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Original Research Article

Adverse Drug Reaction Pattern of First-Line Anti-tubercular Drugs in a Tertiary Care Hospital of Northern India

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Abstract

Background: Adverse drug reactions add directly or indirectly to health care burden in form of hospitalization or mortality. ADRs (adverse drug reactions) of antitubercular drugs are rarely reported but are important cause of morbidity and mortality.

Methods and Material: Patients were called on the days fixed for evaluation. All the information regarding the observed ADRs was noted down in the suspected ADR reporting form version 1.3 issued by Indian pharmacopoeia commission ministry of health and family welfare, Government of India and was also informed to the treating physician. ADRs were followed up till its resolution and management. The causality of the ADR reported was evaluated using WHO UMC causality assessment scale. ADR form was submitted to AMC, CMC Ludhiana.

Results: Total of 107 ADRs were reported from 80 patients in our study. The most common system involved was gastrointestinal system (42.06%) presenting with hepatotoxicity, vomiting and diarrhoea. Causality assessment according to the WHO-UMC revealed that majority of ADRs was in probable category followed by possible category with some of the ADRs in certain category. No death was reported due to any of the ADRs. Most of the ADR's occurred within 30 days from the start of treatment.

Conclusions: ADRs to antitubercular drugs are frequent. Efficient pharmacovigilance can lead to early detection and better management of the ADRs with antitubercular drugs.

Keywords: Antitubercular drugs, Adverse drug reaction, Pharmacovigilance, Causality.

Introduction

India is a high burden country for tuberculosis in various forms of its disease including multi-drug resistant tuberculosis (MDR-TB) and Extensive drug resistant tuberculosis (XDR-TB) which are difficult to treat.[1] According to the global tuberculosis report of world health organisation eight countries accounted for two thirds of the global total with maximum share to India with 26% of the total case load.[2] It is a well-documented fact that due to high attrition rates, resulting from adverse drug reactions

of antitubercular drugs the patients later on present not only with relapse but also resistance to antitubercular drugs. Treating resistant tuberculosis is a double edged sword that not only adds to the increasing costs both for the patient as well as the country but also has a treatment success rate of fifty percent.[3] World health organisation (WHO) definition of an adverse drug reaction (ADR) is "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.[4] First-line antitubercular drugs isoniazid, rifampicin, pyrazinamide and ethambutol have a large number of ADRs.[1] Rifampicin can cause hepatitis (major ADR), cutaneous flushing, pruritus, rash, flu like symptoms, abdominal pain, nausea, vomiting etc. Urine and body secretions become orange red but this is harmless. Serious but rare reactions are purpura, haemolysis, shock and renal failure. Ethambutol can cause vision changes (such as blurred/decreased vision, colour blindness, loss of visual acuity, field defects due to retrobulbar neuritis). Isoniazid may lead to hepatitis (major ADR), peripheral neuritis, lethargy, anaemia and arthralgia. Pyrazinamide can cause hepatotoxicity (major ADR), hypeuricemia etc.[5] Extensive literature searches has revealed that high cure rates were reported for cases with timely recognition and treatment of ADR associated with the antitubercular regimen. The physician are well versed with the ADRs of the antitubercular regimen however there is under reporting observed because of lack of knowledge and awareness about ADR reporting system.[6] Indian Council of Medical Research (ICMR) has included tuberculosis in its thrust areas.[7] Pharmacovigilance Programme of India (PvPI) is a national programme for ADR reporting by Indian Pharmacopoeia Commission, Ministry of Health.[8] PvPI is emphasizing on focused pharmacovigilance of antitubercular drugs. Hence, we planned this study to evaluate the pattern of adverse drug reactions of first-line antitubercular drugs and evaluate the causality of the ADRs reported.

Materials and Methods

Study design and study group

This study was a prospective and observational study which was conducted in total of eighty (80) patients reporting with ADRs visiting to the outpatient departments Study was approved by IEC. Enrolment of the patient was done according to inclusion and exclusion criterion. Patient information sheet was given antecedent to enrolment along with written informed consent. Patient particular sheet was filled, after they signed the consent form. In this study, overall 125 patients were screened to get a total of eighty patients reporting with the ADRs who were eventually enrolled in the study. The rest 45 patients were excluded from the study due to various reasons like non-compliant patients [9-12], not willing to be a part of the study [9], loss to follow up [11] and migration [13] as depicted in Figure 1.

Eligibility

Inclusion criteria included patients between 20-80 years, newly diagnosed with tuberculosis i.e. category I (Indian classification) and who reported ADRs while taking first line antitubercular therapy. Patients who were not willing to take part in this study and non-compliant patients were excluded.

Study procedure

Patients were enrolled after they signed the written informed consent. Patient particular sheet was also filled which included patient's initials, mobile number, landline number and any other alternate number. Patients were told the purpose of taking their phone

numbers i.e. for asking them about any ADRs on the days fixed for evaluation i.e. on the 7th day, 30th day and 60th day after starting the drugs. All the information regarding the observed ADRs was noted down in the suspected adverse drug reaction reporting form version 1.3 issued by Indian pharmacopoeia commission Ministry of Health and Family Welfare, Government of India and subsequently it was also informed to the treating physician. The ADR form of PvPi was used. All details as per the form were collected. The patients themselves also reported any ADRs if they felt, either physically or telephonically. ADRs were followed up till its resolution. Patients were encouraged to share relevant investigations through WhatsApp. The causality of the ADR reported was assessed using WHO UMC causality assessment scale. ADR form was submitted to AMC, CMC Ludhiana. Finally, information was collected on management of the ADR.

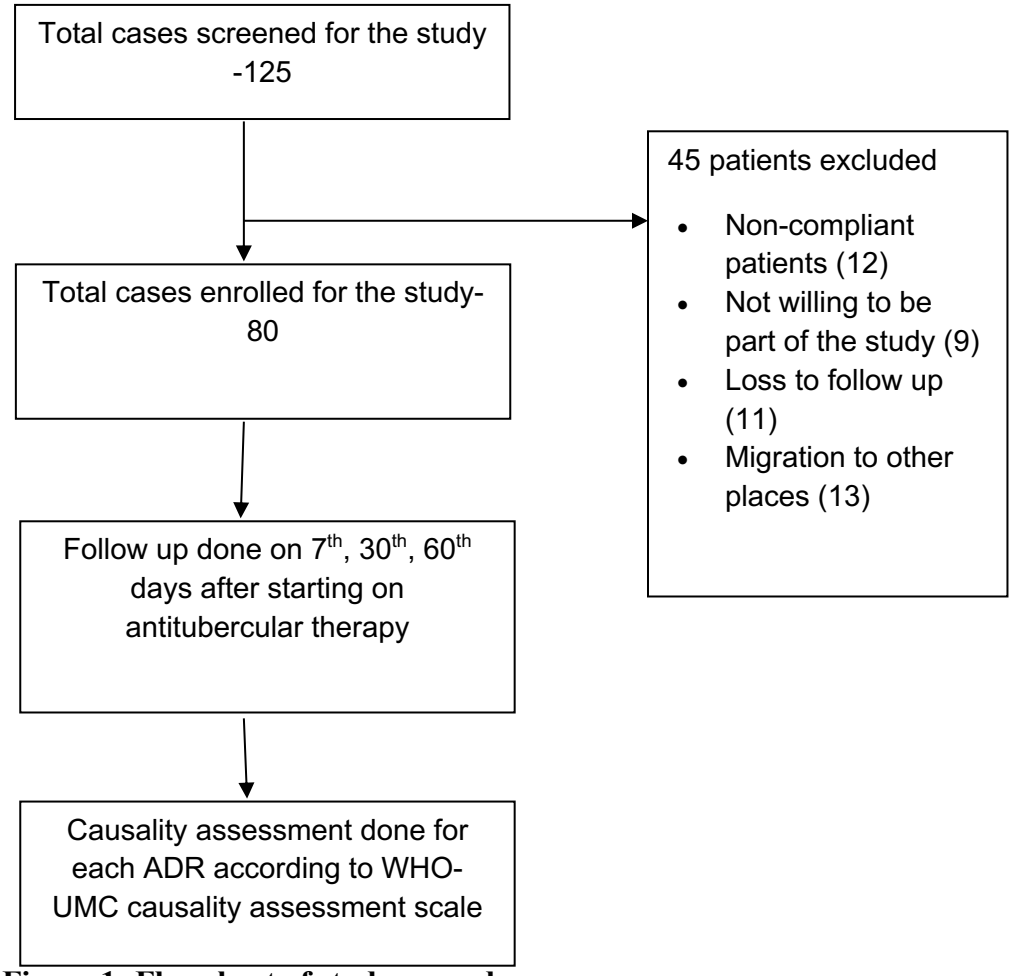

Figure 1: Flowchart of study procedure

Statistical Analysis

Data was summarized using frequency distribution and descriptive analysis. Chi square test was used to find the association of categorical variables. T-test or Mann-Whitney test was used to find the association of continuous variables. The p value <0.05 was considered significant. All statistical analysis was performed using SPSS

(Statistical Packages for Social Sciences, version 21.0. Armonk, NY: IBM corp.).

Results

During the 18 months study period a total of 107 ADR reports were received by us from 80 patients selected according to the inclusion and exclusion criteria mentioned in the protocol. The reports were verified, analysed, assessed and reported to PvPI. The details of the observations of our study are summarized here. ADR incidence is comparable for males and females, 54% males vs. 46% females. Age distribution is shown in Table 1 with the highest involvement of patients in 20-29 years age group and the least involvement of patients in 60-69 years age group. Gastrointestinal system was majorly involved due to Pyrazinamide and Ethambutol, with the respiratory system involvement being the least as shown in figure 2. Out of the four drugs Type A ADRs were more frequent with Isoniazid (72%), Type B most frequent with Rifampicin and Type C was comparable with all the four drugs as shown in the figure 3. Severity assessment of the ADRs was done according to Hartwig's severity assessment scale. 66 % were in moderate followed by 34% in mild category. None of the ADRs were in the severe category. The recovery was most with Pyrazinamide and least with Ethambutol. The number of patients recovered and recovering was most frequent with Pyrazinamide as shown in figure 4. Action taken was comparable in all the four drugs with the dose not being changed in majority of the cases as shown in figure 5.

Table 1: Demographic details of the study population

Age group	n	Cases (%)
20-29	35	33%
30-39	18	17%
40-49	18	17%
50-59	6	6%
60-69	20	19%
above 70	10	9%

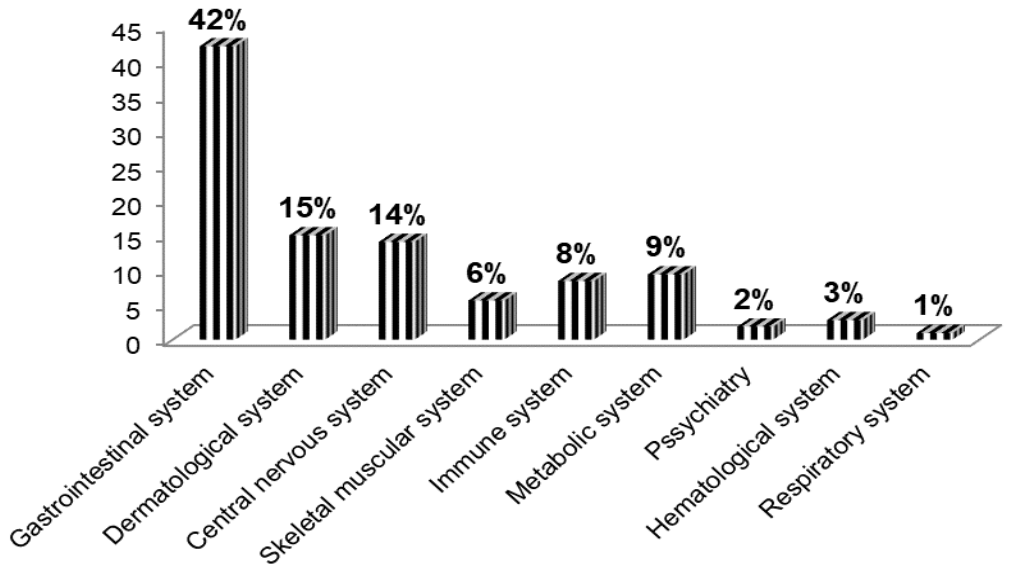

Figure 2: System wise distribution of ADRs (n=107)

ADR-Adverse drug reaction

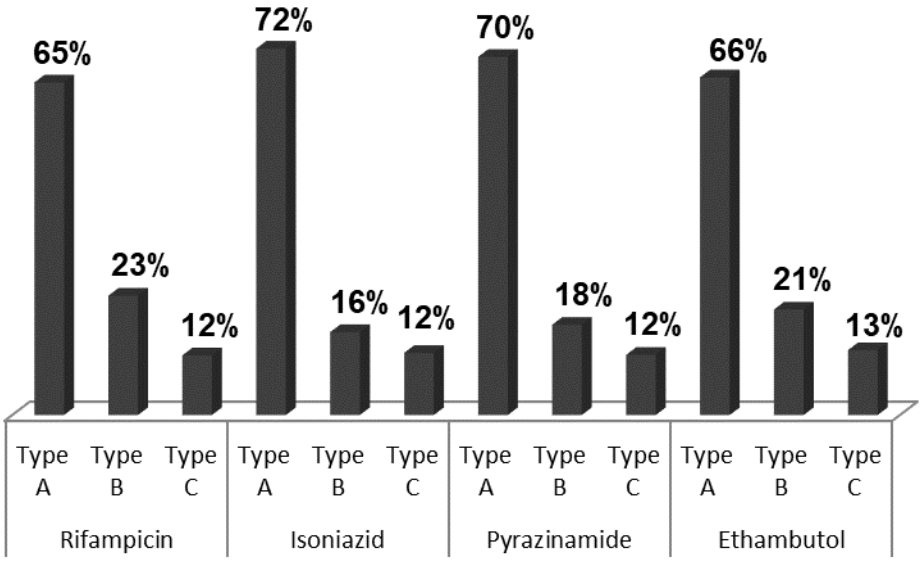

Figure 3: Types of ADRs to individual drugs

ADR-Adverse drug reaction

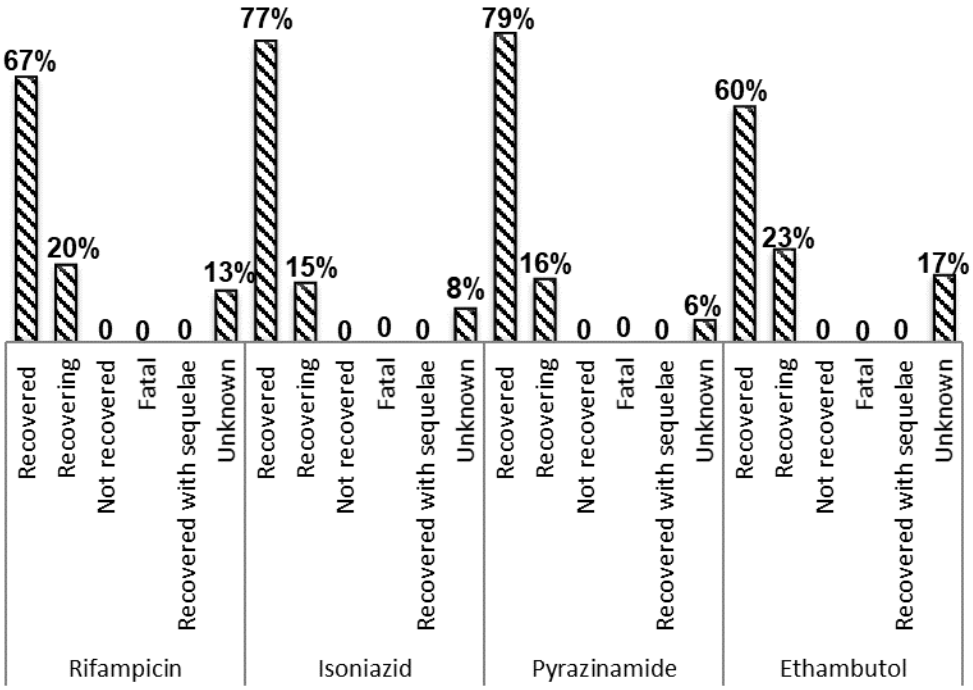

Figure 4: Outcome of ADRs –drug wise

ADR-Adverse drug reaction

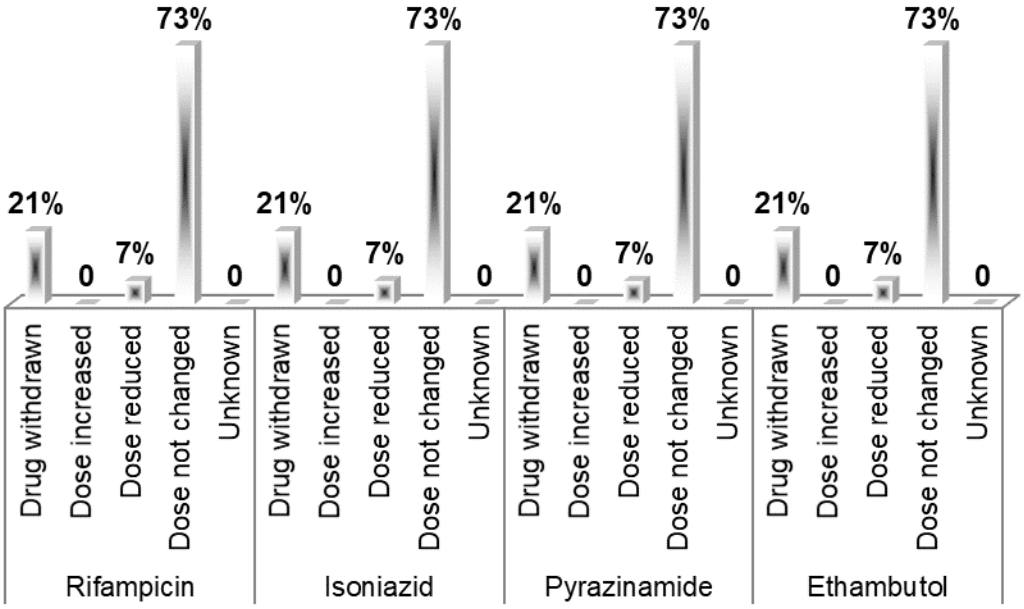

Figure 5: Action taken ADRs –drug wise

ADR-Adverse drug reaction

Discussion

Unattended ADRs of antitubercular drugs can increase morbidity and mortality on these patients. In our study we analysed ADRs due to antitubercular drugs. The baseline demographic details included age and gender. Mean age of the study participants in our study was 41 years. The mean age of the patients in our study was comparable to other multicentric study done in Thailand on tubercular patients where the mean age of the patients enrolled was 43 years. In one of the studies done in Indonesia, the majority of TB patients were male (62%) compared to females (38%).[9]

It is found that males were more prone to tuberculosis when compared to females. Secondly, males are supposedly socially more active and visit public places more often than the females. These risks make them more vulnerable for TB infection.[10] Another study concluded that males were more likely to have poor compliance than females so that it could be a contributing factor to increase the risk of TB. Some studies have shown females to have a higher incidence of ADRs females 57% compared to males 43%.[11] In our study, most patients were in the productive age group 20-29 years followed by age group 60 years and above. This parameter is in line with other study that also mentions that majority of pulmonary tuberculosis patients were in productive age group. Working class were mainly prone to TB, probably because of exposure outside of their homes as they go outside and from work, etc.

It can be a serious adverse effect on the socioeconomic status of a country since the reproductive and economically productive age groups are the most affected. One of the studies done in Indonesia does go in agreement with our findings in which it was also reported that majority of the cases 42% were in the productive age group from 20-35

years of age.[12] This finding was also in line with one such study done in Nepal.[13]In our study, gastrointestinal system was majorly involved which included adverse drug reactions like nausea, vomiting, diarrhoea and hepatic function abnormality. This system involvement is in agreement with world health organisation report on their website which also mentions gastrointestinal system involvement as one of the major organ system to be involved due to pyrazinamide and ethambutol.[14] After gastrointestinal system involvement next major organ system to be involved in our study was dermatological system, which included adverse drug reactions like rash and pruritus due to pyrazinamide. This system involvement is also in line with the study done in a tertiary care medical centre in India.[15]

After detection of the ADR, its management play an important role in reducing the economic burden on the patient's part. Majority of the ADRs requiring treatment were vomiting, itching, diarrhoea, pyrexia, muscular and joint pain. These results matched with one of the similar studies done in southern India, which showed that majority of the patients did require some treatment intervention for symptomatic relief.

The reasons for this are that in both the studies effective pharmacovigilance program focusing on antitubercular therapy was operational during the study period, which resulted in early detection of the adverse drug reaction at initial stages itself. This resulted in early and effective management of the ADR thus not requiring any secondary treatment intervention.[16]

Majority of the cases did not require any treatment while very few patients required treatment. This finding was also consistent with other similar study done in Southern India. In our study there was no ADR in which death was reported due to any of the adverse drug reactions due to intake of rifampicin. This was due to early detection of the ADR due to a robust focussed pharmacovigilance program and effective management of the ADR resulting in no fatality. This finding in our study matched with one such similar study done in rural area of Northern India.[17] In this present study, due to isoniazid majority of the patients recovered and included reactions like diarrhoea, vomiting, anorexia followed by recovering adverse drug reactions like psychosis, peripheral neuropathy. Again there was no death reported due to any of the adverse drug reactions due to intake of isoniazid. This result parameter is in line with study done in Tucson, Arizona.[18]

If we talk about adverse drug reactions due to pyrazinamide then again similar pattern was seen with majority of the patients which recovered and included reactions like vomiting, diarrhoea, dizziness and anorexia followed by recovering adverse drug reactions which included reactions like hepatic function abnormality, rash, arthralgia and hypeuricemia. No deaths were reported due to any of the adverse drug reaction due to use of pyrazinamide. This parameter is in line with one of the study done in South Korea.[19] In our study due to ethambutol, majority of the patients recovered and included reactions like vomiting, diarrhoea and itching. This was followed by adverse drug reactions which were recovering like arthralgia, hypeuricemia and hepatic function abnormality.

Due to intake of ethambutol no deaths were reported. These findings pertaining to ethambutol were in line with one of the similar studies done in London.[20]One such study done on a similar topic, in a tertiary care centre from India showed six deaths due to ADRs. This may be due to various factors like late detection of ADR and further ineffective management of that particular

ADR.[21] It is a known fact that sooner the ADR is detected better is the outcome of that ADR.

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References

1. Dua R, Sindhwani G . Exgoliative dermatitis to all four first line oral anti tubercular drugs. Indian J Tuberc. 2010; 57:53–6.
2. World health organisation (WHO).A practical handbook on pharmacovigilance of medicines used in the treatment of tuberculosis. Available from: https://who.int.com. [Accessed on 28 June 2020].
3. World bank.In India, eliminating tuberculosis isn't just a health issue — it's an economic one.Available from: https://blogs.worldbank.org/endpovertyinsouthasia/india-eliminating-tuberculosis-isnt-just-health-issue-its-economic-one.[Accessed on 22 June 2022]
4. Rakesh D. Challenges in pharmacovigilance. Indian J Pharmacol. 2010;42:333–4.
5. Tandon VR, Mahajan V, Khajuria V, Gillani Z. Under-reporting of adverse drug reactions: A challenge for pharmacovigilance in India. Indian J Pharmacol. 2015;47:65–71.
6. Mistry CB, Shah SM, Modi VA, Mistry SD. Study of knowledge, attitude, and practices towards current updates of pharmacovigilance and adverse drug reaction reporting among doctors in a tertiary care teaching hospital of Western India. Int J Basic Clin Pharmacol. 2018;7:524.
7. Indian council of medical research (ICMR).Thrust areas for medical research.Available from :https://www.icmr.nic.in/content/thrust-areas.[Accessed on 21 June 2020]
8. Pharmacovigilance Programme of lndia (PvPI).National programme of India. Available from: https://www.ipc.gov.in/PvPI/pv_home.html. [Accessed on 23 June 2020]
9. Rajeswari R, Balasubramanian R, Muniyandi M, Geetharamani S, Thresa X, Venkatesan P. Socio-economic impact of tuberculosis on patients and family in India. Int J Tuberc Lung Dis. 1999; 3: 869–77.
10. Laue NC Von, Schwappach DLB, Koeck CM. Vonlaue2003. Wien Klin Wochenschr. 2003;12:407–15.
11. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of Serious Side Effects from First-Line Antituberculosis Drugs among Patients Treated for Active Tuberculosis. Am J Respir Crit Care Med. 2003;167:1472–7.
12. McCarver DG. Applicability of the Principles of Developmental Pharmacology to the Study of Environmental Toxicants. Pediatrics. 2004;113:969–72.
13. Chhetri AK, Saha A, Verma SC, Palaian S, Mishra P, Shankar PR. A study of adverse drug reactions caused by first line anti-tubercular drugs used in Directly Observed Treatment, Short course (DOTS) therapy in western Nepal, Pokhara. J Pak Med Assoc. 2008;58:531–6.
14. World health organissation (WHO). A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis. Available from: https://www.who.int.com. [Accessed on 28 June 2022].

15. Yee D, Valiquette C, Pelletier M, Parisien I, Rochir I and Menzies D.Incidence of serious side effects from first line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med 2018;167:1472–77.
16. Tutu S, Adhaulia G, Jain S, Kant S, Verma A, Sachan AK, *et al*. Study to Find Out Predisposing Factors, Causality, Severity and Avoidability of Adverse Drug Reactions among Patients Treated under DOTS Centre of Northern India. J Clin Diagnostic Res. 2019;13:6.
17. Kuriachan S, Krishnan P, Chogtu B, George MM. Assessment of adverse drug reactions to antituberculosis regimen in a tertiary care hospital. Int J Basic Clin Pharmacol. 2019;8:2202.
18. Si M, Li H, Chen Y, Peng H. Ethambutol and isoniazid induced severe neurotoxicity in a patient undergoing continuous ambulatory peritoneal dialysis. BMJ Case Rep. 2018;2018:1–5.
19. Kwon BS, Kim Y, Lee SH, Lim SY, Lee YJ, Park JS, *et al*. The high incidence of severe adverse events due to pyrazinamide in elderly patients with tuberculosis. PLoS one. 2020;15:23-64
20. Kumar R, Shalimar, Bhatia V, Khanal S, Sreenivas V, Gupta SD, *et al*. Antituberculosis therapy-induced acute liver failure: Magnitude, profile, prognosis, and predictors of outcome. Hepatology. 2010;51:1665–74.
21. Mishra V, Desai M. Pattern of Adverse Drug Reactions and its Potential Impact on Drug Resistant Clinical Journal of Pharmacology and Pharmacotherapeutics Pattern of Adverse Drug Reactions and its Potential Impact on Drug Resistant Tuberculosis Patients at a Tertiary Care Te. Clin J Pharmacol Pharmacother. 2018;1:1–7.