciloscopy and/or culture, and use of pyrazinamide as part of the treatment. The existence of signed informed consent for antitubercular treatment was verified in all patients.

Procedure to identify DILI by pyrazinamide

We used the DILI Expert Working Group criteria [4], which consists of the presence of one of the following findings: alanine aminotransferase (ALT) levels equal to or five times the upper normal limit (UNL); alkaline phosphatase (ALP) levels equal to or greater than twice the UNL (especially if accompanied by elevation in the concentration of 5'-nucleotidase or gamma-glutamyl transpeptidase (GGT), in the absence of known bone pathology that increases alkaline phosphatase); or elevation of ALT concentration equal to or greater than three times the UNL and simultaneous elevation of bilirubin concentration above the UNL [4]. Regarding severity, DILI was considered mild when bilirubin was <2 mg/dL, moderate when bilirubin was ≥2 mg/dL or if symptoms related to hepatitis were present, and severe if bilirubin was ≥2 mg/dL plus one of the following criteria: international normalized ratio (INR) ≥1.5, ascites, encephalopathy, another organ disfunction and death or transplant related to the DILI [4].

To identify the association with pyrazinamide, the four-phase process was verified in the clinical records: exposure, drug withdrawal, re-exposure [6], and evolution (follow-up). The exposure phase included the administration of drugs (for example, rifampicin, isoniazid, ethambutol, and pyrazinamide in the scheme for sensitive tuberculosis) and identification of the DILI criteria. The drug withdrawal phase consisted of the withdrawal of all the drugs, until the normalization of the liver enzymes was achieved. The re-exposure phase is where the drugs are progressively administered again one by one, generally starting with ethambutol then rifampicin, followed by isoniazid and finally pyrazinamide. The second method used to determine the specific association of DILI with pyrazinamide was the verification of the sole and exclusive suspension of pyrazinamide and not the observation of DILI criteria during the evolution and follow-up of the patient.

Study variables

In the review of medical records, data such as age, sex, alcohol and cigarette consumption, weight and height were obtained. To identify the characteristics of DILI, symptoms, signs, number of days of hospitalization, ALT, ALP, GGT levels were included. The registration of the pyrazinamide re-exposure process and anti-tuberculosis treatment at patient's discharge was verified.

Statistical analysis

Variables were analyzed as frequencies by using median, range and percentages. To obtain the number of times the ALT and ALP increased over the UNL in the reported cases, the serum value obtained from the patient with the LSN was divided by the UNL.

Ethical aspects

This study was approved by the Ethics Committee of the Almenara Hospital. The necessary strategies were established to maintain the privacy of patient information.

FINDINGS

Patient characteristics

Durante el periodo del estudio, 507 casos de tuberculosis fueron internados en el Hospital Almenara, de los cuales 10 (1,9%) fueron por DILI asociados a pirazinamida (Tabla 1 y 2). La mediana de días de hospitalización por DILI asociados a pirazinamida fue de 41 (rango 11-130). El diagnóstico fue tuberculosis pulmonar, pleural y multisistémica en 7, 2 y 1 casos, respectivamente. La mediana de edad fue de 40,5 años. La evolución fue favorable en todos los pacientes.

DILI characteristics

DILI was diagnosed in 7 patients with ALT ≥5 times more than the UNL. They also presented ALP ≥2 times more than the UNL (especially if accompanied by a GGT concentration increase, in the absence of bone pathology known to increase ALP), in 3 patients. Additionally, 4 patients had an ALT concentration increase greater than or equal to 3 times the UNL and an increase of bilirubin concentration greater than 2 times the UNL (Table 1 and 2).

Tabla 1. General characteristics of tuberculosis patients with pyrazinamide-induced liver injury.

Characteristics	Value
Age median (range)	40.5 (22.76)
Men, n/N (%)	5/10 (50%)
Alcohol Consumption, n/N (%)	3/10 (30%)
Cigarette consumption, n/N (%)	2/10 (20%)
Median Body Mass Index (range)	21.8 (16.1-26.5)
Median days of hospitalization (range)	41 (11-130)
Jaundice, n/N (%)	4/10 (40%)
DILI criteria	
ALT (5 times over UNL), median (range)	6.85 (1.4-43.4)
ALP (>2 times over UNL), median (range)	2.15 (1-4.4)
Total bilirubin (mg/dL), median (range)	1.1 (0.5-9.5)
GGT (times over UNL), median (range)	4.52 (1.1-13.55)
RUCAM	
Hepatocellular, n/N (%)	5/10 (50%)
Cholestatic, n/N (%)	2/10 (20%)
Mixed, n/N (%)	3/10 (30%)
Causality analysis *	
Definitive or Highly probable, n/N	4/10 (40%)
Probable, n/N (%)	6/10 (60%)
Phase of re-exposure to Z, n/N (%)	8/10 (80%)

ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; UNL: upper normal limit, RUCAM: Roussel Uclaf causality assessment method.
* RUCAM causality attribution instrument with scores from, excluded (score <1), unlikely (1-2), possible (3-5), probable (6-8) and highly probable (>8)

The median duration of the illness was 14 days (range 3-46). Jaundice was observed in 4 (40%) of the patients; and 2 (20%) patients presented skin rash and itching. According to RUCAM criteria, the injury pattern was hepatocellular in 5 (50%) patients, mixed in 3 (30%) patients, and cholestatic in 2 (20%) patients. The mean and standard deviation of ALP and ALT was 2.11 (0.93) and 12.24 (12.7) times the UNL, respectively. The mean and standard deviation of total bilirubin was 2.51 mg/dL (3.05). One patient developed DILI during pregnancy. The associated comorbidities were HIV infection (1), diabetes mellitus (1). The DILI was mild in 6 (60%) patients, moderate in 3 (30%) and severe in 1 (10%).

Causality of DILI and pyrazinamide

The association of DILI with pyrazinamide was made in 8 patients through the re-exposure process; 2 patients were left out because only pyrazinamide was suspended, and the remission of the event was verified. Eight patients with pan-susceptible tuberculosis at the time of DILI, were taking rifampicin, isoniazid, ethambutol, and pyrazinamide and were referred and hospitalized because of DILI. During hospitalization, the re-exposure process was performed, which identified pyrazinamide as associated with DILI and ruled out isoniazid and rifampicin. Regarding the pregnant patient, re-exposure was carried out during the postpartum period, which identified pyrazinamide as associated with DILI, and continued treatment with rifampicin, isoniazid, and ethambutol (Table 1).

DISCUSSION

In this study, pyrazinamide-associated DILI was found to be more frequent in the third week of administration, 40% of the cases presented jaundice, and the predominant injury pattern was the hepatocellular pattern. Regarding severity, mild and moderate DILI cases were the most frequent. Only 1.97% of the patients were hospitalized for DILI, and the hospitalization duration median was 41 days.

This study's findings can be compared with two previous studies. Abbara *et al.* [7] found that more than half of the cases occur in the first two weeks and the jaundice frequency is 12% of the cases; the DILI and RUCAM criteria were used as a causality tool; and they described the clinical and biochemical characteristics of 105 patients with DILI by antitubercular drugs (rifampicin, isoniazid, and pyrazinamide). However, the process of pyrazinamide reintroduction was not performed. An *et al.* found that DILI is more frequent in

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Table 2. Specific characteristics of tuberculosis patients with pyrazinamide-induced liver injury.

Case	Sex/ age	Diagnostic	Drugs used at the time of DILI	DILI characteristics				RUCAM		Process of re-exposure to Z	Treatment at discharge
				Jaundice	ALT (times over UNL)	ALP (times over UNL)	Total bilirubin (mg/dL)	GGT (times over UNL)	Pattern	Causality analysis *	
1	F/41	Pulmonary TB resistant to H	R, H, E, Z	Yes	14.1	2.01	6.4	12.1	Hepato-cellular	Definitive or very pro-bable	Yes	Levofloxacin -kanamycin, cycloserine, E, R
2	M/69	Pan-susceptible pulmonary TB	R, H, E, Z	No	19.2	2.0	0.5	5.2	Hepato-cellular	Probable	Yes	Levofloxacin, E, H, R
3	F/59	Pan-susceptible pulmonary TB	R, H, E, Z	Yes	43.4	1.6	9.5	13.5	Hepato-cellular	Probable	Yes	E, R, H, levofloxacina
4	M/64	Pulmonary TB resistant to H, R, E, Z	Kanamycin, levofloxacin, ethionamide, cycloserine and Z	No	1.4	4.4	0.5	7.3	Cholestatic	Probable	No**	Amikacin, levofloxacin, imipenem/cilastatin, ethio-namide and amoxicillin/ clavulanic acid
5	F/40	Pulmonary TB resistant to H, R, E, streptomycin and ethionamide	Kanamycin, levofloxacin, Z, E, ethiona-mide, cyclo-serine	No	19.1	1.8	0.9	4.6	Hepato-cellular	Probable	Yes	Kanamycin, levofloxacin, E, cycloserine, para-amino-salicylic acid, amoxicillin/ clavulanic acid
6	M/22	Pan-susceptible multisystemic TB	R, H, E, Z	No	1.6	2.7	0.7	4.5	Cholestatic	Probable	Yes	R, H, E, levofloxacin
7	M/76	Pan-susceptible pleural TB	R, H, E, Z	Yes	5.7	2.2	2.5	3.4	Mixed	Probable	Yes	R, H y levofloxacin
8	F/34	Pan-susceptible Pulmonary TB	R, H, E, Z	Yes	4.9	2.1	2.4	4.3	Mixed	Definitive or very probable	Yes	Kanamycin, ciprofloxacin, cycloserine, ethionamide
9	F/36	Pan-susceptible/ pregnant pulmonary TB	R, H, E, Z	No	8.0	1.31	0.6	1.1	Hepato-cellular	Definitive or very probable	Yes	R, H, E, levofloxacin
10	M/33	Pan-susceptible pleural TB	R, H, E, Z	No	5.0	1.0	1.1	1.3	Mixed	Definitive or very probable	No**	R, H, E

W: women; M: men; TB: tuberculosis; DILI: drug-induced liver injury; RUCAM: Roussel Uclaf causality assessment method; Z: pyrazinamide; R: rifampicin; H: isoniazid; E: ethambutol; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; UNL: upper normal limit.

*RUCAM: causality attribution instrument with scores from, excluded (score <1), unlikely (1-2), possible (3-5), probable (6-8) and highly probable (>8); **remits DILI with Z-suspension.

women, 21% of the population with DILI had jaundice, and in 75% it occurred before 2 months and was more frequent in those who received the scheme with pyrazinamide; the report did not describe the causality instrument used [8], nor did it separate its findings from the Z-induced DILI.

The two strategies used to study phenotyping of pyrazinamide-associated DILI consist of excluding rifampicin and isoniazid from the schemes, and using pyrazinamide together with rifampicin and isoniazid compared to only rifampicin and isoniazid. Younossian *et al.* studied patients with latent tuberculosis, treated with pyrazinamide and ethambutol, both drugs were discontinued in 58% of the patients at 119 days because of hepatotoxicity, elevation of liver enzymes more than 4 times the normal value, and gastrointestinal symptoms [9]. Bedini *et al.* studied patients with latent tuberculosis, treated with Z and levofloxacin, 41% of the patients presented DILI, with an AST and ALT increase of more than 4 times the normal values [10]. Chang et al. compared the treatment schemes of pyrazinamide, rifampicin and isoniazid, with those who received only rifampicin and isoniazid; the study found that the DILI in the group with pyrazinamide and without pyrazinamide was 2.6% and 0.8%, respectively [11]; this study used the elevation of ALT in more than 3 times the UNL as the hepatotoxicity criteria [11]. A meta-analysis compared the risk of hepatotoxicity of the pyrazinamide and rifampicin scheme compared to only isoniazid and found that the scheme with pyrazinamide did not increase the risk of hepatotoxicity, the hepatotoxicity criteria was ALT equal or more than 3 times the UNL [12].

Pyrazinamide-associated DILI represents about 2% of the causes for hospitalization in patients diagnosed with tuberculosis but requires more than 45 days of hospitalization. Worldwide, DILI associated with antitubercular medication and/or multidrug resistance is one of the main causes of prolonged hospitalization [13-16].

The limitations of this study are related to the retrospective design, which restrict the registration of clinical and laboratory data. Another problem was the lack of standardization of the operational definitions for phenotyping DILI associated to antitubercular medication. The reviews by Tostmann *et al*. and Hosford *et al.* [17] include up to 5 and 8 operational definitions of DILI [2], respectively. Another limitation was that RUCAM is not designed for chronic DILI nor for the coexistence of pre-existing liver diseases [18].

In conclusion, pyrazinamide-associated DILI starts at the third week of exposure, presents jaundice in more than a third of the cases, the hepatocellular pattern predominates and has prolonged hospital stay.

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