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Original Research Article

Analysis of Reporting Pharmacovigilance in a Rural Tertiary Care Hospital in South India: A Retrospective Study of Two Years Survey

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Conflict of interest: Nil

Abstract:

Introduction: In India the Adverse Drug Reaction (ADR) reporting have to enhanced in the tertiary care teaching institute and corporate hospital. Majority of the drug fate will be revealed if there is documental evidence of ADR reporting. In many countries ADR ranks among the top ten leading cause of morbidity and mortality. Objective of the Present study was planned to evaluate and analyses the incidence and pattern of various ADR reported from both the outpatient and inpatient department in a tertiary care teaching hospital. The study objective is with special emphasize on causality assessment tool using Naranjo Algorithm and World Health Organization – Uppsala Monitoring Centre (WHO-UPC).

Materials and Methods: This study was an observational, retrospective and Cross-sectional study conducted by analyzing the spontaneous ADR forms collected from various clinical departments over a period of 16 months from January 2020 to April 2021. Causality analysis was done based on the two recommended assessment of Naranjo Algorithm and WHO-UPCA. A total of 139 patients ADR were collected and analyzed.

Results: Among the total reported ADR, it shows female predominance of 54.68%. The majority of the ADR event occurred in the age group between 51–60 years of 20.86%. Among the various departments, dermatology had higher occurrence with 33.81%. Based on the type of reaction, urticaria was predominant with 30.22% followed by Fixed drug eruption and Maculopapular drug rashes. Parenteral and Oral antibiotics were the major ADR reported in our study with 54.67% followed by other systemic drugs. The causality assessment of both the study reveals that 32.37% were identified in serious reaction.

Conclusion: ADR Reporting is an ongoing and continuous process which is need of the hour to create awareness among health care profession and patients. “Probable” was the most common causality category identified in both the assessment method.

Keywords: Pharmacovigilance, ADR Reporting, Causality Assessment, Naranjo Algorithm, WHO-UPC.

Introduction

Reporting ADR in India has been an ongoing process which was started almost 30 years back with physician from academic institution [1]. India is a country with large ethnic variability with variable disease pattern and different system of medicine ranging from ancient tradition to the modern medicine [2]. Pharmacovigilance (PV) deals with the detection, assessment, understanding and prevention of Adverse drug reaction [3]. The ADR refer to any unintended side effect of medicine that occurs during clinical usage and is not related to the drugs intended therapeutic benefits ADR [4]. In today’s world as every week a new drug is approved for use, monitoring of ADR becomes even more important whose ADRs database is required for risk–benefit analysis in the patients. In India and developing countries, ADR are the one of the leading causes of morbidity and mortality rate, which show negative impact on the patient’s quality of life and also on health-care system [5]. The proactive Pharmacovigilance throughout the life cycle of drug is need of the hour. It is related to the protection of public health and monitoring of ADRs which are incurred when drug is made available in the market and used in different physiological conditions [6]. Tracking of

ADR is now required by our regulatory agencies in order to identify and prevent adverse drug reactions. Methods that can accurately predict those most are at risk for an adverse drug reaction have been developed. The active involvement of the health care professionals such as doctors, pharmacist, nurses are the success of a pharmacovigilance program of India (PvPI) [7,8].

Spontaneous ADR reporting is an important to monitor all type of adverse effects of medicines. The Drug Control General of India (DCGI) and Indian Council of Medical Research (ICMR) have direct contact with National Pharmacovigilance Programme of India to monitor various ADR Centers and Peripheral PV Centers has been established in various medical colleges and in corporate hospitals. Thus ADR monitoring is of utmost importance of not only for drugs of narrow therapeutic index but also especially in patients advised poly pharmacy and establishing a causal relationship with the drug in use will help to establish treatment modification, reduce the cost of healthcare and provide ideal benefit to the patient by rational use of medicines, reduce ADR related hospital admissions, determine predisposing risk factors, estimation of cost of ADRs in terms of ADR-related excess hospital stay [9,10,11].

The adverse drug events can occur from single dose or prolonged administration of a drug or results from the combination of two or more drugs.

The importance of adverse drug reactions is often underrated, they can be life threatening and unnecessarily expensive since there are a wide range of drugs available. The manifestation of toxicity varies and can affect any organ system. The pattern of toxicity is likely to change with the introduction of new products.

Causality assessment of ADRs is a method used for estimating the strength of relationship between drug exposure and occurrence of ADR. There are many methods and algorithms available for causality assessment which includes the Jones' algorithm, the Naranjo algorithm, the Yale algorithm, the Karch algorithm, the Begaud algorithm, the ADRAC, WHO-UMC and a newer quantitative approach algorithm. The basic concept involved behind all these methods or algorithms is to establish proper relationship between ADR and drug.

The causality assessment system proposed by World Health Organization Collaborating Centre for International Drug Monitoring, The Uppsala Monitoring Centre (WHO-UMC) and the Naranjo algorithm are most widely used and accepted methods for causality assessment of ADR due to their simplicity of analysis. Both of them have their own way of establishing causality in distinct manner with their own advantages and disadvantages [12-16].

The WHO-UMC system takes into account the clinical-pharmacological aspects of case history, with a less prominent role of previous knowledge and statistical chance. The Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, and previous patient experience with the medication. None of the causality assessment tools have been universally accepted as the gold standard [17]. Hence, the present study was conducted to assess all the parameters starting from the demographic details to the detailed drug category and the agreement between the WHO-UMC criterion and Naranjo algorithm-the two widely accepted tools in pharmacovigilance.

Materials and Methods

Study design and settings

Our Study was an observational, retrospective, record-based study conducted by analysing the spontaneous ADR forms, collected over a period of 16 months from January 2020 to April 2021 at Trichy SRM Medical College Hospital and Research Centre, which is a 1750 bedded tertiary care reference centre and a teaching hospital located in Trichy, Tamil Nadu, India.

The Study centre is a recognized ADR monitoring centre of Trichy and it is one of the peripheral ADR monitoring centres of the National PvPI. The ADR monitoring centre has been coordinated by the Trichy SRM Institute's Department of Pharmacology, where the analysis of the report done.

Study Procedure

The study was commenced after obtaining approval from the Institutional Ethics Committee of TSRMMCH&RC/ME-1/2020-IECNo 93(A). All spontaneously reported ADR forms (Version 1.3) were collected and evaluated as part of Pharmacovigilance program of India. The reporting physician was contacted for the collection of any further information when it was necessary. The data on the reported ADRs were analysed and evaluated under various parameters as: -

Patient characteristics

The patient's age and sex were considered for evaluation.

Reaction characteristics

The individual reactions were classified, depending on the organ system which was affected.

Drug characteristics

The offending drug causing ADR were classified into drug classes and were further classified, based on their route of administration.

Causality assessment

Each ADR was assessed for its causality by using the causality assessment for suspected drug in terms of "Definite," "probable," "possible" and "doubtful," were done with the help of Naranjo's algorithm. The WHO-UMC Causality assessment for suspected drug in terms of "Certain/Definite," "probable," "possible" and "unlikely," were done[16,17].

Statistical Analysis

The data were analysed using SPSS, IBM Corporation, version 24 and summarized using percentages and frequencies.

Results

During the entire study period, there were a total of 139 patients ADR reported from various clinical departments. Regarding the demographic details of gender distribution, the collected ADR shows with female predominance of 76 cases (54.68%) and male patients of 63 cases (45.32%), which is depicted in the Table 1.

Table 1: Gender Distributions of Patients

Gender	No of Patients	Percentage
Male	63	45.32
Female	76	54.68

The maximum number of ADR event occurred in the adult age group between 51-60 years of 29 patients (20.86%) followed by adolescent age group between 21-30 years of 26 cases (18.70%), and in the elderly age group of above 60 years shows 22 cases (15.82%), which is depicted in the Table 2. The youngest patient was 3 years old and the oldest patient was 90 years old.

Table 2: Age and Gender Distributions of Patients for ADR

Age Category	Male (n=63), (n%)	Female (n=76), (n%)
0 – 10 Years	01 (1.58)	03 (3.94)
11 - 20 Years	07 (11.11)	06 (7.89)
21 - 30 Years	16 (25.39)	10 (13.15)
31 - 40 Years	08 (12.70)	11 (14.47)
41 - 50 Years	11 (17.46)	11 (14.47)
51 - 60 Years	09 (14.28)	20 (26.31)
61 - 70 Years	06 (9.52)	07 (9.21)
71 - 80 Years	03 (4.76)	01 (1.31)
Above 81 Years	02 (3.17)	03 (3.94)

ADR: Adverse drug reaction

Among the various departments reported the ADR, dermatology had the highest occurrence with 47 cases (33.81%) followed by General Medicine of 36 cases (25.90%) and emergency medicine with 10 cases (7.19%). While the department of anaesthesia, cardiology and gastroenterology were the lowest reported events of each 2 cases (1.44%), which is elicited in the Table 3. Based on the type of adverse drug reaction occurred, urticaria manifestation was predominant with 42 cases (30.22%) followed by Fixed drug eruption of 32 cases (23.02%) and Maculopapular drug rashes with 12 cases (8.63%). The other type of reaction with occurrence is displayed in the Table 4. Many Drugs were prescribed, among which, Parenteral and Oral antibiotics were the major ADR reported in our study with (54.67%) followed by other systemic drugs. Injection cefotaxime, Injection ceftriaxone each occurrence of (6.47%) of the parenteral antibiotics, followed by Injection Ciprofloxacin, Metronidazole each shows (3.60%) and Injection Cefoperazone + sulbactam, levofloxacin, azithromycin each shows (2.88%), depicted in the Table 5.

Table 3: Department wise distribution of Reported ADR

Department	No of Patients n=139, n (%)
Dermatology	47 (33.81)
General Medicine	36 (25.90)
Emergency Medicine	10 (7.19)
General Surgery	09 (6.47)
Chest and TB	06 (4.32)
Obstetrics and Gynecology	06 (4.32)
Paediatrics	06 (4.32)
Orthopedics	05 (3.60)
ENT	05 (3.60)

Radiology	03 (2.16)
Anaesthesia	02 (1.44)
Cardiology	02 (1.44)
Gastroenterology	02 (1.44)

ADR: Adverse Drug Reaction

Table 4: Distribution of ADR based on Type of Reaction

Type of Reaction	Frequency	n %
Urticaria	42	30.22
Fixed Drug Eruption	32	23.02
Maculopapular Drug rashes	12	8.63
Hypotension with rigor	10	7.19
Palpitation	09	6.47
Angioedema	08	5.75
Photosensitive drug rashes	07	5.04
Erythema Multiforme	07	5.04
Erythroderma	05	3.60
Anaphylactic shock	04	2.88
Drug induced hepatitis	03	2.16

ADR: Adverse drug reaction

Among the oral antibiotics, Ciprofloxacin and Cotrimoxazole were the major suspected ADR of (3.60%) occurrence, shown in Table 6. Other parenteral drugs responsible for ADR were Injection Ironsucrose, ranitidine and Iohexol of each show (2.88%), followed by other oral drugs such as diclofenac sodium (5.75%), followed by paracetamol (2.88%) and Aceclofenac +paracetamol (2.16%). The least occurrence drug was syrup sucralfate (0.72%) were shown in Table 7.

Table 5: Parenteral Antibiotic Responsible for ADR

Parenteral Suspected Antibiotics	Frequency	n(%)
Inj. Cefotaxime	09	6.47
Inj. Ceftriaxone	09	6.47
Inj. Ciprofloxacin	05	3.60
Inj. Metronidazole	05	3.60
Inj. Cefoperazone + sulbactam	04	2.88
Inj. Levofloxacin	04	2.88
Inj. Azithromycin	04	2.88
Inj. Piperacillin + Tazobactam	03	2.16
Inj. Ofloxacin	02	1.44
Inj. Vancomycin	01	0.72
Inj. Amphotericin B	01	0.72

Inj: Injection, ADR: Adverse drug reaction.

The causality assessment of Naranjo algorithm and WHO-UMC scale were done for 139 reported ADR, which reveals that 45 reports (32.37%) were identified in serious reaction and 94 reports (67.62%) were in Non-serious ADR. In Naranjo algorithm majority of the assessment falls into “probable” category of 101 cases (72.66%) followed by “possible” category of 27 cases (19.42%) and few of them in the “definite” category of 11 cases (7.91%). In WHO-UMC scale shows most of the assessment fits into “probable” category of 71 cases (51.07%) followed by “possible” category of 52 cases (37.41%), which is portrayed in the Table 8.

Table 6: Oral Antibiotic Responsible for ADR

Oral Suspected Antibiotics	Frequency	n%
Tab. Ciprofloxacin	5	3.60
Tab. Cotrimoxazole	5	3.60
Tab. Cefixime	3	2.16
Tab. Dapsone	3	2.16
Tab. Azithromycin	2	1.44
Tab. AKT 4 kit	2	1.44
Tab. Levofloxacin	1	0.72
Cap. Doxycycline	1	0.72
Tab. Griseofulvin	1	0.72

Cap. Amoxicillin + Clavulanic acid	1	0.72
Tab. Hydroxychloroquine	1	0.72
Tab. Ofloxacin	1	0.72
Tab. Linezolid	1	0.72
Tab. Fluconazole	1	0.72
Tab. Methotrexate	1	0.72

Tab: Tablets, Cap: Capsules, ADR: Adverse drug reaction

Table 7: Other drugs responsible for ADR

Suspected Drug	Frequency	n%
Inj. Iron sucrose	4	2.88
Inj. Ranitidine	4	2.88
Inj. Iohexol	4	2.88
Inj. Ondansetron	3	2.16
Inj. Low molecular weight Heparin	3	2.16
Inj. Albumin Infusion	3	2.16
Inj. Pantoprazole	1	0.72
Inj. Diclofenac sodium	1	0.72
Inj. Ketorolac	1	0.72
Inj. Mannitol	1	0.72
Inj. Drotaverine	1	0.72
Inj. Methylcobalamine	1	0.72
Tab. Diclofenac sodium	8	5.75
Tab. Paracetamol	4	2.88
Tab. Aceclofenac + Paracetamol	3	2.16
MDI. Levosalbutamol	3	2.16
Tab. Piroxicam	2	1.44
Tab. Phenytoin	2	1.44
Tab. Tramadol	2	1.44
Tab. Aspirin	2	1.44
Tab. Topiramate	1	0.72
Tab. Ticagrelor	1	0.72
Tab. Etoricoxib	1	0.72
Tab. Oxcarbazepine	1	0.72
Tab. Deflazacort	1	0.72
Tab. Teneligliptin	1	0.72
Tab. Indomethacin	1	0.72
Tab. Mefenamic acid	1	0.72
Syp. Sucralfate	1	0.72

Inj: Injection, Tab: Tablets, Cap: Capsules, MDI: Metered Dose Inhaler, Syp: Syrup. ADR: Adverse drug reaction.

Table 8: Causality Assessment by Naranjo algorithm and WHO-UMC Scale

Causality Assessment	Seriousness	
	Serious (n=45)	Non-serious (n=94)
	Frequency (n%)	Frequency (n%)
Naranjo algorithm		
Definite	05 (11.11)	06 (6.38)
Probable	29 (64.44)	72 (76.60)
Possible	11 (24.45)	16 (17.02)
Doubtful	0 (0.00)	0 (0.00)
WHO-UMC Scale		
Certain	05 (11.11)	06 (6.39)
Probable	15 (33.34)	56 (59.57)
Possible	25 (55.55)	27 (28.73)
Unlikely	0 (0.00)	05 (5.31)

WHO-UMC: World Health Organization-Uppsala Monitoring Centre

Discussion

Our Primary objective of the study done for the prevalence of ADR occurring in the society with detailed analysis of the reported events from various departments, in secondary objective we examined the different factors which influence the outcome such as demographic details, distribution of ADR in age groups, various clinical departments involvement, type of reaction, responsible drugs for the events and causality assessment. The current study was well planned and executed from the tertiary care institute located in south India. Our ADR Monitoring center faculty had actively involved in reporting the events to pharmacovigilance Program of India.

Overall study analysis reports that female predominance (54.68%) of the total ADR reported and collected from our study. These results support two previous studies conducted in north India shows female patients with high occurrence for ADR by Singh et al[18] and Rend et al[19]. Majority of the ADR events occurred in the age group between 51 to 60 years (20.86%) followed by adult age group from 21 to 30 years (18.70%) and elderly age group overall shows (15.82%). Our Study is slightly differing from other studies done in north India, Ibel C Fredy et al [20] and Nagaraju et al[21], which shows slight age group variation. As our study done in south India and the prevalence of disease burden, sensitivity to the drugs and environmental factors may vary from individual perspective could be the contributing factors for age group variation.

Department wise distribution of reported ADR revels that majority of the cases were identified and reported from dermatology department (33.81%) followed by general medicine shows (25.90%). Considering other similar study in India shows the same results from various institutional studies such as Aggarwal et al[4]reported the major event from Medicine (21.1%) and Tejas Acharya et al[22],reported the major event from Dermatology department. In fact, super speciality department ADR events (3.60%) also reported in our study, which may be an eyeopener to all the health care professionals to do more insert in these areas.

Distribution of ADR based on type of reaction exhibit urticaria was the highest occurred reaction (30.22%) followed by fixed drug eruption (23.02%) and Maculopapular drug rashes (8.63%). A study by Tejas Acharya et al[22] reported the similar event, but maximum reaction was acneiform eruption followed by fixed drug eruption. Another study by Vijayakumar et al[23]shows that dermatological features are similar incidence. Anaphylactic shock (2.88%) and drug induced hepatitis (2.16%) were reported from our study, show that we have to be vigilant in all aspects of drug therapy.

Parenteral antibiotic responsible for ADR divulge that ceftriaxone and cefotaxime were the major drug each (6.47%) occurred in our study. Followed by ciprofloxacin and metronidazole each (3.60%) identified, which is almost similar report from Patil SB et al[5], Dudhal KS et al[24], Sood et al[25] and Gaur S et al [26],were all those study from north Indian population. Third generation cephalosporins were the preferred drugs by physicians and surgeons for major illness, also the duration of administration was long for this group of antibiotics, could be the reason for ADR in our study. In fact, we had recurrence of levofloxacin and azithromycin were observed, which indicates extended spectrum of anti-bacterial action and most preferred by doctors, could be the reason for ADR. Among the oral antibiotics, ciprofloxacin and cotrimoxazole were the ADR each reported (3.60%), which divulge that both are potent to produce ADR and cost-effective prescription from many rural and urban population by the treating doctors in south India, may be the reason for the occurrence.

Other drugs responsible for ADR were reported such that Iron sucrose injection (2.88%) from medicine department indicate the usage for anaemia, as the study centre from rural area atTamil Nadu, where the prevalence of anaemia was high in the population. Iohexol was the contrast agent used by the radiology department, reported the incidence of (2.88%), as the institute is a tertiary care, were many advanced procedures done here, could be the reason. Considering the NSAID, diclofenac sodium was the major event occurred (5.75%) among the oral drugs, which is almost similar report from Aggarwal et al[4]shows (3.4%)and Singh et al[18] shows (14%), were both the study from north Indian population. Causality assessment scale by Naranjo algorithm confess that (67.62%) were non serious reaction, among that probable assessment (76.60%) followed by possible assessment (17.02%) were identified in our study. Comparing with other study done in north India, there were slightly different events reported by Aggarwal et al[4]shows predominant non serious (87.77%) among that they even reported unlikely category (10.75%), which is not identified in this study. Considering the serious events, there were (32.37%) among which probable category were predominant (64.44%) followed by possible (24.45%). This is opposite to the study by Aggarwal et al[4], shows possible is predominant (90%) followed by probable assessment (9.09%).Another study by Belhekaret al[17], shows contradiction to the assessment of possible was the predominant (99%), the previous both the study were from north India. Considering the WHO-

UMC scale of non-serious reaction, probable assessment was predominant in our study shows (59.57%) followed by possible category (28.73%), which is similar to the study by Gaur et al[26], shows probable (57%) followed by possible (33.40%) and another study by Aggarwal et al[4]shows predominant probable (62.02%) followed by possible (26.58%) category.

But there was a study contradict to ours by Dudhal et al[24], shows possible was predominant (80%) followed by probable (18%). The serious causality assessment by WHO-UMC scale reveals that possible (55.55%) was predominant followed by probable category (33.34%), which is similar to one study conducted in north India by Aggarwal et al[4]. In South Indian Population ADR, our study is the only detailed classification done as serious category and non-serious category for both the Naranjo algorithm and WHO-UMC scale. Which reflects the quality of study and further study should follow this method for appropriate results.

Conclusion

Analysis of pharmacovigilance study exhibit many inherent works. Awareness to all the healthcare professionals and their active participation with ADR reporting has been documented. Many further studies to be done to achieve the vision and mission of pharmacovigilance program of India, by reporting and analysing various ADR from all the departments. Initiation from our institute has contributed more to the PvPI and WHO-UMC. Drug safety evaluation is the prime important especially in the post marketing surveillance, as new drugs has been entering in the market for various disease conditioning. Our study clear cut revealed the prevalence of ADR in south Indian population, emphasizing the demographic, age and gender distribution showed female predominance and adult age group. Dermatology and general medicine department with higher parenteral and oral antibiotics were the reported ADR from our institute. Detailed causality assessment by Naranjo algorithm and WHO-UMC scale were used by dividing into serious and non-serious reaction. This study is the first detailed causality assessment study from south India. Yet we need more similar study to support our national PvPI.

Strength and Limitation of the Study

Our study is a first and an elaborative retrospective study from south Indian population, which is more or less in accordance with the previous study conducted in north India. Follow up the patients who had been reported ADR was a lacuna in our study with limited sample was analysed. Yet, prospective observational study would be preferred for further analysing the reporting ADR with large sample size could predict more information. As we used only Naranjo algorithm and WHO-UPC, all other various type of causality assessment could be used for further research studies.

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