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Anti-Tuberculosis Drug - Induced Hepatitis – A Case Report

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ABSTRACT

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Introduction: This is a case report focusing on a 32 years male patient who experienced hepatotoxicity after administration of anti tubercular drugs. Isoniazid, Rifampacin, Pyrazinamide, Ethambutol are the first line agents in the treatment of Tuberculosis. The incidence rate of anti-TB induced hepatotoxicity is found to be 2% to 28%. **Case:** In this case, the patient was receiving anti-tubercular drugs from 3 months and developed hepatitis which is a severe adverse drug reaction. Naranjo's causality assessment algorithm was used to assess the adverse effect and it indicated anti-tubercular drugs as probable cause of hepatitis.

Keywords: Hepatitis, Anti-tubercular drugs, SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase).

INTRODUCTION

According to WHO, one third of the population is affected by TB and 1 in 4 adult male deaths is attributed to TB.[1] The first line anti-TB drugs are potentially hepatotoxic.[3, 4] From first line anti-TB drugs, isoniazid (INH), rifampin (RIF), and pyrazinamide (PZA) causes hepatotoxicity such as transaminasitis and fulminant hepatic failure.[2] The incidence rate of anti-TB induced hepatotoxicity is found to be 2% to 28% based on hepatotoxicity diagnosis criteria.[5] The risk factors for anti-TB induced hepatotoxicity includes high alcohol intake, older age, pre-existing chronic liver disease, chronic viral infection due to hepatitis B (HBV) and hepatitis C viruses (HCV), human immunodeficiency virus (HIV) infection, advanced TB, Asian ethnicity, concomitant administration of enzyme-inducers, inappropriate use of drugs and poor nutritional status.[2,5,6] The goal of this study was to evaluate the risk factor, alteration in liver enzymes, approach and outcome of anti-TB drugs induced hepatotoxicity in Esra hospital patient.

CASE REPORT

A 32 year old male patient was brought to the hospital in unconscious state associated with frothing from mouth and sweating. The patient consumed alcohol at night before sleeping and did not get up in the morning. Shortness of breath grade IV was observed but was not associated with seizures. Patient was diagnosed as pulmonary Koch's 3 months back and he was on regular medication.

On the 1st day, patient was brought to the hospital with pulse rate 135/min, BP was found to be 100/60 mm Hg with SPO_2 95% with high flow oxygen and General random blood sugar was dropped to 23 mg/dL. The patient was evaluated for hypoglycaemia and received following medications:

- Injection thiamine – 100 mg
- Nebulization salbutamol (100 mcg), ipratropium bromide (20 mcg) and budesonide (100mcg)
- Injection ceftriaxone - 1gm
- Injection tramadol - 1 ampoule
- Tablet chlordiazepoxide - 25mg
- 25% dextrose intravenously immediately
- Multivitamin tablet

The physician advised the following investigations: Arterial blood gases, Liver function test, Blood urea, Serum creatinine, Complete blood picture, Chest X-ray, Complete urinary examination, Serum electrolytes and monitor general random blood sugar 4th hourly.

On the same day, pulmonologist prescribed the following drugs to the patient after examination:

- Tablet Theophylline - 50 mg
- Tablet Montelukast - 10 mg
- Tablet Levocetirizine - 5 mg
- Tablet Methyl Prednisolone -16 mg
- Tablet Ursodeoxycholic acid - 150 mg
- Injection Pantoprazole - 40 mg
- 2 units normal saline intravenously - 100ml/hour

On the 2nd day hypoglycaemia was resolved but the patient complained of acute abdominal pain which was evaluated by gastroenterologist who prescribed the following medications:

- Injection Dexrabeprazole - 10 mg
- Injection Metoclopramide -10 mg
- Injection L-orthinine,L-aspartate - 1 ampoule
- Syrup Sucralfate - 20 ml

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Injection Butyl Scopolamine 1 ampoule intramuscular immediately was given to the patient by pulmonogist at 9.00 p.m and Methyl Prednisolone was stopped.

Parameter	Test Values		Normal Range
	Day 1	Day 2	
LFT			
SGPT	150 U/L	412 U/L	17-63
SGOT	124 U/L	482 U/L	Up to 35
Total Bilirubin	-	1.6mg%	0.2-1
Direct Bilirubin	-	0.7mg%	0-0.2
$ABGPO_2$	140.3	-	75-100
BIOCHEMISTRY			
Ammonia	130µmol/L	-	10.47
Serum Amylase	-	95 U/L	28
Serum Lipase	-	28 U/L	38
CBP			
Lymphocytes	$0.282\times10^3/mm^3$		
Platelets	$1182\times10^3/mm^3$		150-500
URINE ANALYSIS			
Albumin	++		
Sugar	++++		
Acetone	++		
Calcium Oxalates	1-2		
USG			
Abdomen	Grade IV fatty infiltration of liver		

The results of investigations are given below:

On the 3rd day, alcoholic syndrome withdrawal symptoms such as contractile delirium were seen in the patient. B.P was recorded as 110/70 mm Hg and pulse rate was 61/min. The patient was prescribed with injection Diazepam 5mg in 10ml normal saline and rest of the treatment was continued.

On the 4th day patient was shouting and agitated with irritability and restlessness, to reduce the anxiety he was prescribed with tablet Lonazepam 0.25mg for 5 days. B.P. was normal i.e. 120/70 mm Hg and P.R. 16/min with SPO_2 concentration 99.2%.

On the 5th day nutritional assessment was done and the patient was on soft liquid food, moderate protein and low fat liquid and same treatment was continued.

On 6th day no fresh complaints were seen and temperature was normal, B.P. 110/80, R.R. 20/min, P.R. 101/min with SPO_2 concentration 98% on Bi-level positive airway pressure. On 7th day, patient was considered to be the case of ALD with acute hepatitis.

On 8th day, the patient was diagnosed as the case of anti-TB drug – induced hepatitis.

On 9th and 10th day, patient was with no fresh complaints and plan for discharge was made.

On 11th day patient was discharge with appropriate discharge medication chart and patient counselling.

DISCUSSION

Anti-TB drugs induced hepatotoxiciy is a serious problem and it was reported that 2-28% of TB patients experience drug related hepatotoxicity (DIH) during the course of the treatment.[7]

The incidence rate of drug induced hepatotoxicity in India is 8-36%. The higher incidence of DIH was found in the Asian countries which may be due to ethnic susceptibility, inherent peculiarity of drug metabolism and/or the presence of various known risk factors such as HBV infection, malnutrition, and alcoholism.[8]

According to a study, overall incidence of serious adverse effects was three times higher with pyrazinamide than with isoniazide, or rifampicin.[9] (Fig. 1)

Alcoholism is one of the main risk factor which aggravates the anti-TB induced hepatotoxicity. In this case, the patient is chronic alcoholic and consumed large amounts of alcohol which may lead to following liver conditions – fatty liver, hepatitis and cirrhosis. In this case, hepatitis was seen in the patient. For all types of liver disease caused by alcohol, the main treatment is to stop consumption of alcohol completely. In our case, on withdrawal of alcohol the patient developed alcohol withdrawal syndrome such as delirium and the patient which was treated. Nutritional assessment was done and patient was on soft liquid food, moderate protein and low fat liquid during the course of the treatment. Taking all the information under consideration, a causality assessment of the entitled medical conditions was done by using Naranjo Causality Assessment Algorithm and the results indicated Antitubercular agents and alcohol as possible cause hepatotoxicity with Naranjo score of 4. (Fig. 2)

Upon discharge, patient was counselled regarding the medications and course of the treatment. The discharge medication includes:

- Tablet multivitamin - 1 week
- Tablet Ursodeoxycholic acid - 1 week
- Tablet montelukast/levocetirizine - 1 week
- Syrup sucralfate
- Syrup lactulose

CONCLUSION

Patient developed hepatotoxicity and severe alcohol induced hepatitis following the administration of 1st line anti-TB drugs, which were administered for the treatment of

Fig. 1

INCIDENCE OF SERIOUS SIDE EFFECTS, BY PERSONS AND PERSON-MONTHS

	n	Person-months	Side Effect	No. of Persons	No. of Events	Incidence*	95% CI
All drugs	429	8,488	All	37 (9%)	46	0.55	0.48 to 0.62
			Rash	18 (4%)	21	0.25	0.20 to 0.30
			Hepatitis	12 (3%)	12	0.14	0.10 to 0.18
			GI	8 (2%)	11	0.13	0.10 to 0.16
Isoniazid	427	2,747	All	17 (4%)	13.3	0.49	0.42 to 0.55
			Rash	4 (1%)	4	0.15	0.11 to 0.18
			Hepatitis	8 (2%)	5	0.18	0.14 to 0.22
			GI	5 (1%)	4.3	0.16	0.12 to 0.20
Rifampin	425	2,972	All	14 (3%)	12.83	0.43	0.37 to 0.49
			Rash	10 (2%)	9	0.30	0.25 to 0.35
			Hepatitis	0	0	0	—
			GI	5 (1%)	3.8	0.13	0.10 to 0.16
Pyrazinamide	405	1,336	All	24 (6%)	19.83	1.48	1.36 to 1.60
			Rash	9 (2%)	8	0.60	0.52 to 0.68
			Hepatitis	10 (2%)	7	0.52	0.45 to 0.59
			GI	4 (1%)	2.8	0.21	0.16 to 0.25
Ethambutol	329	1,433	Visual	1 (0.3%)	1	0.07	0.04 to 0.10

Definition of abbreviations: CI = confidence interval; GI = gastrointestinal.
*Incidence is expressed as events per 100 person-months of treatment.

Fig. 2

BTS recommendations for restarting the therapy in patients developing hepatotoxicity

- INH should be introduced initially at a dose of 50 mg/day, increasing sequentially to 300 mg/day after 2–3 days if no reaction occurs, and then continued.
- After a further 2–3 days without reaction to INH, rifampicin at a dose of 75 mg/day can be added, increasing to 300 mg after 2–3 days, and then to 450 mg (<50 kg) or 600 mg (>50 kg) as appropriate for the patient's weight after a further 2–3 days without reaction, and then continued.
- Finally, pyrazinamide can be added at a dose of 250 mg/day, increasing to 1.0 g after 2–3 days and then to 1.5 g (<50 kg) or 2 g (>50 kg).

pulmonary koch's. Following the withdrawal of alcohol, standard treatment and standard care, we were able to achieve a favourable outcome. Clinicians need to be made aware of these potentially fatal adverse effects associated with anti-TB drugs.

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