ADVERSE EFFECTS OF ANTITUBERCULOSIS DRUGS IN PATIENTS UNDER DOTS CATEGORY-1

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ABSTRACT

BACKGROUND

This study intends to analyse the clinical findings, haematological and biochemical parameters of adverse drug effects of antituberculosis drugs in patients started on DOTS category-1. Since, ATT is an effective treatment strategy it is very important to identify these adverse effects at the earliest, treat them and improve compliance. Different studies have stated varying incidence of these adverse effects leading to discontinuation of ATT. Hence, this study intends to find out the occurrence of side effects of antituberculosis drugs in patients under DOTS category-1 (CAT-1) in our setup.

MATERIALS AND METHODS

Tuberculosis patients who were started on DOTS category-1 were observed for Adverse Drug Reactions (ADR) during the course of the treatment. 50 patients were analysed and studied. They were evaluated with clinical data, haematological and biochemical investigations.

RESULTS

Out of the 50 patients selected for this study, 30 patients developed atleast one or more types of ADR and a total of 9 types of adverse drug reactions were observed. The most common symptom ADR observed in this study were GI symptoms like nausea (56%), vomiting (30%), loss of taste (14%), dyspepsia (24%), abdominal pain (20%), diarrhoea (4%), jaundice (8%), others were malaise (16%) and skin rash (2%). The mean onset time of the adverse drug effects were observed within 7 days and mean duration time of the adverse drug effects were seen up to 2 months after start of ATT.

CONCLUSION

This study showed that DOTS treatment is an effective and safe treatment strategy as most of the adverse drug reactions noted were of a mild variety (Hartwig's scale level 1) and were managed with symptomatic medications. Gastrointestinal symptoms were the most common observed ADR and most of the symptoms subsided within the intensive phase of the treatment. The most common laboratory abnormality seen was rise in liver enzymes and bilirubin.

KEYWORDS

Antituberculosis Drugs; Drug Reactions; Haematological; Tuberculosis.

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BACKGROUND

In 1990, the world health organization reported on the global burden of diseases and ranked tuberculosis as the 7th most common disease causing morbidity in the world and expected it to continue in the same position up to 2020.[1] Tuberculosis (TB) was considered one of the common problems worldwide each year affecting eight million new people and causing two million deaths every year.[1,2,3]

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The World Health Organization declared Tuberculosis (TB) as a global emergency in 1993.[4,5] The number of TB cases has increased since 1983 due to HIV/AIDS. India is considered to be in a unique position with respect to the global tuberculosis epidemic.[6]

In response to the tuberculosis epidemic and inadequate treatment strategies, a pilot project using the World Health Organization (WHO) recommended strategy of directly observed treatment, short-course (DOTS),[7] the Revised National Tuberculosis Control Program was begun in 1993.[6] The world adopted the DOTS strategy for TB control through the national TB control programs in different countries and was said to make good progress.[8] In spite of implementation of DOTS, it was still a major health concern.[3]

The WHO defined Adverse Drug Reaction (ADR) as 'A response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of

physiological function."[4,9,10,11] Among the drugs used, antitubercular drugs was considered one of the most common drugs causing ADR.[9] Moreover, the Adverse Drug Reactions (ADRs) to the drugs used was one of the major reasons for the patient default for treatment.[4]

Adverse drug reactions to antituberculosis drugs occurred during treatment of tuberculosis and was expected in 10% of the patients treated for pulmonary tuberculosis.[12]

Major adverse reactions to antituberculosis drugs caused significant morbidity and compromised treatment regimens for Tuberculosis (TB). Side effects resulting in modification or discontinuation of therapy or hospitalization were attributed on the basis of resolution after withdrawal and/or recurrence with rechallenge.[13-16]

A general knowledge of the various ADRs and their management was considered essential for the effective management of TB.[17] All antitubercular drugs were known to cause adverse drug reactions[6] and may result in ADRs involving almost all systems in the body including the gastrointestinal tract, liver, skin, nervous system, otovestibular apparatus and the eyes.[4,18]

For this, careful patient monitoring clinically, haematologically and biochemically especially during first few weeks of chemotherapy and patient counselling regarding side effects of the anti-TB medications were necessary. Drug-related side effects might be minor or major. In general, stated that a patient who has minor side effects should be encouraged to continue the treatment with symptomatic measures such as antacids, antihistamines, antiemetics or analgesic. It was said that if major side effects occurred, the regimen or the offending drug, if identified was to be stopped. Further management was depending on the nature of side effects and had to be done in a hospital.[8]

Hartwig's scale[19] (study by Hartwig, 1992) was widely used for the purpose. This scale categorises the reported adverse drug reactions into different levels as mild, moderate or severe. In mild (Level 1), the ADR requires no change in the treatment with the suspected drug and mild (Level 2) the ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required and there is no increase in length of stay. In moderate (Level 3), the ADR requires that the suspected drug be withheld, discontinued or otherwise changed and/or an antidote or other treatment is required with no increase in length of stay. Moderate (Level 4 (a)) is any level 3 ADR that increases the length of stay by at least one day and in moderate (Level 4 (b)) the ADR is the reason for admission. The severe (Level 5) is any level 4 ADR that requires intensive medical care, severe (Level 6) is the ADR causing permanent harm to the patient and severe (Level 7) being the ADR either directly or indirectly leading to the death of the patient.[3]

It was seen that it is essential for the healthcare professionals to counsel the patients regarding the early identification of ADRs in the first few weeks. Regular monitoring of the patients during the initial weeks was considered essential for early detection of ADRs.

Hence, this study was done to analyse the clinical findings, haematological and biochemical parameters of adverse drug effects of antituberculosis drugs.

MATERIALS AND METHODS

Study Design

Prospective study was conducted on 50 tuberculosis patients who were started on ATT under DOTS category-1 (CAT-1) in Father Muller Medical College Hospital, Mangalore, for a period of one and a half year from January 2009 to June 2010.

Study Patients

50 patients with newly-diagnosed pulmonary or extrapulmonary tuberculosis who were started on DOTS category-1 and age >15 years were selected for the study using purposive sampling technique. Patients who had clinical jaundice or elevated levels of bilirubin, AST, ALT, ALP, blood urea, serum creatinine, uric acid before initiating treatment were excluded.

Before initiating antituberculosis treatment, a detailed clinical assessment, which included history and clinical examination was done. Haematological investigations included haemoglobin, WBC count, differential count, platelet count, prothrombin time and ESR. Biochemical investigations included total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, random blood sugar, blood urea, S. creatinine and uric acid. Clinical evaluation, haematological tests as well as biochemical tests were done pretreatment, 1st week, 1st month and 4th month. Patients were instructed to report any symptoms they would experience during the course of treatment. Symptoms looked for during the follow up period were fever, nausea, vomiting, anorexia, bitter taste sensation, loss of taste, abdominal pain, diarrhoea, lethargy, myalgia, arthralgia, jaundice, bleeding diathesis, photosensitivity, itching, rashes, confusion, blurring of vision, tingling and numbness, dizziness, loss of balance, convulsions, psychosis and depression. Physical examination included skin rashes, bleeding manifestations, jaundice, hepatomegaly, hepatic tenderness, ascites, oedema, signs of peripheral neuropathy. Hartwig scale was used to assess the severity of ADRs.

Statistical Analysis

Data analysis was done by Analysis of Variance (ANOVA) to analyse pretreatment versus post treatment values at 1st week, 1st month and 4th month. Pairwise comparison was also done among the pretreatment, 1st week, 1st month and 4th month values. Chi-square test was done to find out significance and P value of less than 0.05 was considered significant. The collected data was analysed and represented in the form of tables, pie diagrams and bar diagrams.

RESULTS

A total of 50 patients were selected for this study out of which 72% were males and 28% were females and maximum distribution of 24% was seen in the age group of

41-50 yrs. followed by 22% each among 21-30 and 31-40 yrs. In this study group, 2 patients (4%) were HIV positive and 11 patients (22%) consumed alcohol. Pulmonary tuberculosis constituted 82% and extrapulmonary tuberculosis was 18% of the study group. Out of the 50 patients, 30 patients developed atleast one or more types of ADR. ADR was seen in 71% of female population and 56% of male population, which showed that female gender is more susceptible to develop ADR. ADR in this study was seen more common in the age group of 51-60 yrs. and <20 yrs. However, the Fisher's exact test p=0.098, hence not statistically significant. It was seen that, out of 11 patients who consumed alcohol, 73% developed ADR indicating that alcohol consumption could be a strong risk factor for increased incidence of ADR. A total of 9 types of adverse drug reactions were observed. The most common being involvement of the Gastrointestinal (GI) system that is nausea, vomiting, loss of taste and appetite, dyspepsia, abdominal pain, jaundice and others included malaise and skin rash. The mean onset time of the adverse drug effects were observed within 7 days and mean duration time of the adverse drug effects were seen upto 2 months after start of ATT. One patient developed skin rash at 45 days after ATT. It was observed that most of the ADR subsided within 2 months after start of ATT. But, most patients had malaise lasting for upto 4 months.

Among the investigations done, it was observed that there was significant increase in the total bilirubin, SGOT, SGPT in the first week after the onset of treatment. Out of the 30 patients who developed ADR, 44% required symptomatic treatment. Hartwig's scale was used to assess the severity of ADR. Majority of patients (53%) developed level 3 reactions. In this study, 3 patients (10%) discontinued treatment. One patient discontinued treatment due to skin rash, 2 patients due to increased GI intolerence, mortality rate seen was 4% (2 patients). Reasons concluded were 2 patients expired due to extensive involvement of tuberculosis with poor general condition of the patient. One patient due to extensive involvement of tuberculosis with raised liver enzymes on a background of alcoholic liver disease. Most of the patients who developed ADR were managed symptomatically with antiemetics, antacids and antihistaminics and could continue ATT.

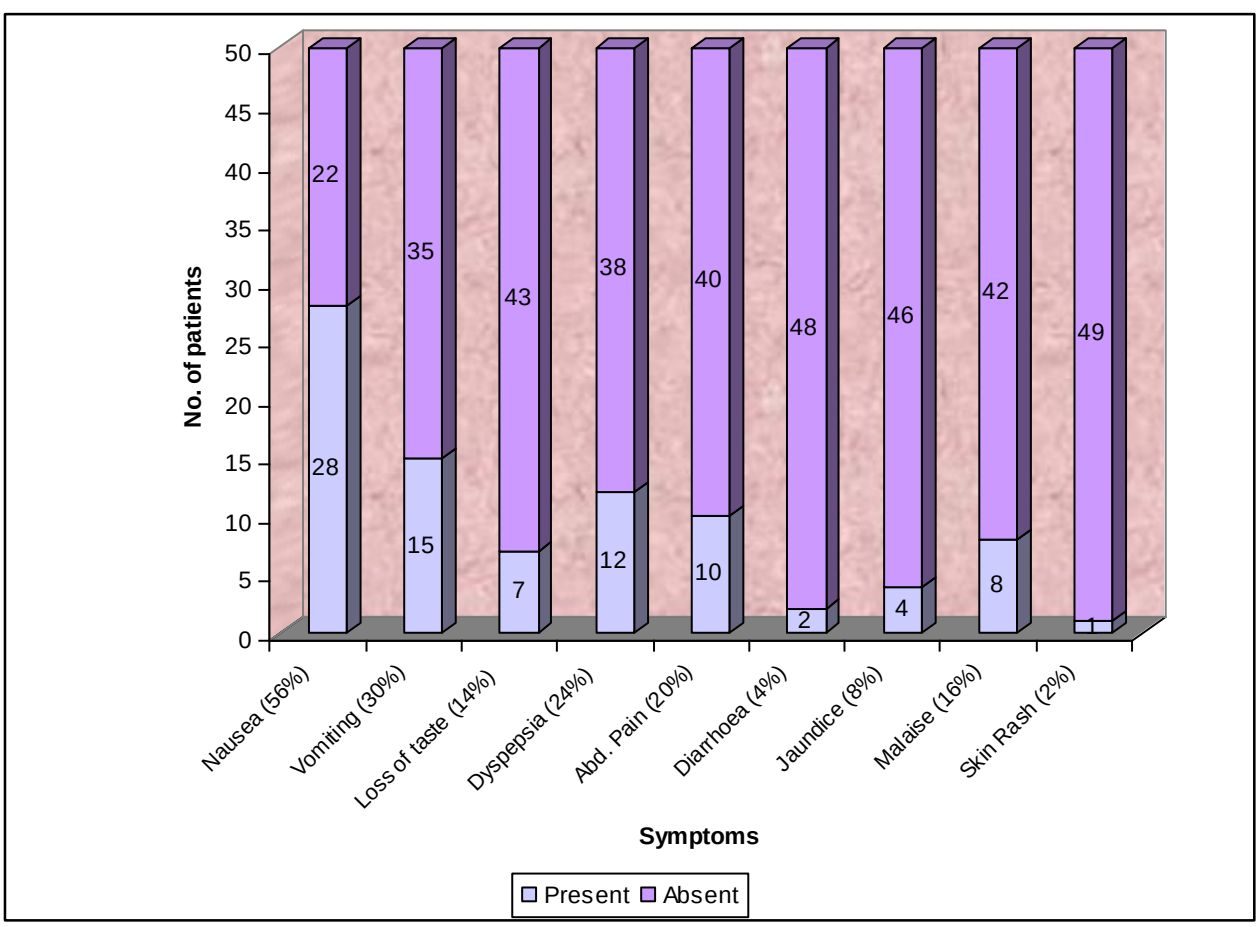

Figure 1. Distribution of Patients in Each ADR

The most common symptom observed in this study were GI symptoms like nausea (56%), vomiting (30%), loss of taste (14%), dyspepsia (24%), abdominal pain (20%), diarrhoea (4%), jaundice (8%), others were malaise (16%) and skin rash (2%).

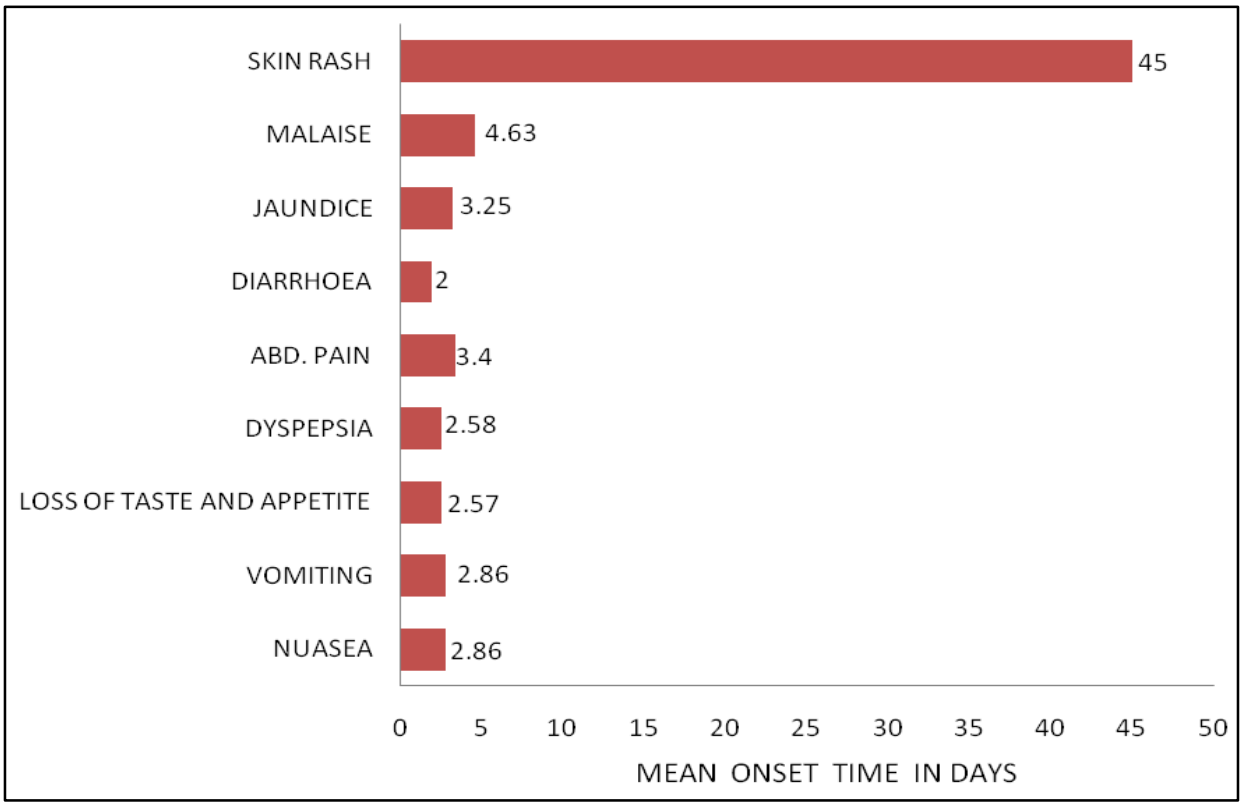

Figure 2. Mean Onset Time of ADR

It was observed that most of the patients developed ADR within 7 days after starting ATT. One patient developed skin rash at 45 days after ATT.

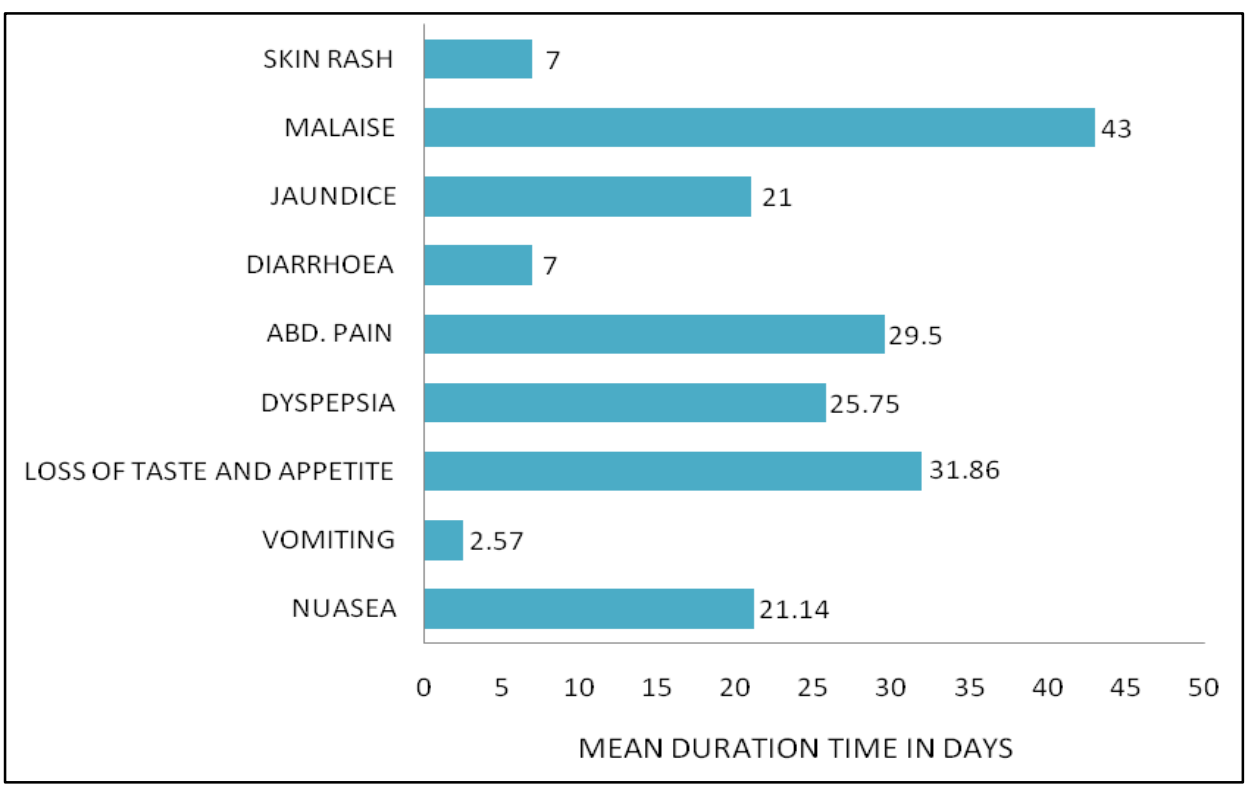

Figure 3. Mean Duration Time of ADR

It was observed that most of the ADR subsided within 2 months after start of ATT. But, most patients had malaise lasting for up to 4 months.

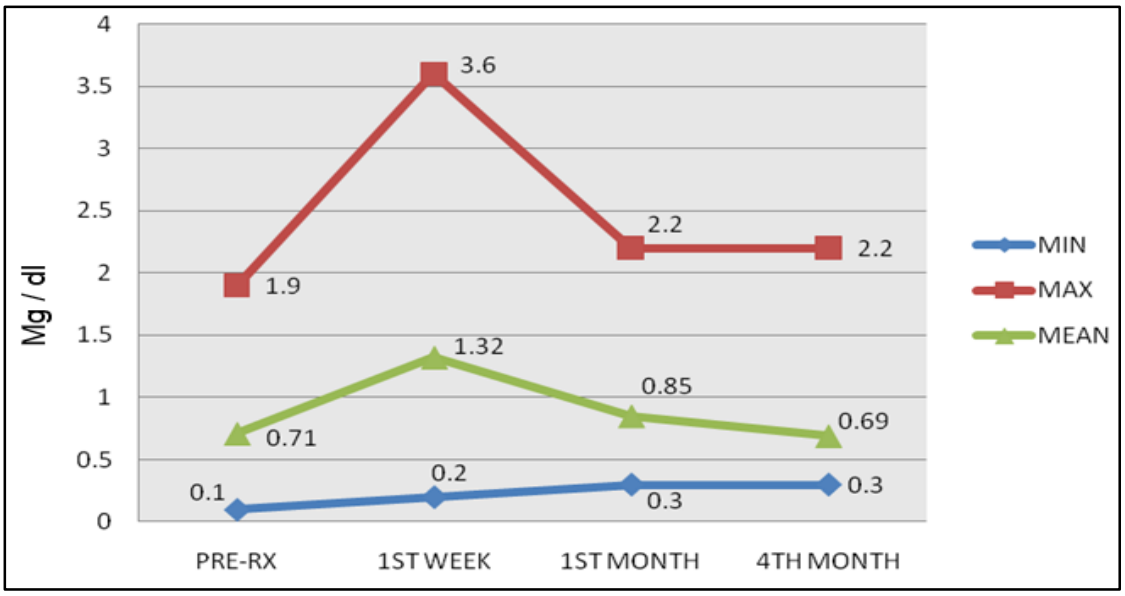

Figure 4. Pattern of Rise of Total Bilirubin (in mg/dL) During the Course of Treatment

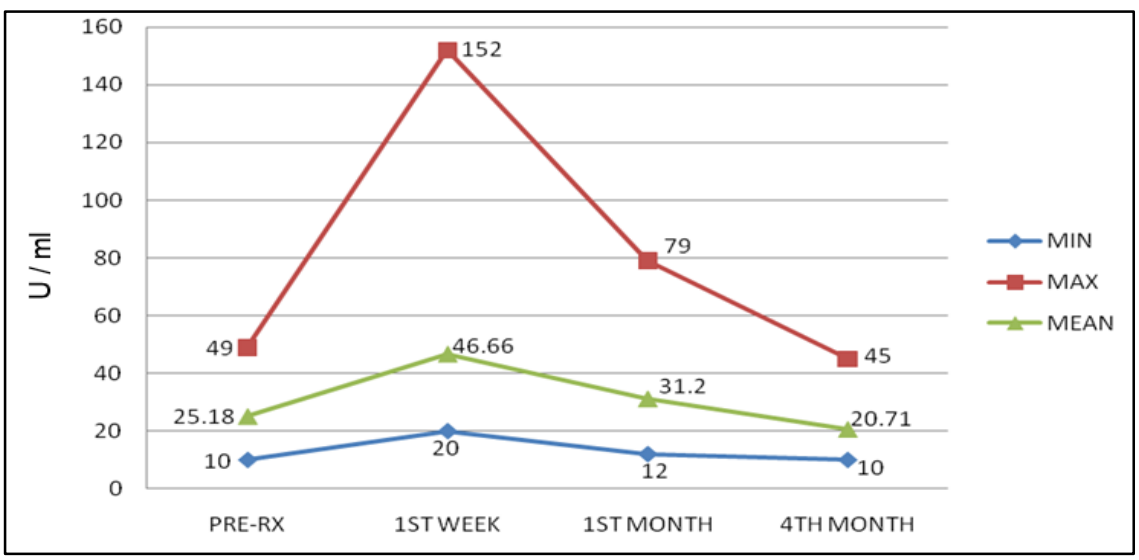

Figure 5. Pattern of Rise of SGOT (in Units/mL) During the Course of Treatment

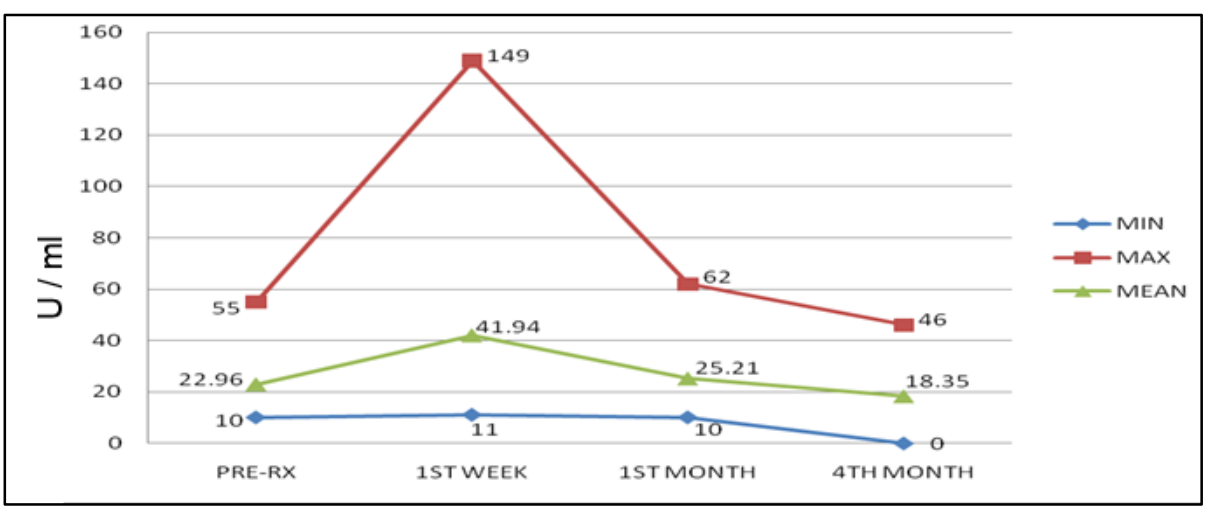

Figure 6. Pattern of Rise of SGPT (in Units/mL) During the Course of Treatment

It was observed that there was significant increase in the total bilirubin, SGOT, SGPT in the first week after the onset of treatment. The pair wise comparison done among the pretreatment values, 1st week, 1st month and 4th month values also showed that there was significant increase in the total bilirubin, SGOT, SGPT in the first week after the onset of treatment. The pair wise comparison of other haematological and biochemical investigations did not show any significant difference.

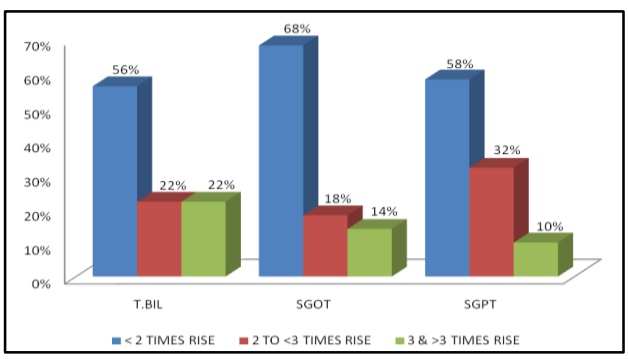

Figure 7. Percentage Distribution of Patients and Rise in T. Bili, SGOT and SGPT in the First Week After Start of ATT

Percentage distribution of patients for less than 2 times rise in total bilirubin, SGOT, SGPT was found to be maximum of 56%, 68% and 58%, respectively.

DISCUSSION

Antitubercular therapy, identifying adverse drug reactions, treating them and improving compliance is a very important aspect in the treatment of tuberculosis. Directly observed treatment, short-course (DOTS) is a very effective treatment strategy adopted by Revised National Tuberculosis Control Programme (RNTCP).

In our study, it was noted that out of the 50 patients studied, 30 patients (60%) developed one or more types ADR; out of which 56% among male population and 71% among female population developed ADR. A total of 9 types of adverse drug reactions were observed. ADR was found to be more common in female gender and those who consumed alcohol.

Comparing with a study done among 430 patients who were treated in Montreal Chest Institute (Montreal, Canada) between 1990 and 1999, 37 patients developed major adverse drug reactions and 46 types of serious adverse reactions were observed.[20]

In another study conducted on the patients of German-Nepal Tuberculosis Project and Korean-Thimi Friendship Hospital in 2005, of the 70 patients treated for tuberculosis, 80% of the total number of patients reported at least one type of side effects. Female gender (38.10%), alcoholics (38.89%) and sputum-smear positive (32.14%) were associated with increased occurrence of major side effects.[8]

In a study in Blackburn Chest Clinic between 1978 and 1992, out of the 1317 patients 67 (5.1%) had 70 reactions to antituberculosis drugs. Females had significantly higher reaction rates than males. A study conducted by Ormerod and others showed that 64 patients had single adverse drug reactions, while 3 patients suffered from two drug reactions in each case giving a total of 70 ADRs.[21]

Another multicentre study conducted in five hospitals in Nepal identified that 15.87% of the drug-related complications were due to ATT drugs (Shrestha and others, 2006).[22]

Also, studies from India - Dhingra and others 2004, 67% of the ADRs occurred in the first four weeks. Females had a higher incidence of ADRs. Dhingra and others showed that 8.37% of ADRs occurred in patients on DOTS treatment at the New Delhi Tuberculosis Center. In a study at the DOTS Centre Kasturba Hospital, Manipal and at the DOTS Centre, Udupi, out of 94 TB patients, a majority of them were males (70%) and belonged to the age group of 18-40 years (52%). The incidence of ADRs was 17.02%. Dose, age and alcoholism were found to be the other predisposing factors in 1 (4.76%), 3 (14.28%) and 1 (4.76%) cases, respectively.[23] The high incidence of ADR seen in our study could be probably due to inclusion of even very minor symptoms like loss of taste and appetite and nausea, whereas few studies mentioned above have considered only major adverse drug reactions.

Adverse Drug Reactions (ADRs) to the drugs used is one of the major reasons for the default of treatment. These events may incur substantial additional costs because of added outpatient visits, tests and in more serious instances hospitalisations. Onset of the ADRs is an important factor helpful in early detection of the ADRs. It is essential for the healthcare professionals to counsel the patients regarding the early identification of ADRs in the first few weeks.

In this study, among the 30 patients who developed ADR, 44% required symptomatic treatment. Hartwig's scale was used to assess the severity of ADR. Majority of patients (53%) developed level 3 reactions, 27% patients developed level 1 reaction. The mean onset time of the adverse drug effects were observed within 7 days and mean duration time of the adverse drug effects were seen up to 2 months after start of ATT. The most common being involvement of the gastrointestinal system that is nausea (56%), vomiting (30%), loss of taste and appetite (14%), dyspepsia (24%), abdominal pain (20%), jaundice (8%), diarrhoea (4%) and others were skin rash (2%) and malaise (16%). Patients with minor adverse effects improved with symptomatic medications like antacids, antihistamines and antiemetics and could continue the treatment and the symptoms subsided. The most common laboratory abnormality seen was rise in liver enzymes and bilirubin in the first week after the onset of treatment.

Comparing with the study conducted on 430 patients who were treated in Montreal Chest Institute (Montreal, Canada) between 1990 and 1999, the incidence of serious side effects, especially hepatitis and rash was highest with PZA. The consequences of these adverse events included hospitalisations, prolonged therapy and more clinic and home visits.[20]

In the study conducted in Blackburn Chest Clinic between 1978 and 1992, out of the 1,317 patients, 67 patients (5.1%) who had 70 reactions to antituberculosis

drugs and required modification of treatment and symptomatic treatment.[21]

In the study done on 326 TB patients at the Manipal Teaching Hospital, Pokhara, Nepal, during the period from 1st January, 2001, till 31st December, 2006, the most common ADR was elevated liver enzymes (24 (57.14%)) and hepatobiliary system was the most common system affected (24 (58.5%)). More than half the ADRs (21 (52.55%)) developed within 20 days of initiation of therapy. Isoniazid and pyrazinamide were the suspected drugs responsible for 32.32% each of the total ADRs. The most common laboratory abnormality observed was elevated SGOT level (21 patients (52.5%)). Seven (17.5%) patients needed specific drug treatment for managing the ADRs and 10 (25%) needed symptomatic management. Thirty five (87.5%) patients recovered following the ADR. Majority (19 patients (47.5%)) of the ADRs were mild (level (1)).[3]

In the study from India (Dhingra and others, 2004), hepatobiliary ADRs were the most common laboratory abnormality, which was derangement of liver enzymes. In the study at the DOTS Centre, Kasturba Hospital, Manipal, and at the DOTS Centre, Udupi, gastritis was the most common ADR and multiple drug therapy was the major predisposing factor and it was seen that 28.51% of the total ADRs belonged to type-A ADRs. In 87.1% of the cases, the suspected drug was continued in spite of the ADR without any complications. The severity assessment of ADRs showed that 31 (51%) reactions were moderate and 30 (49%) were of the 'mild' nature and found DOTS therapy to be safer and showed that regular monitoring is required for ADRs, so that certain percentage of ADRs can be prevented. Outcome of the ADR in 13 (61.90%) cases, the patients recovered from ADRs without any complications and in 6 (28.57%) cases, the reactions continued on discharge and there was no fatal reactions during the study period.[23]

CONCLUSION

This study shows that DOTS treatment is an effective and safe treatment strategy as most of the adverse drug reactions noted were of a mild variety (Hartwig's scale level 1) and were managed symptomatically. Gastrointestinal symptoms were the most common observed symptoms and most of the symptoms subsided within the intensive phase of the treatment. The most common laboratory abnormality seen was rise in liver enzymes and bilirubin. The healthcare professionals must be vigilant during the intensive phase of the treatment, identify symptoms at the earliest and hence help in minimising morbidity.

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REFERENCES

[1] Agarwal SP, Chauhan LS. Tuberculosis control in India. Directorate General of Health Services /Ministry of Health and Family Welfare, Government of India, New Delhi 2005.

[2] Nehaul LK. Tuberculosis. In: Walker R, Edwards C. eds. Clinical Pharmacy and therapeutics. 3rd edn. Edinburgh: Churchill Livingston 2003:583-595.

[3] Kishore PV, Palaian S, Ojha P, et al. Pattern of adverse drug reactions experienced by tuberculosis patients in a tertiary care teaching hospital in western Nepal. Pak J Pharm Sci 2008;21(1):51-56.

[4] Tak DK, Acharya LD, Gowrinath K, et al. Safety evaluation of antitubercular therapy under revised national tuberculosis control programme in India. Journal of Clinical and Diagnostic Research 2009;3(2):1395-1401.

[5] Maher D, Raviglione M. Global epidemiology of tuberculosis. Clin Chest Med 2005;26(2):167-182.

[6] Khatri GR, Frieden TR. Controlling tuberculosis in India. N Engl J Med 2002;347:1420-1425.

[7] World Health Organization, International Union Against Tuberculosis and Lung Disease, Royal Netherlands Tuberculosis Association. Revised international definitions in tuberculosis control. Int J Tuberc Lung Dis 2001;5(3):213-215.

[8] Koju D, Rao BS, Shrestha B, et al. Occurrence of side effects from anti-tuberculosis drugs in urban Nepalese population under dots treatment. Kathmandu University Journal Of Science, Engineering and Technology 2005;1(1):1-8.

[9] Sharma H, Aqil M, Imam F, et al. A pharmacovigilance study in the department of medicine of a university teaching hospital. Pharmacy Practice 2007;5(1):46-49.

[10] Edwards IR, Aronson JK. Adverse drug reactions: definition, diagnosis, and management. Lancet 2000;356(9237):1255-1259.

[11] Parthasarthi G, Nyfort-Hansen K, Nahata MC. A text of clinical pharmacy practice, essential concepts and skills. 1st edn. India: Orient Longman 2004:84-97.

[12] Hand K. Tuberculosis-pharmacological management. Hospital Pharmacist 2006;13:81-85.

[13] Kopanoff DE, Snider DE, Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. Am Rev Respir Dis 1978;117(6):991-1001.

[14] Franks AL, Binkin NJ, Snider DE, et al. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public Health Rep 1989;104(2):151-155.

[15] Durand F, Bernuau J, Pessay D, et al. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculous treatment including isoniazid. Hepatology 1995;21(4):929-932.

[16] Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J 1996;9(10):2026-2030.

[17] Devi S, Ramachandran R, Santha D. Adverse reaction to antituberculosis drugs and their management. Bulletin 1997;4(3&4):1-4.

[18] Tandon RK, Garg PK. Antituberculosis treatment induced hepatotoxicity. In: Sharma SK, Mohan, Tuberculosis. New Delhi: Jaypee Brothers 2004:500.
[19] Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49(9):2229-2232.
[20] Yee D, Valiquette C, Pelletier M, et al. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respire Crit Care Med 2003;167(11):1472-1477.
[21] Ormerod LP, Horsfield N. Frequency and type of reactions to anti-tuberculosis drugs: observations in routine treatment. Tuber Lung Dis 1996;77(1):37-42.
[22] Shrestha R, Shakya S, Bista D. Case studies of hospitalized patients due to drug related complications. Kathmandu Univ J Sci Eng Technol 2006;2(1):1-9.
[23] Dhingra VK, Rajpal S, Aggarwal N, et al. Adverse drug reactions observed during DOTS. J Commun Dis 2004;36(4):251- 259.