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A 5 year retrospective analysis of adverse drug reactions associated with antimicrobials in a teaching hospital of Andaman and Nicobar islands

Mangesh Bankar [1], Priyanka Pravinbhai Hotha *[2], Nimisha Elezebeth Zachariah[3]
[1]Department of Pharmacology, Andaman and Nicobar Islands Institute of Medical Sciences (ANIIMS), Port Blair, India
[2]Department of Pharmacology, University College of Medical Sciences, Delhi, India
[3]Pharmacovigilance associate, Department of Pharmacology, Andaman and Nicobar Islands Institute of Medical Sciences (ANIIMS), Port Blair, India

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ABSTRACT

Antimicrobials are used widely especially in developing countries, due to the high prevalence of various infectious diseases. Inappropriate use of antimicrobials are associated with adverse drug reactions. The present study was done to analyze the patterns of Adverse Drug Reactions (ADR) due to antimicrobials reported to Adverse Drug Reaction Monitoring Centre (AMC) during the last five years. This was a 5 year retrospective and cross-sectional study. After collecting demographic details of patients, ADR forms, and ADR associated with the antimicrobial class of drugs, data were analyzed for further details. A total of 877 ADRs, 360 ADRs belonged to the antimicrobial group. When data was analyzed data, it revealed that the majority of ADRs (73.05%) were reported in the adult group, 75.27% of reactions belonged to A category, Ceftriaxone (17.2%) was the most common drug-associated with ADRs, majority of ADRs were related to skin (56.66%), rash (27.5%) was the most common ADR encountered with antimicrobial use, 73.61% reactions were non-serious, 69.44% of ADRs recovered, and 77.77% of ADRs were probable category. Ceftriaxone was responsible for the maximum number of ADRs. The study results provide information regarding the pattern of ADRs associated with antimicrobials, and this might be helpful for improving the awareness of healthcare providers about PvPI and subsequently increase the spontaneous reporting of ADRs.

Keywords: Adverse drug reaction, antimicrobial drugs, pharmacovigilance, ceftriaxone

Corresponding author:
Priyanka Pravinbhai Hotha
Department of Pharmacology, University College of Medical Sciences, Delhi, India
Email: priyankahotha@gmail.com

INTRODUCTION

Antimicrobials are used widely especially in developing countries, due to the high prevalence of various infectious diseases. Inappropriate use of antimicrobials are associated with adverse drug reactions (ADRs) and antimicrobial resistance. (Patil et al., 2016; Vijaishri and Andhuvan, 2018) To ensure the safety of medicines in Indian Population, Pharmacovigilance Program of India (PvPI) was launched nationwide in July 2010 by the Government of India to monitor adverse drug reactions with the main objective of generating signals from the reported information. The information sent by a network of 311 ADR monitoring centers (AMC) to the National Co-ordination center (NCC) are then analyzed and submitted to the national regulatory authority for further actions. This information is also communicated to healthcare professionals to ensure the safe use of medicines. (Agrawal et al., 2019).

The pattern of antimicrobial utilization depends on various factors such as prescription practices, the prevalence of diseases in the specific region, genetic differences in population and the availability of the antimicrobials in the hospital. The manifestation of ADRs depends on such factors. (Bhattacharjee et al., 2019). A study conducted in India reported that 45% of ADRs were implicated only due to antimicrobials. (Singh et al., 2017) Another prospective study from South India reported that the majority of ADRs (24.01%) were due to antimicrobials. (Venkatasubbaiah et al., 2018).

Although previous studies conducted across India had concluded that antimicrobials are most commonly associated with ADRs, data on the ADR pattern specifically due to antimicrobials have remained a neglected area. Moreover, the data on ADR patterns associated with use of antimicrobials are scarce from Andaman & Nicobar Islands, which are comprised of a group of 572 islands with varied tribal communities and ethnicities. Hence the present study was undertaken with the aim of determining the pattern of ADRs due to antimicrobials by analyzing the existing data of ADRs reported to the AMC of a tertiary teaching hospital in Port Blair.

MATERIALS AND METHOD

Materials

This study was a retrospective and cross-sectional (descriptive) research. The study was conducted in AMC, ANIIMS, Port Blair. The approval was obtained from the Institutional Ethics Committee of Andaman & Nicobar Islands Institute of Medical Sciences (ANIIMS), Port Blair. All the suspected ADRs associated with antimicrobials were collected during five years between July 2015 to June 2020. All the ADRs were reported to AMC through a spontaneous reporting system as well as active surveillance by the Patient safety Pharmacovigilance Associate (PsPvA). PsPvA regularly visited the ward and OPDs of the hospital and filled the suspected ADR reporting Form (ADR Form) designed by the National Co-ordination Centre Pharmacovigilance Programme of India (NCC-PvPI). Data were collected after analysis of filled ADR forms which include details of patients' demographics, suspect adverse reaction, suspected medication, management and outcome of reaction. The reported information was entered into the Vigiflow software provided by NCC after causality assessment.

Methods

Demographic detail analysis

Demographic details of patients i.e, age and sex, were collected from suspected ADR forms and analyzed.

ADR Analysis

Drugs and ADRs were translated to anatomical therapeutic chemical (ATC) codes and MedDRA (Medical Dictionary for Regulatory Activities) classifications, respectively. The seriousness of reaction (i.e. death, life-threatening, prolonged hospitalization, disability, required intervention to prevent permanent impairment/damage, congenital anomaly), number of ADRs, Nature, and type of reaction [classified as type A (Augmented); type B (Bizarre); type C (Continues Use); type D (Delayed) and type E (End of Use), route of drug administration and the outcome of reaction (outcome

was described as fatal, recovering, recovered, unknown, continuing or other) as per recommended standard operative procedure (SOP) of PvPI were recorded for every reported ADR. The causality assessment was done using WHO-Uppsala Monitoring Centre (UMC) causality assessment scale by Causality Assessment Committee (CAC).

Antimicrobial analysis

Data were assessed to find the antimicrobial class of drugs as well as offending antimicrobial agents causing the maximum number of ADRs.

Data Analysis

Descriptive statistics were used to analyze the data, and values are expressed in numbers and percentages.

RESULT AND DISCUSSION

A total of 877 ADRs were received to AMC, Port Blair from five year study period. Out of 877 ADRs, 360 ADRs belonged to the antimicrobial group and were included for further analysis

Data evaluation based on Demographics:

Baseline characteristics of the patients are presented in Table 1. The majority of ADRs (73.05%) were reported in the adult age group. More ADRs were reported in males (53.05%) as compared to females (46.94%).

Table 1. Age and gender distribution of ADRs due to antimicrobials (n=360)

Baseline Characteristics	No. of ADRs (%)
Age	
Paediatric (<18 years)	45 (12.5%)
Adult (18-65 years)	263 (73.05%)
Geriatric (>65 years)	52 (14.44%)
Gender	
Male	191 (53.05%)
Female	169 (46.94%)

Department wise distribution of ADRs

Out of the 360 ADRs, the Medicine department (30.28%) was reported maximum ADRs followed by Surgery (23.33%) and Orthopaedics (16.67%). Further details of the department-wise distribution of ADRs are shown in Figure 1.

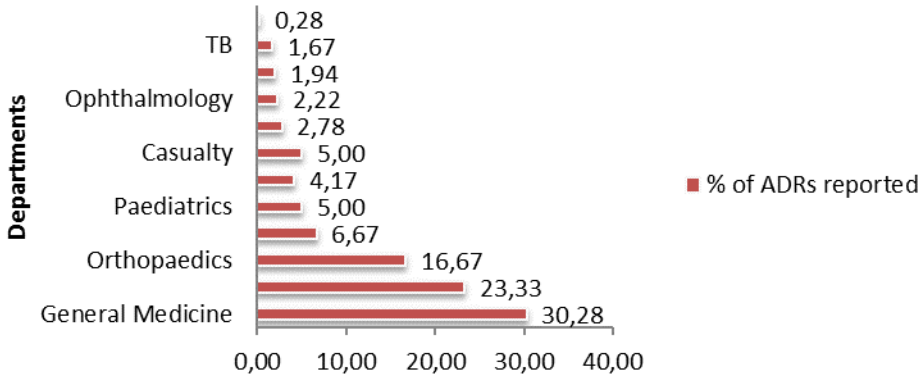

Figure 1: Department wise distribution of reported ADRs due to Antimicrobials (n=360)

Route of administration used

Out of the 360 ADRs, the parenteral route of drug administration accounted for 69.72% of the total ADRs followed by the oral route (28.05%) and topical route (2.22%).

The seriousness of ADRs

73.61% of reactions were non-serious, whereas 26.38% of reactions were of serious types. Further distribution of ADRs based on the seriousness is depicted in Table 2.

Table 2. Various analyses of the reported ADRs due to antimicrobials

Type of Analyses	No. of ADRs	Percentages
Outcome of the ADRs (n=360)		
Recovered	250	69.44
Recovering	87	24.16
Not Recovered	12	3.33
Unknown	9	2.5
Recovered with sequelae	2	0.55
Details of Serious ADRs (n=95)		
Hospitalisation/Prolonged Hospitalisation	47	49.47
Life Threatening	15	15.78
Other Medically Important	33	34.73

Nature of ADRs

Based on Rawlin and Thomson ADR classification, out of 360 ADRs, 75.27% of reactions belonged to A category, followed by 23.33% to the B category and the remaining 1.38% belonged to the D category.

Outcome of ADRs

Out of 360 ADRs, 69.44% of ADRs recovered whereas 24.16% were recovering, 3.33% were continuing, 0.55% recovered, but with sequelae resulting from ADR, and in 2.5% of the cases, outcomes were unknown at the time of the report.

Causality assessment

Upon causality analysis using the WHO-UMC scale, the majority (77.77%) of ADRs were probable, followed by possible (21.66%) and certain (1.11%).

De-challenge and re-challenge

The offending antimicrobial drug was withdrawn (De-challenge) in 96.38% of cases, and in 5% of cases re-challenge was performed. Further details about de-challenge and re-challenge are depicted in Table 3.

Table 3. Details about de-challenge and re-challenge

Type of Analyses	No. of ADRs	Percentages
De-challenge (n=360)		
Drug Withdrawn	347	96.38
Dose Reduced	1	0.27
Dose Not Changed	10	2.77
Not Applicable	1	0.27
Unknown	1	0.27
Rechallenge (n=18)		
Reaction Reappeared	6	33.33
Reaction Not Reappeared	4	22.22
Effect Unknown	8	44.44

Organ system affected

The majority of ADRs were related to skin (56.66%), followed by Musculoskeletal System (11.38%), GIT (10.27%), Immune System (5%), and CNS (4.44%). The involvement of other systems is depicted in Table 4.

Table 4. Characterization of organ systems affected with ADRs (n=360)

Organ System	No. of ADRs (%)
Skin	204 (56.66%)
Musculoskeletal System	41 (11.38%)
GIT	37 (10.27%)
Immune System	18 (5%)
CNS	16 (4.44%)
Respiratory System	11 (3.05%)
CVS	10 (2.77%)
General	8 (2.22%)
Eye	6 (1.66%)
Ear	5 (1.38%)
Renal System	2 (0.55%)
Blood & Lymphatic System	1 (0.27%)
Hepatobiliary System	1 (0.27%)

Analysis of antimicrobials causing ADRs:

Maximum ADRs (29.4%) were contributed by Fluoroquinolones (29.4%) followed by Cephalosporins (20.6%), Nitroimidazoles (11.4%), Macrolides (10.6%), and Penicillins (8.6%). Among Fluoroquinolones, Ciprofloxacin was responsible for causing 14.4% of the total ADRs, followed by Levofloxacin (10%). Similarly, among Cephalosporins, Ceftriaxone (17.2%) was the most common drug-associated with ADRs. Antimicrobial class-wise and drug-wise distribution are depicted in Table 5.

Table 5. Analysis of antimicrobial categories causing ADRs (n=360)

Antimicrobial Category	DRUGS	No. of ADRs	Percentage (%)
Fluroquinolones	Ciprofloxacin	52	14.4
	Levofloxacin	36	10
	Ciprofloxacin+Tinidazole	5	1.4
	Norfloxacin+Tinidazole	4	1.1
	Ofloxacin	4	1.1
	Moxifloxacin	4	1.1
	Nadoxifloxacin	1	0.3
Cephalosporins	Ceftriaxone	2	17.2
	Cefotaxime	2	0.6
	Cefpodoxime	2	0.6
	Cefixime	3	0.8
	Cephalexin	1	0.3
	Cefuroxime	4	1.1
Penicilllins	Amoxicillin/Potassium Clavulanate	20	5.6
	Piperacillin/Tazobatcum	4	1.1
	Amoxicillin	2	0.6
	Ampicillin	2	0.6
	Crystalline Penicillin	2	0.6
	Benzyl Penicillin	1	0.3
Nitroimidazoles	Metronidazole	40	11.1
	Tinidazole	1	0.3
Oxazolidinone	Linezolid	15	4.1
Macrolide	Azithromycin	38	10.6
Glycopeptide	Vancomycin	9	2.5
Carbapenems	Meropenem+ sulbactam	12	3.3
	Imipenem+Cilastatin	8	2.2
Tetracycline	Doxycycline	6	1.7
Glycylcycline	Tigecycline	1	0.3
Aminoglycosides	Amikacin	3	0.8
	Kanamycin	4	1.1
	Gentamicin	2	0.6
Lincosamide	Clindamycin	2	0.6
Others	Colistin	3	0.8
	Trimethoprim/Sulfamethoxazole	4	1.1
	Rifaximin	1	0.3

Rash was the most common (27.5%) ADR encountered with antimicrobial use followed by itching (10.27%) and fixed drug eruptions (6.66%). The frequency distribution of other ADRs is depicted in Table 6.

Table 6. Frequency of different ADRs encountered with antimicrobials (n=360)

Reaction	Numbers	Percentages
Rash	99	27.5
Itching	37	10.27
Fixed Drug Eruptions	24	6.66
Hypersensitivity	19	5.27
Rigor	19	5.27
Urticaria	13	3.61
Vomiting	12	3.33
Angioedema	11	3.05
Dyspnoea	11	3.05
Chills	10	2.77
Dizziness	10	2.77
Loose stools	10	2.77
Fever	8	2.22
Muscular pain	7	1.94
Others	70	19.44

In this study, the predominance of male and age group of 18-65 years for ADRs was observed. These findings are similar to the conclusion of previously concluded studies. (Lihite et al., 2017; Shamna et al., 2014; Watson et al., 2019). This may be due to the fact that the male and adult population constitute the maximum workforce of India and hence more likely to get exposed to infectious diseases leading to higher antimicrobial prescriptions and subsequently more number of ADRs. (Richa et al., 2015) One more possible explanation could be the disparity of access to healthcare facilities for males and females that exist in India, such that males have better access to healthcare facilities than females. This may be the reason for the higher number of antimicrobial prescriptions for males and the increased risk of ADRs. (Saikia et al., 2016)

In the present study, the parenteral route of drug administration accounted for maximum ADRs than any other route, which maybe because this is the preferred route in a tertiary care hospital for treating serious patients. (Bansod et al., 2020) Moreover, in the present study, maximum ADRs were reported with Ceftriaxone which was given parenterally.

Compared to previous studies, the rate of serious ADRs was found to be higher in the present study. However, none of the serious ADRs resulted in the death of any patient suggest intensive medical care given to the patient and better management of serious ADRs in the hospital. (Davies et al., 2009; Lombardi et al., 2018)

In the present study, three fourth of ADRs were of type A, followed by type B and type D reactions. Other studies conducted in India have also reported similar findings. These findings suggest that a large number of ADRs were preventable but could not be done may be due to a lack of adequate knowledge about previous drug history to the treating physician. The creation of a digital health database of patients and a computerized prescribing system in the current setting may improve the awareness about the ADRs and rational use of antimicrobials. (Davies et al., 2009)

In the majority of cases, the offending drug was withdrawn after the onset of ADR, and hence, at the time of reporting, maximum percentages of patients either recovered completely or were recovering from the reaction after de-challenge. However, in few cases, the drug was continued based on the risk-benefit ratio of the drug.

Causality analysis by using the WHO UMC scale revealed that more than three fourth of the ADRs were of probable/likely category. Based on the re-challenge, only six ADRs were from a certain category. These findings are analogous to a previous study. (Dhar et al., 2015).

The present study also revealed that skin was the most affected organ system, followed by the musculoskeletal system and gastrointestinal system. Rash was the most common ADR encountered, followed by itching and fixed drug eruptions. These findings are similar to earlier studies. (Kalra et al., 2011; Raja et al., 2017; Sharma et al., 2015) A systematic review by (Patel et al., 2014) on cutaneous adverse drug reactions in Indian Population concluded that the majority of skin-related adverse effects were due to antimicrobials followed by non-steroidal antiinflammatory drugs, antiepileptics and corticosteroids. The most common causative drug groups involved in cutaneous ADRs were Beta-Lactam antimicrobials, Fluoroquinolones, and Nitroimidazoles. In the present study also, the above three classes of drugs are included among the top three groups which were responsible for the maximum number of ADRs, and hence we found skin as the most affected organ system in our study. (Patel et al., 2014)

In this study, maximum ADRs were caused by Ceftriaxone followed by Ciprofloxacin. These findings are similar to the study conducted by (Milind Pore et al., 2018). The most probable reason could be due to higher prescriptions of these drugs, as they are effective against both gram-positive and gram-negative bacteria and hence commonly used antibiotics in the hospital. Many of the reactions due to Ceftriaxone are avoidable by simple measures such as skin testing before administration to prevent hypersensitivity reactions and slow injection to prevent rigors. (Shalviri et al., 2012)

The present study has certain limitations. The possibility of non-reporting of some ADRs in the hospital by health care professionals might exist as the present system is based on voluntary reporting only. Also, as this was a retrospective analysis, missing data of incomplete ADR forms could not be retrieved.

CONCLUSION

Fluoroquinolones and Cephalosporins were responsible for causing the maximum number of ADRs. The most common organ system involved was skin, and the rash was the commonest ADR reported. Adult male patients showed a propensity for antimicrobial-related ADRs. Most of the antimicrobial ADRs were non-serious, and no fatality was reported from any of the serious ADRs. The results of this study will definitely provide some important insights into the pattern of adverse drug reactions to antimicrobials used in a tertiary care teaching hospital of Andaman and Nicobar Islands and might be helpful for improving the awareness of healthcare providers about PvPI and subsequently increase the spontaneous reporting of ADRs. This will improve the rational use of antimicrobials and help in combating antimicrobial resistance.

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