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Original Article

Pharmacology Section

Adverse Drug Reaction Profile in Patients on Anti-tubercular Treatment Alone and in Combination with Highly Active Antiretroviral Therapy

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ABSTRACT

Background and Objectives: Adverse drug reactions are very common among patients on anti-tubercular treatment alone or in combination with highly active antiretroviral therapy but comparatively studied very less. Hence, the current study was done to evalaute the adverse drug reaction (ADR) profile in patients receiving anti-tubercular treatment (ATT) and ATT with highly active antiretroviral therapy (HAART).

Materials and Methods: A one year prospective, cross-sectional observational study was undertaken using suspected adverse drug data collection form available under Pharmacovigilance Programme of India.

Results: Seventy four patients receiving ATT & 32 patients on both ATT & HAART presented with 74 and 45 adverse drug events (ADE) respectively. Males were more affected than females in both the groups. DOTS category- 1 regimen was mostly responsible for ADE in both the groups. Epigastric pain was the most common ADE in TB patients, while anaemia was the most common presentation in TB with HIV group. On comparison, ADE rate of TB with HIV co-morbid patients was more (55.8%) than TB patients (0.36%) ($p < 0.001$). Urban population presented more with ADR in TB/HIV group unlike rural population in TB group ($p<0.0001$). Whereas, illiterate were more involved in TB group unlike literate in TB/HIV group ($p<0.05$). Type A reactions were more common in TB group ($p < 0.001$). Addition of drugs for the management of ADR events was more in TB/HIV group ($p < 0.001$) as compared to TB group. Rest all the parameters were comparable.

Conclusion: The study underscores that concomitant HAART and ATT, result in more ADRs in comparison to ATT alone demanding collaboration & integration of National AIDS Control programme and PvPI to enhance drug safety in this field.

Keywords: Pharmacovigilance, Tuberculosis, HIV

INTRODUCTION

TB/HIV the 'curse duo' is a major public health problem. Adverse drugs reactions (ADR) are a great challenge to national anti-tuberculosis & HIV programme. The ADR can negatively affect the compliance, which can result into therapeutic failure and may indirectly contribute to MDR-TB. Numerous studies have been conducted in the past documenting ADR profile for various ATT [1,2] and HAART regimens [3,4].

While going through the literature however we could only site few studies [5,6] that too from the western part of the world wherein indirect attempt has been made to comment upon the ADR profile among ATT & HAART receiving patients.

Moreover, it is expected that concomitant administration of HAART and ATT therapies may possess significant challenge in the form of cumulative drug toxicities, drug-drug interactions due to complexity of regimens, high pill burden, thereby complicating the treatment outcomes and the natural history of TB/HIV co-infection.

In view of rising trend of TB/HIV co-infection, it demands evaluation of variations in ADR profile likely to exist among the population receiving ATT alone or ATT & HAART which will go long way to understand, early detection, prevention and management of ADRs and to ameliorate the associated morbidity among such patients. Hence, the current study was done to evaluate the adverse drug reaction (ADR) profile in patients receiving anti-tubercular treatment (ATT) and ATT with highly active antiretroviral therapy (HAART).

MATERIALS AND METHODS

This one year prospective, cross-sectional study was conducted with effect from November, 2011 to October, 2012 after getting approved by Institutional Ethical Committee vide no: IEC/Pharma/Thesis/Research/Project/2C/2011/2060 and getting administrative permission. Eligible subjects were recruited from the Chest Disease Hospital and ART centre. Verbal consent was obtained from all the participants.

New and old diagnosed cases of TB admitted in the wards or attending OPD's on ATT, patients of TB with co-morbid HIV receiving ATT and HAART as per RNTCP & NACO programme, who were on regular follow up presenting with any ADR were included for one point analysis in current study using spontaneous ADR reporting form. All ADR patients were followed till final outcome of ADR. Patients with therapeutic failure, over-dosage, non-compliance, medication errors, were excluded from the study. Patient of TB with HIV, who were yet to start Anti-retroviral therapy, were also excluded.

The ADRs were defined and categorized as per the definition of Edwards & Arsonson [7]. Detail Information about ADR were recorded as per the standard operative procedure of Indian Pharmacopeia Commission on suspected adverse reporting form. The severity (as per US-FDA) and seriousness of reaction, the outcome and management of reaction was recorded. The suspected ADRs were classified in term of causality using WHO-UMC scale and [8] Naranjo scale [9].

STATISTICAL ANALYSIS

In the current study the data was expressed in n (%).Chi-square test was applied to prove their statistical significance with p-value < 0.05 was considered to be significant. Analysis was carried out with the help of computer software SPSS Version 15 for windows.

RESULTS

During the study period a total of 106 patients presented with ADRs. Seventy four patients receiving ATT & 32 patients on both ATT & HAART presented with 74 and 45 adverse drug events (ADE)

respectively. On comparison, ADE rate of TB with HIV co-morbid patients was more (55.8%) than TB patients (0.36%) ($p < 0.001$). Males were more affected than females in both the groups. The number of patients in TB was more from the rural areas, while patients in TB with co-morbid HIV were more from the urban areas. DOTS category- 1 regimen was mostly associated responsible for ADE in both groups, affecting (68.91%) and (59.37%) of patients respectively.

AZT+3TC+EFV combination was responsible for (71.87%) of ADE's in TB with co-morbid HIV, while d4T+3TC+EFV combination was responsible for (21.8%) ADE's [Table/Fig-1,2]. Epigastric pain was the most common presentation in TB patients, followed by loss of appetite and vomiting in (9.45%), while in TB with co-morbid HIV patients anaemia was the most common presentation constituting (15.5%) followed by epigastric pain, vomiting and insomnia in (8.88%) each [Table/Fig-3,4]. GIT was the most common body system involved in both the groups (67.56% and 31.11%) followed by nervous system (10.81% and 22.22%) respectively.

Type A reaction were maximum (87.83% in TB group & 62.2% in TB with HIV) followed by type C (24.44% in TB with HIV) and (10.81% in TB group), while B type reactions were least in both the treatment groups (1.13% & 13.33% respectively). In both the groups most of the ADE's were latent in nature (74.3% Vs 75.5%) followed by acute onset (16.21%) in TB patients and sub-acute in (20%) in TB with HIV.

Maximum ADR events were moderate in nature in both the groups (71.62% & 55.5%) followed by severe (35.5%) in TB patients and (25.67%) in TB with co-morbid HIV patients. Most of the ADR events did not warrant any change in treatment in both groups (71.62% & 37.77%), while in (28.37%) of patients in TB patients needed stoppage of treatment and (62.2%) in TB/HIV co-morbid patients. 83.78% were recovered fully in TB and (64.44%) in TB/HIV co-morbid patients. No fatality was reported in either of the groups.

	ADR among TB patients on ATT	ADR among TB patients With HIV on ATT and HAART	Statistical analysis
Total Period of Study	1year	1year	
Total no ADRs cases	74	32	
Total number of ADR events	74	45	
ADR rate (95% Confidence Interval)	Total no of TB patients=20364 during study period 74x100/20364=0.36% (1.01-1.73)	Total No of HIV and TB patients during study period=58 32x100/58=55.8% (37.95-72.39)	p=0.0001; HS
Mean weight±SEM	50.56±10	50.90±11.32	t=0.74; p=0.45; NS
Mean Age±SEM	37.2±10.2	38±9.89	t=0.67 p=0.43 NS
Sex Distribution- Male vs Female Ratio	57(77%)/17(23%)	25(78.1%) /7(21.9%)	χ^2=0.02; p=0.90; NS
Treatment Profile of TB Patients			
DOTS Category-I/ DOTS Category-II	51(68.9%)/23(31.1%)	19(59.4%)/ 13(40.6%)	χ(1)2=0.91; p=0.34; NS
Treatment Profile of TB + HIV Patients			
ART Regimens			
AZT+3TC+EFV	-	23(71.87%)	
d4T + 3TC + EFV	-	7(21.87%)	
AZT + 3TC + NVP	-	1(3.12%)	
d4T + 3TC + NVP	-	1(3.12%)	

[Table/Fig-1]: Demographical Profile of ADRs
AZT-Zidovudine; 3TC-Lamivudine; d4T -Stavudine; EFV-Efavirenz; NVP-Nevirapine; S= significant, NS= Non significant; HS= Highly significant

Parameters	ADR among TB patients on ATT	ADR among TB patients With HIV on ATT and HAART	Statistical analysis
Severity of ADRS – Mild/ Moderate/ Severe/ Fatal	2(2.7%)/53(71.6%)/ 19(25.7%)/0(0%)	4(8.8%)/25(55.6%) /16(35.5%)	χ^2=4.15; p=0.12; NS
Mode of onset – Sub acute/ Acute/ Latent	7(9.5%)/12(16.2%)/ 55(74.3%)	9(20.0%)/2(4.5%) /34(75.5%)	χ^2=5.61; p=0.06; NS
Type of reactions - A,B,C,D,E & Unclassified	65(87.83%)/1(1.13)/ 8(10.8)/0(0%)/0(0%)	28(62.2%)/6(13.3%)/ 11(24.44%)/ 0(0%)/0(0%)	χ^2=12.44; p=0.001; HS
Causality as per Naranjo's Scale - Definite/Probable/ Possible/Doubtful	0/31(41.9%)/ 43(58.1)/0(0%)	0((0%)/21(46.7%)/ 24(53.3%)/0(0%)	χ^2=0.26; p=0.61; NS
Causality as per WHO - UMC scale –Certain/Probable/ Possible/Unlikely/ Unclassified/ Unassessible	0/31(41.9%)/43(58.1)/ 0(0%)/0(0%)/0(0%)	0(0%)/21(46.7%)/ 24(53.3%)/ 0(0%)/0(0%)	χ^2=0.26; p=0.61; NS
Outcome of the ADRs - Recovered/ Recovering/ Continuing/ Unknown	62(83.8%)/12(16.2%) /0(0%)/0(0%)	29(64.4%)/ 15(33.4%)/1(2.2%)	χ^2=6.63; p=0.03; S
Management of ADRs - Intervention required Vs No Intervention	21(28.4%) Vs 53 (71.6%)	17(37.8%) Vs 28 (62.2%)	χ^2=31.79; p=0.0001 ;HS

[Table/Fig-2]: Parameters of ADRs
S= significant, NS= Non significant; HS= Highly significant

Adverse Drug Reactions Events	n	%
Epigastric pain	19	25.67
Vomiting	7	9.45
Loss of Appetite	7	9.45
Gastritis	6	8.10
Epigastric discomfort	6	8.10
Loss of weight	4	5.40
Myalgias	3	4.05
Dizziness	3	4.05
Vertigo	2	2.70
Severe anaemia	2	2.70
Deranged Liver Function Tests	2	2.70
Anxiety	2	2.70
Indigestion	2	2.70
Fever	1	1.35
Rash	1	1.35
Altered behavior	1	1.35
Dyspepsia	1	1.35
Constipation	1	1.35
Loose motions	1	1.35
Psychosis	1	1.35
Glossitis	1	1.35
Sedation	1	1.35
Total	74	100

[Table/Fig-3]: Distribution of Various ADR Events in Tuberculosis Patients on ATT

As per the Naranjo's probability scale, most of the events were of possible nature (58.10%) and (53.33%) and probable (41.89%) and (46.66%) in both the groups respectively. Causality assessment based on WHO-UMC revealed similar trends.

Overall comparative analysis of two groups revealed that point prevalence of TB/HIV co-morbid patients was more than TB patients ($p <0.001$). Urban population presented with more ADR in TB/HIV group unlike rural population in TB group $p<0.0001$. Whereas,

ADR Events	ART+DOT Category-I	ART+DOT Category-II	n (%)
Anaemia	3	4	7(15.55)
Insomnia	0	4	4(8.88%)
Vomiting	2	2	4(8.88%)
Pain epigastrium	3	1	4(8.88%)
Giddiness	3	1	4(8.88%)
Rash	1	2	3(6.66%)
Nausea	2	1	3(6.66%)
Gastritis	2	0	2(4.44%)
Generalized weakness	1	1	2(4.44%)
Loss of apetite	1	1	2(4.44%)
Headache	1	0	1(2.22%)
Diarrhoea	1	0	1(2.22%)
Urticaria	1	0	1(2.22%)
Glossitis	1	0	1(2.22%)
Peripheral neuropathy	1	0	1(2.22%)
Nail hyperpigmentation	1	0	1(2.22%)
Oral candidiasis	1	0	1(2.22%)
Loss of weight	1	0	1(2.22%)
Altered taste sensation	1	0	1(2.22%)
Sedation	0	1	1(2.22%)
Total			45

[Table/Fig-4]: Distribution of Various ADRs in Tuberculosis Patients with Co-morbid HIV Receiving ATT and HAART

illiterate were more involved in TB group unlike literate being more in TB/HIV group with p<0.05.

Type A reactions were more common in TB group (p < .001). Addition of drugs for the management of ADR events was more with TB with co morbid HIV (p < .001) as compared to TB group where no addition or substitution of the drugs was done for treatment of the ADR. Rest all the parameters pertaining to ADRs were comparable [Table/Fig-1,2].

DISCUSSION

Analysis of ADRs in patients receiving ATT revealed that the maximum number of patients were of age group of 41-50 years which in accordance to the study of Ramanath et al., [10]. Whereas, Chhetri et al., reported a total 29.33% of ADRs in the age group 21-30 years [11]. In present study ADR events were more in males in accordance to previous studies [12,13]. The most common system involved among ATT users was GIT comprising of epigastric pain, vomiting, loss of appetite, followed by gastritis and these results are consistent with Tak et al., [14].

The next most common system involved was the nervous system comprising of dizziness, anxiety, psychosis and sedation. Similar observations were made by Chhetri et al., [11]. Tak et al., who also reported CNS to account for 14.28% of which dizziness comprised of 4.76% events [14]. Most likely drugs causing dizziness in present study were isoniazid, rifampicin, and pyrazinamide similar to observations of Ramanath et al., [10].

Myalgias due to pyrazinamide and rifampicin were reported in 4.5% of patients in our study. Similarly, Koju et al., and Ramanath et al., have also reported common involvement of musculoskeletal system in form of myalgia [10,12]. Dermatological system comprising of rash and glossitis was seen in agreement to the findings of Qayyum et al., who observed 7.1% dermatological involvement [1]. However, the highest percentage of dermatological involvement 27.34% was reported by Ramanath et al., unlike our observations [10]. Vertigo was seen in 2.70% in our study. Streptomycin was suspected to be the offending drug. Vertigo was observed in 31.7% of all the ADR reported cases by Qayyum et al., [1].

The least common system involved in present study was the haematological system comprising of 2.7% of anaemia. A similar observation was made by Forget et al., [15].

Deranged LFTs were seen in 2.70% of cases in our study. Ali, observed that transient elevations of serum hepatocellular enzymes alanine aminotraansferase, asparate aminotransferase, in approximately 10% of patients who received a standard combination chemotherapy [16]. A significant increase in the total bilirubin, bilirubin direct, AST, ALT, alkaline phosphatase has been reported by Koju et al., [12].

ADR events experienced by TB patients were predominantly latent in nature. Tak et al., in their study reported that most of the ADRs (33.33%) to be latent in nature [14]. Maximum ADR events in our study were of moderate severity like the findings of Ramanath et al., [10].

Present study reported a recovery in maximum patients with ADRs. Among these majority of ADR events were self-limiting and required no discontinuation of the ATT regimen. In a study by Chhetri et al., majority of the reported ADRs (93.33%) were mild and did not need modification of treatment like our study [11]. Similarly, Tak et al., Kishore et al., & Nahar et al., have reported full recovery in majority of the patients without any complications and mortality [14,17,18].

Type A reaction accounted for almost all of the ADR events in current analysis in accordance to Fellay J et al., [19]. Majority of the ADRs reported by Chhetri et al., were “possible” as per Naranjo algorithm which is in accordance to our reports [11].

The ADRs in TB with co-morbid HIV was recorded in higher percentile of patients. Fellay et al., in their study reported ADR events in 74% and Dean et al., reported ADR’s in 54% like our study [19,20]. Whereas, Anwikar et al., has reported that 222 patients developed about 228 ADRs with a prevalence of 12.36% [21].

Most of the patients in our study were aged between 31-40 years. A study by Bahl et al., reported 75% of the patients were in the age group of 21-40 years [22]. Whereas, Harsha and Gupta reported in their study that majority of the patients were in the age group of 19-49 years [23]. Present study reported that males were more affected. Similar findings have been observed in various other studies (Bahl et al.,) [22].

Majority of the patients in this group belonged to 78.87% urban areas as compared to rural. Similar observations were made by Datiko et al., [24]. In present study more than half of the patients were literates (56.25%). This is in accordance with the study carried out by Brunello et al., [25]. ADR events were observed more with the zidovudine along with lamivudine and efavirenz containing regimen (71.87%) in accordance to Sharma et al., [26].

Gastro intestinal was the most common system involved comprising mainly of vomiting, pain epigastrium, followed by nausea and gastritis in agreement with Cesar et al., [27]. The next most common system involved was the nervous system comprising of insomnia and giddiness, followed by peripheral neuropathy and sedation. The suspected drug to cause CNS toxicity was efavirenz and zidovudine. Berenguer et al., also reported similar observation which is consistent to our study [28]. Anaemia was the most common ADE observed with Zidovudine containing HAART regimen similar to Sharma et al., [26]. Among the dermatological complications which accounted for 15.55% rash was observed in maximum followed by urticaria, glossitis, nail hyperpigmentation and oral candidiasis. Whereas, Cesar et al., reported rash in 3% of their cases [27].

Maximum ADR events reported by the patients in our study were of latent onset and of moderate severity. Our study reported 64.44% recovery of all the patients with ADRs. Only 35.55% of the ADR events required symptomatic treatment. Abdissa et al., reported

that 7.7% of the ADE required a change in the therapy [29]. The suspected drugs had to be stopped in 40% cases as reported by Issakidis et al., [30].

Most of the ADR events (62.22%) were type A reactions. Majority of ADE observed in our study were possible and probable in nature as assessed by the Naranjo Probability Scale and WHO-UMC. Anwikar et al., observed that majority of the ADRs 96.49% were found to be possible and 3.50% were probable according to WHO-UMC assessment criteria [21]. Kwon et al., came up with similar results [31].

Overall comparative analysis of two groups revealed that point prevalence of ADE in TB/HIV co-infection was more than TB alone. This probably may be due to cumulative drug toxicities, drug-drug interactions, complexity of regimens, high pill burden which however remain to be validated in future research. Moreover, the current study does not represent the true volume of the problem due to spontaneous reporting of ADR.

Urban literate population presented more with ADR in TB/HIV group unlike rural illiterate population in TB group. Type A reactions were more common in TB group there suggesting that majority of such reaction could have been prevented. Whereas Type B & C reaction being more in TB/HIV group suggesting a strong need to initiate and extend role of pharmaco-genomics in PV.

LIMITATIONS

The study had some limitations as the patients were not followed and were spontaneous in nature. No attempt was made to establish any correlations with any of the clinical parameters.

The results thus clearly underscore that concomitant administration of HAART and ATT therapies result in more number of ADRs. Thus, outcome of current study stresses upon a need for collaboration of NACO, RNTCP and PvPI to enhance drug safety.

CONCLUSION

The study underscores that concomitant HAART and ATT, result in more ADRs in comparison to ATT alone.

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