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Original Research Article

A pattern of serious adverse drug reactions reported in a tertiary care hospital, Rangaraya Medical College, Kakinada, Andhra Pradesh

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ABSTRACT

Background: Serious adverse drug reactions (ADRs) constitute a major limitation in clinical development of a drug thus necessitating close monitoring. Studies regarding the pattern of serious ADRs are limited in southern India. The present study was conducted in tertiary care hospital in Andhra Pradesh with an objective to evaluate the pattern of severe cutaneous and non-cutaneous ADRs in our hospital and to assess the causality, severity, and preventability of these reactions.

Methods: A retrospective observational study was conducted over two years, from January 2016 till January 2018 in our ADR monitoring center. The pattern of serious adverse drug reactions, the nature of ADR, suspected drug, the outcome and preventability were analyzed using Modified Hartwig and Siegel scale, and modified Schumock and Thorton scale.

Results: Out of 734 ADRs reported, 42 were serious, while 692 were non-serious. Out of 42, 22 were dermatological in origin while the others were acute kidney injury, acute psychosis, febrile neutropenia, gynecomastia, and lipodystrophy. According to WHO causality assessment scale, 27 were probable while 15 were possible. The majority were reported in the age group of 16 to 65 years with female (34) preponderance. The most common drug category responsible was antimicrobials, followed by antiretrovirals, anti-epileptics, and analgesics.

Conclusions: Antimicrobial, anti-epileptics, and analgesics contributed to serious ADRs. Although non-cutaneous ADRs did not result in hospitalization, they caused social inhibition and mental stress in the patient.

Keywords: Pharmacovigilance, Rangaraya medical college, Serious cutaneous adverse drug reactions, Serious non-cutaneous adverse drug reactions, Steven-Johnson syndrome, Toxic epidermal necrolysis

INTRODUCTION

Adverse drug reactions (ADRs) have become a significant part of patient care universally, not only by impacting their quality of life but also by rising health care costs juddering the pharmaco-economic aspect of the health sector. At present, ADR is among the top ten leading causes of morbidity and mortality in hospitalized patients in developed countries and stands among the top five leading causes of death in the United States.

Currently, India is one of the largest contributors to adverse drug reactions (ADRs) under the WHO Programme for International Drug Monitoring (PIDM) and the only country having a maximum number of regional AMCs (250 as in the year 2017).¹

ADR, according to WHO, is defined as “a response to a drug that is noxious and unintended, which occurs at doses normally used in the man for the prophylaxis, diagnosis, or therapy of a disease, or the modification of physiological function.”² Furthermore, the science and

activities relating to the detection, assessment, understanding, and prevention of these adverse effects or any other drug-related problems are referred to as Pharmacovigilance. Pharmacovigilance gained importance after 1961 with the thalidomide tragedy. After around 15 years later, in 1978, WHO established the International Drug Monitoring Programme globally with Uppsala Monitoring Centre (UMC), Sweden, as the collaborating hub. Despite all these measures, ADR monitoring is still mostly unexplored in many developing countries. In India, the ADR reporting rate is 1% as compared to 5% in a developed country.²

Although a drug is intended to cure a condition or mitigate physical or mental suffering, none can deny that it is a double-edged sword. Around 10% of hospital admissions are estimated to be due to ADRs, and about 5-20% of hospitalized patients experience a serious ADR.³ A serious adverse event as categorized by FDA relates to drugs or devices, as one in which “the patient outcome is death, life-threatening, hospitalization, disability, congenital anomaly, or required intervention to prevent permanent impairment.”² Studies on the epidemiology of serious cutaneous and non-cutaneous ADRs have been scarcely reported from India. Therefore, this study was conducted to assess the clinical spectrum of serious cutaneous and non-cutaneous ADRs over 24 months in patients at a tertiary care hospital and to establish the causal relationship between the reaction and the suspected drug by using the WHO causality definitions.

METHODS

The department of Pharmacology at Rangaraya medical college, Kakinada, had been recognized as an Adverse Drug Reaction Monitoring Centre since 2014 under the pharmacovigilance program of India (PvPI). The present study is a retrospective study, done for 24 months, i.e., from January 2016 till January 2018, initiated after receiving the approval from the institutional review board at our institute. Data was collected from the individual case safety reports (ICSRs) submitted to our AMC and then analyzed accordingly. The diagnosis of the serious cutaneous ADRs was made by a consultant dermatologist based on the clinical and morphological grounds, while the rest of the ADRs were considered as non-cutaneous. ADRs were defined as per the definition provided by WHO. Each ADR was analyzed using Microsoft Excel for demographic data and the causality using both the World Health Organization (WHO) causality assessment scale along with the parameters mentioned in the suspected ADR reporting form of version 1.3 of PvPI (Pharmacovigilance program of India). Data of every patient was analyzed regarding demographic information, causative drugs, detailed history about drug intake, reaction time, previous allergic history, duration and type of reaction, relevant investigations (blood culture and/ or serology to rule out infectious etiology), treatment given, complications, and clinical outcome and, improvement

after dechallenge. The criteria considered for the diagnosis of ADRs were the following.

- The reaction was not considered as drug-induced if the reaction occurred before the drug administration.
- The reaction was included if there was any improvement in the condition of the patient after dechallenge/withdrawal of the suspected drug.
- The reaction was included if drug rechallenge produced similar reactions again; however, rechallenge was not done in any of the cases due to ethical issues.

ADRs were categorized as certain, probable, possible, and unlikely based on the WHO defined causality scales. Only certain, probable, and possible cases were considered for analysis. Microsoft Excel was used for calculation and data analysis. The data were analyzed to evaluate the pattern of serious cutaneous ADRs (SCARs) and non-cutaneous serious ADRs to our AMC. The causality and severity of these reactions were assessed in terms of, the time duration between drug intake and the onset of symptoms, BSA involvement, and duration of hospital stay, the implicated drug patterns, and also, assess the treatment outcome of the patient as well as preventability of these reactions. Severity was evaluated using the modified Hartwig and Siegel scale, whereas preventability was assessed using the modified Schumock and Thornton scale.^{4,5}

RESULTS

A total of 734 cases were reported during this time. Of these 734 ADRs, 42 were serious, with an occurrence rate of 5.7%, while 692 (94%) were non-serious as shown in Figure 1.

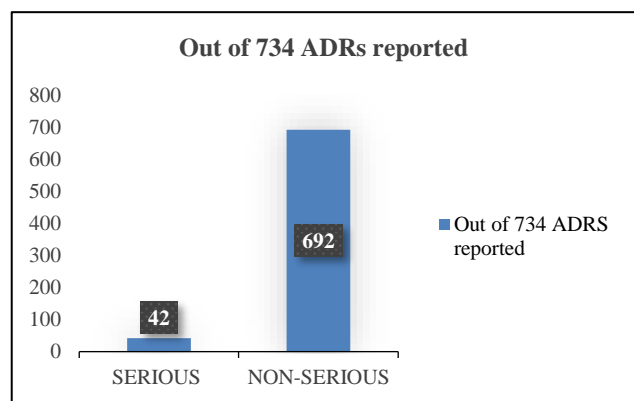


Figure 1: Reported ADRs.

Among these 42 serious cases, females (34) were more predominantly affected than males (8) with a male: female ratio of 1:4.2, shown in Figure 2.

The maximum number of reactions were seen in patients in the age group of 16-65 years with a mean±SEM of 44.77±2.32 years (95% CI, 18.36 to 33.14), Figure 3.

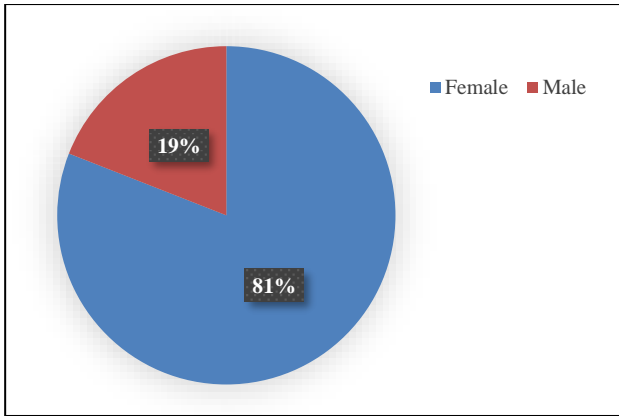


Figure 2: Demographic distribution.

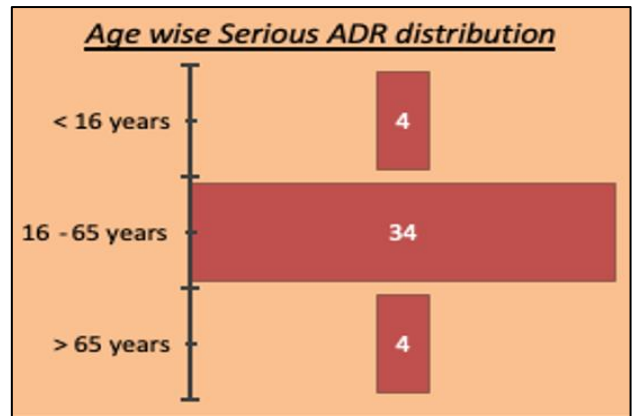


Figure 3: Age wise serious ADR distribution.

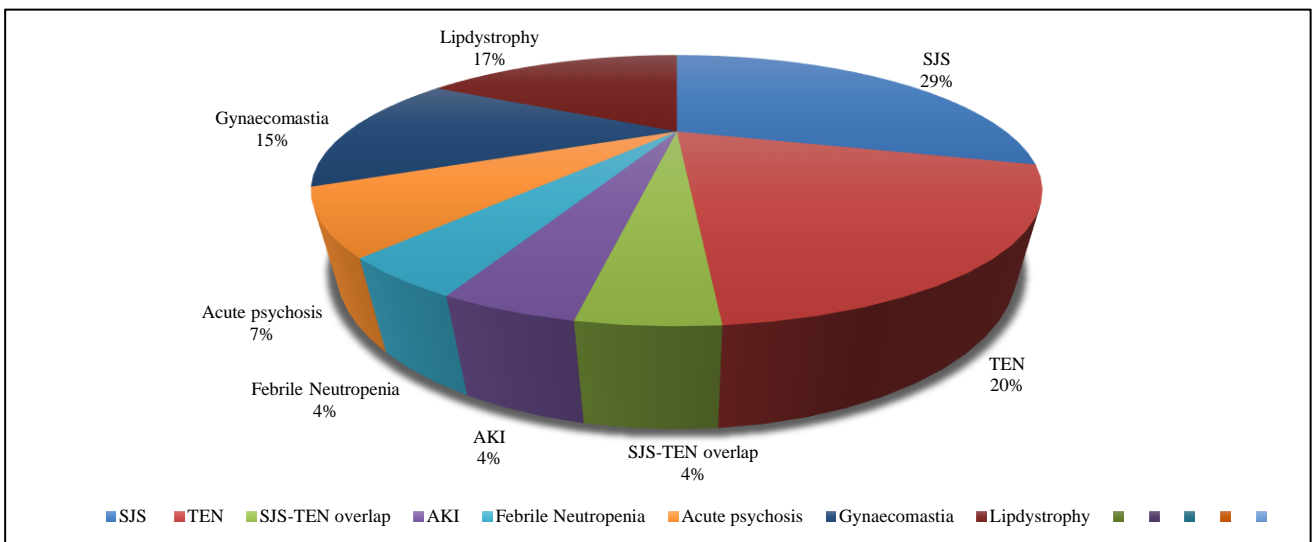


Figure 4: Patterns of SCARs and other non-cutaneous ADRs.

Clinical presentation of serious adverse drug reactions

Among the serious ADRs reported, 22 were serious cutaneous ADRs (SCARs), while the rest 20 were non-cutaneous adverse drug reactions. Among the SCARs reported, SJS (12) was most common, followed by TEN (8) and SJS-TEN (2) overlap, Figure 4.

Among the non-cutaneous ADRs reported, lipodystrophy (7) and gynecomastia (6) were more common, followed by acute psychosis (3), febrile neutropenia (2), acute kidney injury, AKI (2).

Causality assessment

According to the WHO causality assessment, shown in Figure 5, 27 patients were classified as probable, and 15 as possible based on dechallenge test, respectively. However, there were no ADRs with a certain causality relationship, as no data with rechallenge was available.

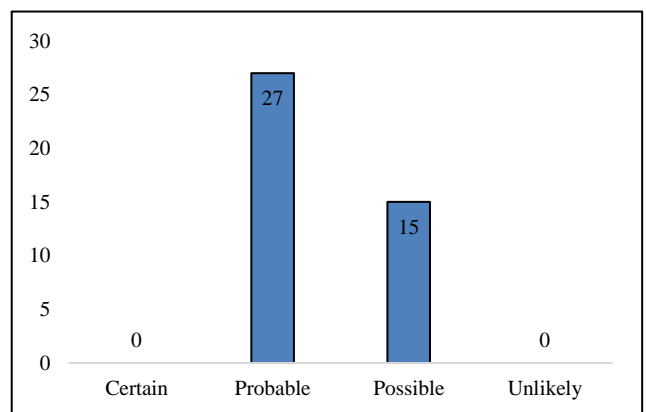


Figure 5: WHO causality assessment.

Casual drug groups

The most affected body system as per system organ class (SOC) was skin and appendages disorders (22, 52.4%).

Among all drugs, antimicrobials (9, 21.4%) were most commonly associated with SCARs, followed by anti-epileptics (7, 16.7%) and analgesics (6, 14.3%); Figure 6 and Table 1.

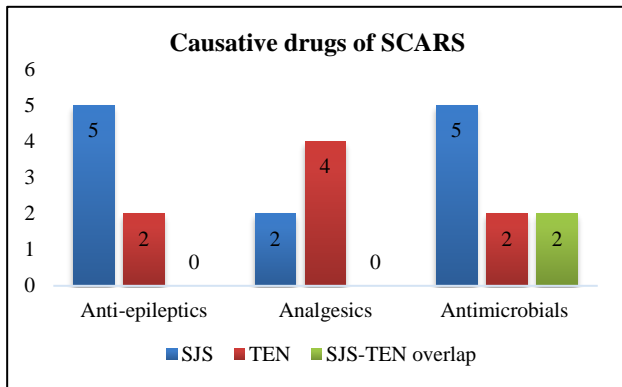


Figure 6: Drugs associated with serious cutaneous ADRs.

Table 1: Casual drug groups.

SCARS		
SJS	TEN	SJS-TEN overlap
Antiepileptics		
Phenytoin (3)	Phenytoin (1)	
Valproate (1)	Carbamazepine (1)	
Levetiracetam (1)		
Analgesics		
Combiflam (1)	Diclofenac (4)	
Diclofenac (1)		
Antimicrobials		
Ofloxacin-ornidazole (3)	Cefexime (1)	Flucanazole (1)
Nitrofurantoin (1)	HRZE (1)	Norfloxacin (1)
Cefpodoxime (1)		

*HRZE- Isoniazide, Rifampicin, Pyrizinamide, Ethambutol

The most common drugs causing non-cutaneous ADRs were ARTs (15, 35.7%), followed by antimicrobials (5, 12%). However, only antimicrobials (4, 9%) were associated with febrile neutropenia and acute psychosis, Figure 7 and Table 2, whereas AKI was purely associated with ARTs (3, 7%).

Table 2: Drugs associated with serious non-cutaneous ADRs.

	ART		Antimicrobials		
	TLE	ZLN	HRZE	HRE	5-FU
AKI	2				
Febrile neutropenia					2
Gynecomastia	4	1	1		
Acute psychosis	1			2	

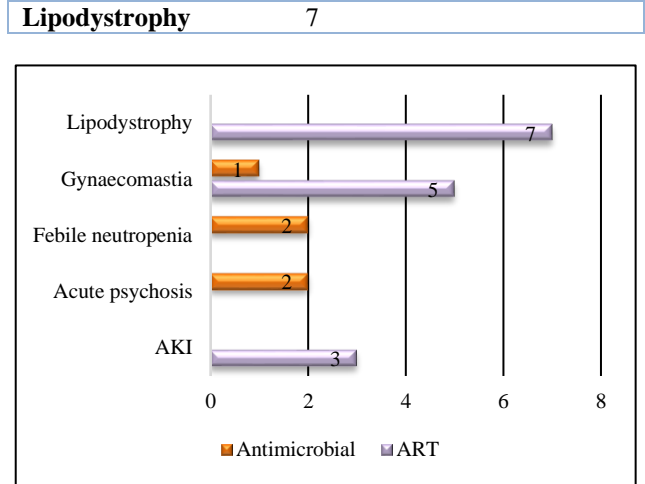


Figure 7: Other serious non-cutaneous ADRs.

Outcome at the time of reporting

Almost all of the serious ADRs at the time of reporting were in the continuous phase. All SCARs cases were hospitalized, and except one, all recovered within two-three weeks. As part of the treatment strategy, systemic steroids were given, the causative drug was withdrawn, and the patients were treated symptomatically. One patient with TEN did not survive. Patients with non-cutaneous ADRs eventually recovered with out-patient management. Although non-cutaneous ADRs did not result in hospitalization, they caused social inhibition and mental stress in patients. Various complications noted in patients with SCARs were secondary infection, septicemia, leukocytosis, leucopenia, thrombocytopenia, hyperglycemia, and acute renal failure. Secondary infection was the most common complication noted. The death occurred in one patient diagnosed with TEN.

Preventability assessment

Out of 42 serious ADRs, the majority were non-preventable (36, 85.7%); however, 6 ADRs were definitely preventable (over the counter drugs misuse). All the 6 ADRs were due to the use of drugs that were used without prescription.

DISCUSSION

The retrospective analysis of serious ADRs showed a reporting rate of 5.7%, which included both serious cutaneous ADRs (SCARs) and non-cutaneous ADRs. The most common clinical presentation involved the dermatological system. The common causal drug group was antimicrobials followed by anti-epileptics and then, analgesics in case of SCARs, while ARTs were more commonly associated with non-cutaneous ADRs followed by antimicrobials. The most common departments to report ADRs were dermatology, ART center and, medicine in the order of reporting. According to the World Health Organization (WHO), SCARs refer

to those requiring hospitalization, with significant morbidity and mortality, or are life-threatening. A higher rate of complications was associated with a higher SCORE of Toxic Epidermal Necrosis (SCORTEN score). The most common criterion for considering as serious ADRs in present study was based on the criteria that intervention was needed to prevent permanent impairment or damage followed by hospitalization.

Present study showed that women, 81%, were more commonly affected, which was quite similar to Arulmani et al (78, 64.5%); however, Kinjal et al reported more ADR predominance in men (58%).^{3,6} We also observed that adults were most commonly affected, while Arulmani et al study showed that the pediatric (14, 17.3%) and geriatric population 23, 14.4%) were more commonly affected.⁶ Present observation that skin was

the most common target to be affected was similar to other studies such as Kinjal et al and Arulmani et al.^{3,6} However, few studies such as Kamalaraj et al and Sriram et al showed GIT as the most common system to be affected.^{7,8}

The majority of the serious cutaneous ADRs occurred within a week of drug intake, while non-cutaneous ADRs mostly occurred after a month of drug initiation. This indicates that close monitoring and follow-up of patients is necessary after the initiation of treatment in order to hasten early detection as well as prevention of serious ADRs. In addition, discouraging misuse of over the counter available medications is also important to prevent serious ADRs. Thus, the physician should understand the necessity of being cautious during this period and also educate his patients.

Table 3: Comparison of ADRs reported in various studies.

	present study (n=42)	Kinjal, et al. ³ (n=375)	Arulmani et al. ⁶ (n=164)	Kamalaraj et al. ⁷ (n=49)
Most commonly affected body system	Skin (22)	Skin (71)	Skin (56) and Central nervous system (31)	Gastrointestinal (25) and Skin (24)
Most common causative drug class	Antibiotics (15)	Antitubercular (129)	Antibiotics (55)	Antibiotics (39)
Causality				
Certain	0	0	10	9
Probable	27	173	102	10
Possible	15	182	52	30
Preventability				
Definitely preventable	6, 14.3%	0.53		Not mentioned
Not preventable	36, 85.7%	96	100, 61% not predictable and potentially preventable	

Nevertheless, the drugs responsible for the majority of ADRs in present study were Antibiotics (namely cephalosporins, fluoroquinolones, and fluconazole); Antiepileptics and analgesics in that order in case of SCARs whereas ARTs and ATT were more commonly associated with non-cutaneous ADRs. Other studies showed an overall predominance of anti-tubercular and antiretrovirals in causing serious ADRs, Shown in Table 3

The majority of drugs showed a probable causality relationship in present study, which was relatively similar to other studies. The majority of serious ADRs were not preventable in present study, which can be explained by an individual patient's genetic vulnerability. However, considering the number of ADRs reported at our AMC, there was definitely underreporting of ADRs, and because of this, actual incidence and prevalence rate might be misjudged.

Limitations

Further, there are few limitations in present study, for example, lack of follow-up until recovery, lack of

information on patients' history of drug allergy, single-center, and only reporting from few clinical departments.

In spite of these limitations, a few strong points to consider in this study are:

- We have included both cutaneous and non-cutaneous serious ADRs that were more commonly reported.
- Antimicrobials, antiepileptics, and analgesics are the most common drugs causing SCARs, whereas ARTs and antimicrobials are commonly associated with non-cutaneous ADRs.
- Misuse of over-the-counter drugs is associated with definitely preventable ADRs, so caution is required.

CONCLUSION

Life-threatening conditions like SCARs adversely influence the quality of life and also increase the economic burden. Lack of awareness among physicians and time constraints is one of the major reasons for the under-reporting of ADRs, making it difficult to assess the burden and take preventive action. Thus, the study of

ADRs will contribute to patient safety by (1) sensitizing the clinicians in the respective institute, (2) by a better understanding of the disease pattern, and (3) also guiding in the judicious prescription of medicines. Additionally, proper labelling and precautions should be mentioned in the drug label for patient safety. Similarly, misuse of over the counter (OTCs) should be avoided.

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REFERENCES

1. Singh KN, Kanase HR. Pharmacovigilance programme of India: The beginning, current status and recent progress. *Adv Pharmacoepidemiol Drug Saf.* 2017;6(4):1-4.
2. Barvaliya M, Sanmukhani J, Patel T, Paliwal N, Shah H, Tripathi C. Drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS-TEN overlap: a multicentric retrospective study. *J Postgrad Med.* 2011;57(2):115.
3. Prajapati K, Desai M, Shah S, Panchal J, Kapadia J, Dikshit R. An analysis of serious adverse drug reactions at a tertiary care teaching hospital. *Perspect Clin Res.* 2016;7(4):181.
4. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hospital Phar.* 1992;49(9):2229-32.
5. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hospital phar.* 1992;27(6):538.
6. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. *Br J Clin Pharmacol.* 2008;65(2):210-6.
7. Kamalaraj R, Revathy J, Vijey Aanandhi M, Murugan M, Ramanakumar KP. Incidence, severity and financial burden associated with suspected unexpected serious adverse reactions (SUSARs) that arise in clinical trials. *Asian J Pharm Clin Res.* 2012;5:198-201.
8. Sriram S, Ghasemi A, Ramasamy R, Devi M, Balasubramanian R, Ravi TK, et al. Prevalence of adverse drug reactions at a private tertiary care hospital in south India. *J Res Med Sci.* 2011;16(1):16.

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