Case Study

ASSOCIATION OF FOOD AND DRUG ALLERGY WITH ANTI-TUBERCULOSIS DRUG RELATED HEPATITIS OR SKIN REACTIONS: A CASE CONTROL STUDY

Dassanayake DLB[1], Asanga Upul BKM[1], Wickramasekara K[1], Ileperuma SK[1], Siribaddana A[1], Wijewardena KA[2]

[1] Respiratory Unit, Teaching Hospital, Kandy, Sri Lanka

[2] Base Hospital, Kanthale, Sri Lanka

ABSTRACT

Introduction: Anti-tuberculosis drugs can cause adverse reactions including hepatitis and skin reactions. This case control study was aimed at finding out whether allergy to drug or food acts as a risk factor for the development of anti-tuberculosis drug induced hepatitis or skin reactions. Patients with tuberculosis on category 1 regimen, who presented to the Teaching Hospital Kandy Sri Lanka, due to anti-tuberculosis drug induced hepatitis or skin reactions from 1st July 2010 to 30th June 2011 were recruited.

Methodology: Patients with drug induced hepatitis or skin reactions were grouped as cases and patients who didn't develop hepatitis or skin reactions during the treatment period were selected as controls. Controls were matched for age, gender, weight, and consumption of alcohol. Cases and controls were inquired for the presence of allergy to drugs or food. Two groups were compared using odds ratio.

Results: There were 61 cases [33 (54.1%) males, 28 (45.9%) females] and 61 controls .Ten patients (16.39%) among the cases had allergy to food or drugs while in control group only 2 (03.2%) had allergy. Odds ratio for the development of drug reactions in patients with a history of allergy was 5.8 (confidence interval 1.2 to 27.6).

Conclusion: Patients with allergy to drugs or foods have 5.8 times risk of developing anti-tuberculosis drug induced hepatitis or skin reaction.

Key words: Drug reactions, Hepatotoxicity, Idiosyncratic

INTRODUCTION

Tuberculosis is a global health problem with 8.8 million patients reported in 2010, and causing 1.1 million deaths in the world.[1] It is a major health burden in Sri Lanka as well, with an annual incidence of 46 per 100000 population leading to 1900 deaths in 2010.[2] Unlike other infections, treatment of tuberculosis requires administration of several antibiotics together for a long period of time, exposing patients to a significant risk from drug side effects. Literature provides information that serious adverse reactions induced by anti-tuberculosis (anti-TB) drugs also contribute to the increased morbidity and mortality of tuberculosis infection. Therefore, special emphasis on adverse effects of anti-TB drugs is required in the management of tuberculosis.[3]

The commonest adverse reaction to anti-tuberculosis drugs is dyspepsia but hepatitis and skin reactions[4] are 2 of the significant reactions that lead to interruption of therapy and use of alternative drugs. The rate of side effects of Anti-TB drugs has a geographical variation and higher rates are observed in India compared with the west. The incidence of anti TB drug induced hepatitis is around 9.5%[5] in Sri Lanka but the incidence of skin reactions is not known. Hepatitis can be fatal and skin reactions can lead to exfoliative dermatitis which can be fatal as well.

Correspondence:
Dr. Dinesh Dassanayake
Senior Registrar, Respiratory Medicine
Teaching Hospital Kandy
Sri Lanka
E-mail: dlbdassanayake@gmail.com

All four category 1 medications are known to cause exfoiative dermatitis.[6] In addition side-effects such as hepatitis, dyspepsia, exanthema and arthralgia are responsible for termination of therapy in up to 23% of patients during the intensive phase.[7]

Age, gender, body weight and consumption of alcohol have been described as risk factors for the development of anti TB drug induced hepatitis.[5] Identification of high-risk patients would be useful to allow early detection of adverse reactions and to reduce the morbidity and mortality.[8] However, the role of drug or food allergy as a risk factor has not been studied. We noticed the increase in incidence of anti-TB drug induced adverse effects in patients with history of drug or food allergies during the past years, which prompted us to perform this study and to provide objective evidence through this study. Immune reactions have been described as mechanisms of such allergies as well as adverse reactions making a possible link between the two. This study was carried out to find out whether allergy to drug or food acts as a risk factor for the development of anti-tuberculosis drug induced hepatitis or skin reactions.

METHODOLOGY

This nested case control study was conducted in the Respiratory Unit of Teaching Hospital Kandy and Chest Clinic Kandy. This is a major referral center in the island which drains nearly a third of the population. Around 350 new tuberculosis patients are diagnosed in this center annually.

Study was carried out over a period of one year from 1st July 2010 to 30th June 2011.Ethical clearance was granted by the Ethical Committee of Teaching Hospital Kandy. Written informed consent for participation in the study was obtained from participants, or where participants are children, a parent or guardian. The consent form was approved by the above mentioned ethical committee.

Study population was the patients with tuberculosis who presented to the Respiratory Unit of Teaching Hospital Kandy and Chest Clinic Kandy due to anti-tuberculosis drug induced hepatitis or skin reactions. Out of them the patients who fulfilled the following inclusion criteria were enrolled in to the study.

Inclusion criteria

- Patients with tuberculosis who developed drug induced hepatitis or skin reactions while on Isoniazid, rifampicin, ethambutol and pyrazinamide (Category 1 regime).

Patients who met the following exclusion criteria were excluded from the study.

Exclusion criteria

- Patients on regimes other than the standard (CAT 1) regime
- Patients on long term steroids and anti-histamine
- Patients with decompensated cirrhosis and active liver disease prior to start of Anti-TB drugs
- Patients with active skin diseases prior to drug treatment
- Patients with HIV

All consecutive patients with eligible characteristics, after applying inclusion and exclusion criteria were recruited to the study. Category 1 treatment was commenced according to body weight as stated in the WHO guideline for the management of tuberculosis 2009.[9]

Definitions

Cases:

Cases were defined as the patients with tuberculosis, who fulfilled inclusion and exclusion criteria, who developed anti-TB drug induced hepatitis or skin reactions during the 6 month treatment period.

Anti-TB drug induced hepatitis:

The definition used by Rohit Singla et al was used with slight modification for our study.[10]

Anti TB drug induced hepatitis was defined if any one of the following 1 to three criteria were met along with criteria 4.

Criteria

1. a rise of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) more than three times the normal value of

40 IU/L (> 120 IU/l) on three consecutive occasions;

2. a rise in the level of serum total bilirubin level > 1.5 mg/dl
3. increase in serum AST and or ALT two times above pre-treatment values together with anorexia, nausea, vomiting and jaundice;
4. Improvement in liver functions (serum bilirubin < 1 mg/dl, AST and ALT <100) after withdrawal of anti-TB drugs.

Anti-TB drug induced skin reactions:

Anti-TB drug induced skin reactions were defined as presence of following criteria.

1. Any rash or skin eruption with or without itching that occurs after the start of anti-TB drugs
2. Disappearance of such symptoms and signs following the withdrawal of anti TB drugs and reappearance of the same symptoms and signs when anti TB drugs were reintroduced

Food or drug allergy

Food or drug allergy was defined as documented urticaria, angioedema, skin eruption or anaphylaxis directly related to the ingestion of a particular food or drug.

Controls

Controls were defined as patients with tuberculosis on category 1 regimen, who had no exclusion criteria and who didn't develop hepatitis or skin reactions during the 6 month treatment period.

Cases and controls were inquired for the presence of allergy to drugs or food and were recorded using an interviewer administered questionnaire. Adverse reactions were managed according to WHO guideline for treatment of tuberculosis 2009 [9].

Matching

Controls were matched with cases for age, gender, weight and consumption of alcohol which are confounding factors for the development of anti TB drug induced hepatitis. One matched control was chosen for an each case.

Statistical analysis

Due to the limited study period and low incidence of adverse reactions all consecutive cases were enrolled and analyzed. Characteristics of cases and controls were compared using percentages. Incidence of anti-TB drug induced hepatitis or skin reactions were analyzed using absolute numbers as well as percentages. Food or drug allergy in each group was similarly analyzed using absolute numbers and percentages. Incidence of hepatitis or skin reaction by each drug was calculated with percentages for descriptive purposes. Strength of association between allergy and drug induced hepatitis or skin reaction was assessed using odds ratio. Confidence interval for significance was set at 95% for analysis of odds ratio.

RESULTS

A total of 122 patients were included in the study. Out of them 61 were cases and 61 were controls. Average age of cases was 47.4 (SD 15.1).There were 66 males [54.1%] (cases 33, controls 33), and 56 [45.9%] females (cases 28, controls 28). Out of 61 cases 41 (67.3%) had anti-TB drug induced hepatitis and 20 (32.7%) had anti-TB drug induced skin reactions.

Offending drug was identified during the desensitization process in 18 patients (29.5%) and all of them had to be put on an alternative regimen excluding the offending drug. All the alternative regimens had to be continued for more than 6 months. Main culprit drug out of the identified drugs was pyrazinamide which caused hepatitis in 10 patients (out of 41 hepatitis patients) (24.5%).

Table 1. Characteristics of cases and controls				
	Cases		Controls	
	No	%	No	%
Total	61		61	
Males (n)	33	54.1	33	54.1
Females (n)	28	45.9	28	45.9
Average age (males) years	43.75 (SD 4.5)		43.2 (SD 3.7)	
Average age (females) years	37.5 (SD24.35)		38 (SD 4.7)	
age range(years)				
15 - 24	3	4.9	3	4.9
25 - 34	7	11.5	7	11.5
35 - 44	11	18.0	11	18.0
45 - 54	19	31.1	19	31.1
55 - 64	10	16.4	10	16.4
65 - 74	8	13.1	8	13.1
>75	3	4.9	3	4.9
Average weight (kg)	48 (SD 10.7)		47.3 (SD11.2)	
Weight bands (kg)				
20 - 29	1	1.6	1	1.6
30 - 39	7	11.5	7	11.5
40 - 49	25	41.0	25	41.0
50 - 59	21	34.4	21	34.4
>60	7	11.5	7	11.5
Alcohol consumers	11	18.0	11	18.0

Table 2. Offending drugs and the number of patients with adverse reactions			
Adverse reaction	**Offending drug**	**n**	**%**
Hepatitis	Pyrazinamide	10	24.5
	Rifampicin	3	7.3
	Isoniazid	2	4.8
	Rifampicin+ Pyrazinamide	1	2.4
	Total	16	39
	Unidentified	25	61
Skin reactions	Isoniazid	1	5
	Rifampicin	1	5
	Total	2	10
	Unidentified	18	90

Out of cases 10 had past history of drug or food allergy while only 2 patients in control group had a history of allergy [Odds ratio = 5.8 (confidence interval 1.2 to 27.6, p=0.028)].

Table 3. Distribution of exposures between cases and controls			
		cases (anti-TB drug induced hepatitis or skin reactions)	controls (No anti -TB drug induced hepatitis or skin reactions)
Exposures	Presence of food or drug allergy	n = 10 (16.4%)	n = 2 (3.2%)
	No food or drug allergy	n = 51 (83.6%)	n = 59 (96.8%)

DISCUSSION

This study shows that patients with history of drug or food allergy have 5.8 times risk of developing anti-TB drug induced hepatitis or skin reactions. Although many risk factors for anti-TB drug induced adverse reactions have been described, drug and food allergy as risk factor has not been described in medical literature so far. Sri Lankan diet includes both vegetarian as well as non-vegetarian components food and drug reactions are a common occurrence in day today medical practice.

Adverse reactions to anti-TB drugs are a major concern because of their seriousness as well as the higher frequency of incidence. Most of the reactions are idiosyncratic (they cannot be predicted and not dose dependent).Isoniazid induced hepatitis is thought to be idiosyncratic and is driven by a toxic metabolite of the parent drug.[8] The mechanism of rifampicin induced hepatotoxicity is not known but is unpredictable. Unlike in isoniazid, a toxic metabolite is not the cause. Mechanism of pyrazinamide hepatotoxicity is also not known but its effects are thought to be due to dose dependent mechanism as well as idiosyncratic reactions. Ethambutol is not known to be hepatotoxic. Incidence of hepatitis caused by each drug is difficult to assess as these drugs are used in combination.[9]

There are many mechanisms of drug allergies as well as food allergies. A significant proportion

of them are idiosyncratic. These idiosyncratic reactions are immune mediated.[11] Therefore it is possible that patients with drug and food allergy are immunologically susceptible to anti-TB drug induced hepatitis and skin reactions. Cross allergy between drugs have been very well described in medical literature. For example a patient with penicillin allergy could develop an allergic reaction to cephalosporin if exposed, due to cross allergy.[12] Similarly a person with allergy to one food type can have a cross allergy to other food types as well. This cross allergy could be a reason for the development of anti-TB drug induced adverse reactions in patients with drug and food allergy.

Finding of an association between drug or food allergy and anti -TB drug induced adverse reactions can have a significant impact on the management of patients with tuberculosis.

Starting anti-TB drugs in a patient with history of drug and food allergy should be a cautious procedure and special protocols on initiation of these medications on such patients are necessary to minimize reactions and to improve compliance. At the moment there is no way of predicting drug reactions. Therefore close monitoring of patients with risk factors, especially if there is a history of drug and food allergy should be practiced.

As with previous medical literature[8] pyrazinamide was the main culprit for anti-TB drug induced hepatitis in our study. But the offending drug could be identified in only 29.5%.This makes prediction of reactions even more difficult.

All though anti-TB drug induced hepatitis and skin reactions are separate sub groups, due to the limited time frame and low incidence, the numbers were too small to do a sub group analysis. However a sub group analysis will be done in a future study to clarify the association among individual sub groups.

A cohort study will be necessary to confirm the exact causal relationship suggested in this study.

CONCLUSION

Patients with allergy to drug or food have 5.8 times risk of developing anti-tuberculosis drug induced hepatitis or skin reaction during standard regimen for tuberculosis. Therefore commencing anti-TB drugs on such patients should be a cautious procedure and special protocols may be necessary to minimize these major adverse reactions.

ACKNOWLEDGEMENT

We acknowledge all the staff members of the respiratory unit, of Teaching Hospital Kandy and Chest Clinic Kandy who helped us to make this research a success.

REFERENCES

1 World Health Organization: WHO report on Global Tuberculosis Control 2011.World Health Organization 2011;115.

2 National Program for Tuberculosis Control and Chest Diseases: Distribution of new cases of TB by Age & sex – 2009. Annual Report 2009. Ministry of Health, Sri Lanka 2009;51-52.

3 Singla R, Sharma SK, Mohan A, Makharia G, Sreenivas V, Jha B, et al. Evaluation of risk factors for antituberculosis treatment induced hepatotoxicity. Indian J Med Res. 2010;132:81-6.

4 Daphne Yee, Chantal Valiquette, Marthe Pelletier. Incidence of Serious Side Effects from First-Line Anti-tuberculosis Drugs among Patients Treated for Active Tuberculosis. Am J Respir Crit Care Med 2003; 167:1472–77.

5 Senaratne WV, Pinidiyapathirage MJ, Perera GAMHE, Wickremasinghe AR. Anti-tuberculosis drug induced hepatitis – a Sri Lankan experience. Ceylon Medical Journal March 2006;51:9-14.

6 Dua R, Sindhwani G,Rawat J.Exfoliative dermatitis to all four first line anti- tubercular drugs. Indian J Tuberc 2010;57:53-56

7 Schaberg T, Rebham K, Lode H. Risk factors for side-effects of isoniazid, rifampicin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J 1996;9:2026-30.

8 Tostmann A, Boeree M J, Aarnoutse R E, Lange W C M, Van der Vens A J AM,Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: Concise up-to-date review. Journal of Gastroenterology and Hepatology 2008;23:192–202.

9 World Health Organization. Treatment of tuberculosis. Guidelines for National Programmes 4th Edition. WHO/TB/97.220.Geneva: World Health Organization 2009;59–60.

10 Singla R, Surendra K. Sharma et al. Evaluation of risk factors for anti-tuberculosis treatment induced hepatotoxicity. Indian J Med Res, 2010;132:81-86.

11 Riedl MA, Castillas AM: Adverse drug reactions: types and treatment options. Am Fam Physician 2003;68**:**1781-90.

12 Garg PK, Tandon RK. Antituberculosis treatment induced hepatotoxicity. In: Sharma SK, Mohan A, editors. *Tuberculosis* 2nd ed. New Delhi: Jaypee Brothers Medical Publishers 2009;783-95.