RESEARCH PAPER

A 5 year retrospective analysis of pharmacovigilance study, completeness and quality of suspected adverse drug reaction forms at adverse drug reaction monitoring centre Port Blair.

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Received: 10.06.2021 Accepted: 02.08.2021

Abstract

In India, Adverse Drug Reaction (ADRs) related morbidity and mortality is one of the leading health problem. ADRs result in diminished quality of life, prolonged hospital stay, morbidity and mortality. The present study was planned to scrutinise suspected ADRs forms and evaluate completeness with quality assessment of ADR reports at AMC Port Blair. The study was a 5 year retrospective observational study. The collected data was evaluated based on patients' demographic, adverse drug reaction and drug characteristics with completeness and quality of reactions. A total of 877 ADRs from 715 offending drugs in 671 patients were reported. In India, 9.5% hospital admissions were because of ADRs. 52% female experienced ADRs which was more than male. The occurrence of ADRs in adult patients was high. Antibiotics (39%) was most commonly prescribed class of drug followed by NSAID (10.9%). Majority of ADRs (45%) were observed in the skin followed by musculoskeletal system (12.7%). In our study, 60.2% of patients recovered in the outcome parameters. 83.6% of drugs withdrew for management of ADRs. Rechallenge was made only in 12.3% patients, 71.6% of patients had non-serious reactions and 71.7% ADRs were probable. We received the highest completeness score in 2020 which was 0.98. ADRs remain as a challenge in modern healthcare. The health system should promote spontaneous reporting of ADRs. The proper documentation and periodic reporting to ADR monitoring centres (AMC) reduce the incidence of new ADRs and maintain the public confidence toward safe use of drugs. This good quality reporting increases the potential for signal generation.

Keywords: Adverse drug reaction; Adverse drug monitoring centre; Completeness score; Pharmacovigilance

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Introduction

World Health Organization (WHO) defines an adverse drug reaction (ADR) as noxious and unintended result which occurs in normal doses used in human for prophylaxis, diagnosis or therapy of disease or for the modification of physiological functions.[1] ADRs related to morbidity and mortality is one of the leading health problem in our country.[2] In the past 60 years, around 462 drugs had been withdrawn due to ADR.[3] In India, ADRs had been reported in 10 to 20% of hospitalized patients.[4] To address this issue, the Pharmacovigilance Program of

India (PvPI) was launched with a broad objective to safeguard the health of Indian population. WHO defined Pharmacovigilance (PV) as the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. In India, pharmacovigilance was initiated in 1986 with a formal ADR monitoring system, under supervision of the drug controller of India. India joined the WHO Programme for International Drug Monitoring in 1998.[5] Government of India has been functioning as the National Coordination Centre (NCC) for PvPI since April 2011. The NCC-PvPI IPC was launched as a WHO Collaborating Centre for Pharmacovigilance on 30 October 2017. [6] At present, about 250 ADR monitoring centres (AMCs) have been established in government and private hospitals, medical colleges and pharmacy colleges all over India.[6] The Suspected ADR reporting forms is the source document for the PvPI that captures information from the patient. This form is available in multiple languages.[7,8] In India, the completeness and quality of an ADR form assessed by NCC completeness score. The report completeness score is 0 to 1, calculated from the information provided in a structured format. [8] Worldwide, it is assessed through EudraVigilance feedback report by the European Medicines Agency, vigiGrade completeness score by UMC, clinical documentation tool by the Netherlands Pharmacovigilance Centre and the quality of ADR reports algorithm in Italy.[9] ADRs result in diminished quality of life, increase the number of work loss days, physician visits or hospital stay, morbidity and mortality The present study was planned to scrutinise the suspected ADRs forms and evaluate completeness with quality assessment of ADR reports using the NCC score at AMC Port Blair.

Methods

Present study was a retrospective observational study. It was planned over a period of 5 year from July 2015 to June 2020 in Andaman and Nicobar Institute of Medical Sciences (ANIIMS), AMC Port Blair, India. **ANIIMS Port Blair joined PvPI as an AMC in July 2015. Suspected** ADR reporting forms were available for voluntary reporting of adverse reactions by Healthcare Professionals (HCP). The HCPs either fill the suspected ADR reporting forms themselves or inform the AMC telephonically. In addition, the Patient Safety Pharmacovigilance Associate (PSPA) regularly visited outdoor patient department(OPD) and indoor patient departments (IPD). After collecting ADRs, PSPA filled ADR forms. All ADR forms have been entered in vigiflow software to report the NCC. The ADRs from OPD, IPD and emergency care units were included for the study. Suspected ADRs due to over the counter drug, taken by patients themselves were also reported. We excluded ADRs and ADR forms associated with other medical fields such as herbal medicine, homeopathy, unani. Antivenom, contrast media, vaccines & sera, and diagnostic agents associated ADRs, incomplete ADRs forms were also excluded. All mentally retarded, drug addicts, comatose patients' related ADRs were also excluded from the study.

Evaluation of collected data:
a. Patients demographic characteristics

The ADRs were characterized based on patient demographics such as gender and age i.e. patients were divided into four age groups such as paediatrics (0–12years), adolescents (13–17years), adults (18–65), and geriatrics >65.

b. Adverse drug reaction characteristics

We assessed all ADRs such as types of ADRs based on Rawlin and Thomson ADR classification [10] i.e. type A (pharmacological), type B (idiosyncratic), type C (dose and time dependent (chronic) reactions), type D (delayed reactions), type E (withdrawal reactions), and type F (failure of therapy), ADRs were also classified according to symptom organ class from the Medical Dictionary for Regulatory Activities (MedDRA), [11] Causality assessment i.e. WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO–UMC);[12] outcome of ADRs i.e. recovered, recovering, not recovered, fatal, unknown and recovered with sequelae; action taken for management of ADRs such as de-challenge i.e. drug withdrawn, dose increased, dose decreased, dose not changed, not applicable and unknown and re-challenge of suspected drug. Non-serious ADRs and seriousness of ADRs i.e. death, life threatening, hospitalization or prolonged, congenital anomaly, disability and other medically important events.

c. Drug characteristics

We assessed drug characteristics such as most common class of the drug and offending drug associated with ADRs and route of administration.

d. Completeness and quality of ADRs i.e. NCC completeness score and Reporter details.

Results

A total of 877 suspected ADRs forms from 671 patients were received by AMC, Port Blair from July 2015 to June 2020. 715 suspected drugs were reported in the ADR forms. Reports were scrutinized based on patient demographics, drugs and ADRs characteristics.

a. ADR form version:

Suspected ADR form version 1.1, 1.2 and 1.3 were used since five years respectively. Recently, version 1.3 is used by HCP and AMC for ADR reporting.

b. ADR forms collection:

AMC Port Blair had received 28 ADRs form from July 2015 to June 2016, 191 ADRs forms from July 2016 to June 2017, 53 ADRs forms from July 2017 to June 2018, 153 ADRs forms from July 2018 to June 2019 and 246 ADR forms from July 2019 to June 2020.

c. Data assessment based on demographics of the patients:

The majority of ADRs was reported in adult group (83%) followed by paediatrics (7%), geriatrics (6%), and adolescents (4%) groups (Figure 1). Of the 671 patients, 52% female had developed ADRs. (Figure 2).

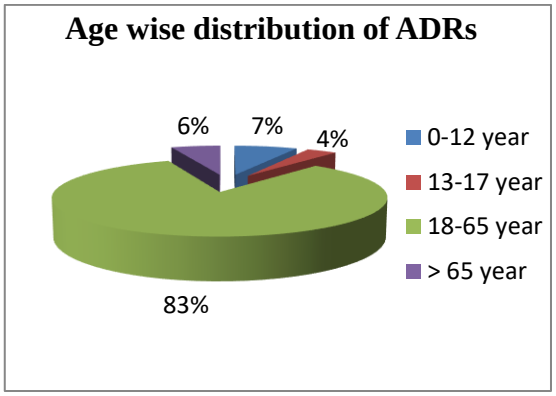

Figure 1 Age-wise distribution of ADRs

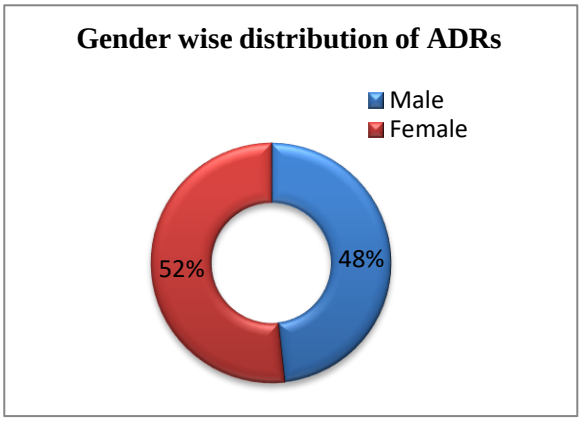

Figure 2 Gender-wise distribution of ADRs

d. Hospitalised and prolonged hospital stay:
Overall 401 (59.7%) patients had to extend their hospital stay because of ADRs. 206 (30.7%) patients had experienced ADRs at home but were not hospitalised. Whereas 64 (9.5%) patients were admitted to hospital only because of ADRs.

e. Number of ADRs:
Out of 671 patients, 506 patients (75.4%) had experienced 01 ADRs followed by 130 patients (19.3%) had 02 ADRs, 30 patients (4.4%) had 3 ADRs, 04 patients (0.5%) had 04 ADRs and 01 patients (0.1%) had 05 ADRs.

f. Drug characteristics:
Antibiotics (39%) was most commonly attributed class of drug followed by non-steroidal anti-inflammatory drugs (NSAIDs) (10.9%), antipsychotics drugs (5.4%), anti- tubercular drugs (3.3%), Corticosteroids (2.7%) and anticonvulsant (1.9%). (Figure 3) Ciprofloxacin (15%) from antibiotic class of drugs, was most commonly prescribed offending drug which has maximum skin related ADRs i.e. itching, rash, urticaria, angioedema etc. Likewise, paracetamol was commonly prescribed offending drug which was associated with rash and drug eruption. (Table 1) Out of 715 drugs, maximum number of ADRs were occurred due to oral route administration 342 (47.8%) followed by parenteral route 324 (45.3%), topical route 43 (6%) and inhalational route 06 (0.8%).

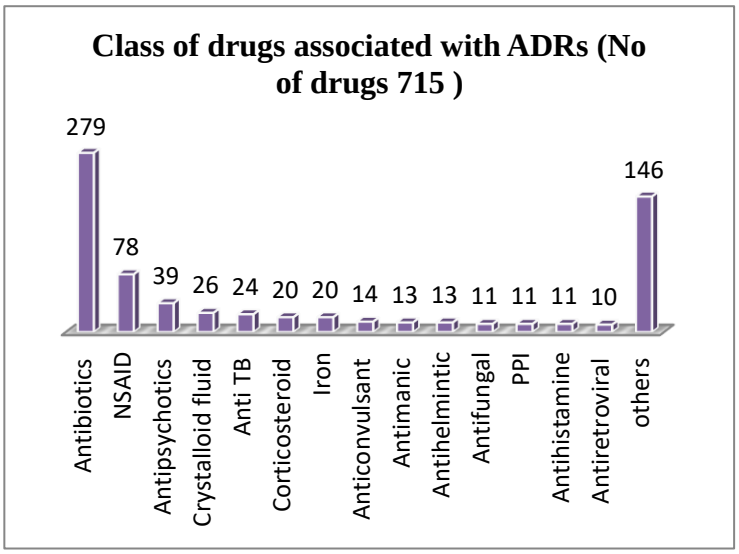

Figure 3 Most commonly prescribed class of drugs.

g. Analysis of ADRs
Based on Rawlin and Thomson ADR classification, we categorised 632 (72.1%) ADRs in Type A, 208 (23.7%) in Type B, 02(0.2%) in Type C and 35(3.9%) in Type D. Out of 877 ADRs, majority of ADRs (45%) were observed from skin (45%) followed by musculoskeletal system (12.7%), CNS (10%), GIT (8%), immune system (4.2%) and CVS (3.8%). Among the skin reactions, rash (42.6%) was most commonly observed ADR followed by itching (13.9%) and angioedema (11.4%). Likewise, rigors (41.9%) and muscular pain (26.7%) were reported in musculoskeletal system, EPS (16.6%) and headache (11.4%) were noted in CNS, loose stool (25.3%) and vomiting (36.6%) were seen in GIT, hypersensitivity (37%) was noted in immune

system and tachycardia (23.5 %) and pedal oedema (20.5%) were detected in CVS. (Table 2) 598 (83.6%) offending drugs were withdrawn (dechallenge) as a measure of ADR management whereas 88 (12.3%) drugs were reintroduce. Reintroduction of offending drug was done by patients themselves or unknowing by HCP and as a result, reaction reappear with 07 suspected drugs, reaction not reappear with 13 drugs and 68 drugs effect were unknown. Out of 877, majority (60.2%) of ADRs totally recovered after management or/and treatment followed by recovering (30.2%) of ADRs. In our study, maximum ADRs were non-serious (71.6%) whereas 28.3% ADRs were serious. After causality assessment, we observed that majority 513 (71.7%) of ADRs were probable followed by Possible (26.2%) and certain (0.9%). (Table 3)

h. Completeness of NCC score:

We have received lowest completeness NCC score in 2017 which was 0.71 and highest in 2020 which was 0.98. (Figure 4)

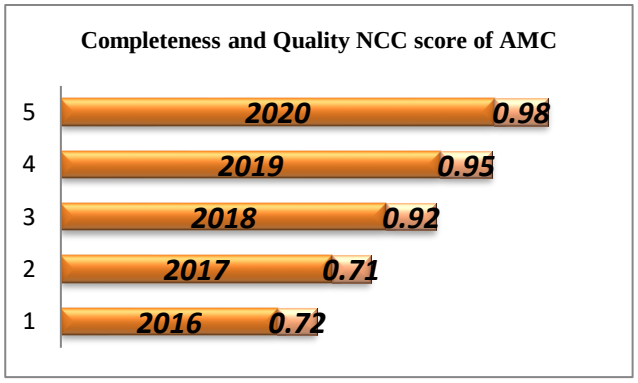

Figure 4 AMC- NCC completeness score per year.

i. Reporter details :

Maximum number of ADRs 241(35.9%) were reported by PSPA from AMC followed by physicians 183 (27.3%), nurses 133 (19.8%), MBBS students 100 (14.9%), patients 12 (1.7%) and interns 02 (0.3%).

Discussion

In India, PvPI collects the ADRs related information from all the AMCs through vigiflow software. After assessing the resources, PvPI refer the significant ADRs related data to drug regulatory authorities for required action on the drugs. PvPI sensitize the HCPs as well as the layman persons regarding the risk of ADRs, encourages safe use of medicine and maintain the public confidence toward safety drugs. In this regard, AMC Port Blair have received a total of 877 ADRs from 715 offending drugs in 671 patients. Women have lower body weight, small organ size, more fat distribution and with low glomerular filtration which modifies absorption, distribution, metabolism and elimination of drugs.[13] Hence, female patients have a greater risk of ADR compared with male. In Vries st de et al. study [14], female patients had experienced 67% ADRs which was similar with our study result. Adult age group (18–65 year) population frequently attends hospital for morbidity and receives multiple drug therapy. Majority of ADRs (83%) were seen in adult age group in our study. Yu ym et al study 64.0%[15] and Dhar k. et al study 57.5% [16] have also concluded same for adult age group. ADR is associated with a significantly prolonged length of hospital stay, increased economic cost burden of treatment, associated with negative outcomes and recovery with increased risk of mortality. In our study, 59.7% patients' hospital stay were prolonged only because of ADRs which was high as compare to Davies ec et al study (26.8%)[17] and Giardina C et al study (3.2%) [18]. Tumwikirize W et al [19] and Pirmohamed M et al study [20] showed patients admitted only because of ADRs were 1.5% and 6.5% respectively while in our study it was 9.5%. In India, antibiotics were

responsible for 40% of ADRs. [21] In our study, Antibiotics (39%) was the most common offending class of the drug associated with ADRs followed by NSAIDs. Our result was similar with Naldi L at el (38.6%) [22], Bhattacharjee P et al (38.09%) [23], Rani S et al. (38.65%) [24]studies. Our result was comparatively high with Richa et al. (15.15%) [25]study and comparatively low with Mahatma N et al.(48%)[26], Anjaneyan G et al. (54%) [27], Jung IY et al (62.8%) [28]studies. MedDRA is a standardised medical terminology, published by the International Council for Harmonisation, used in particular for coding cases of adverse effects in pharmacovigilance databases.[11] Skin was the most common organ system to be affected in drug induced ADRs. Our result (45%) was nearly equivalent with Jung IY et al (43.1%)[28] , Naldi L at el (44.7%)[22] and Arulappen AL et al. (48%) [29]study. Based on Rawlin and Thomson ADR classification, Type A (72.1%) ADRs were most common compared to type B (23.7%) ADRs in our study. This result was nearly similar with Shamna M et al. study (Type A 77.55%, Type B 22.44%).[30] If all the valuable informations in the ADR form are filled, it quickens the process of signal generation which will prove to be beneficial at not only the AMC level but also on a national and worldwide level. NCC completeness score of our study was 0.98 which was significantly high as compare with Mahajan MM et al study (0.86).[9] In our study, we assessed ADR parameter with informative values and our study concluded 60.2% patients' recovered in outcome parameter, 83.6% drug withdrawn for management of ADRs , reintroduction of offending drug was done only in 12.3% patients, 71.6% patients were non-seriousness and 71.7% ADRs were probable. Similar observations have been reported by Patel SR et al. [31]The present study was retrospective study so preventability and severity of reactions were not assessed. The number of ADR reports were comparatively less as the AMC Port Blair is functioning since 5 year only. For reporting of a good number ADRs and achieving public confidence toward drug safety, HCPs and other health department staff still need pharmacovigilance training. These were limitation of the present study.

Conclusion

An ADRs are highly expected to occur with medicines. It remain as challenge in modern healthcare and some of them resulted in increased healthcare cost due to need of interventions, prolonged hospital stay and rising multimorbidity. Our study data show that among antibiotics class of drug, ciprofloxacin was commonly reported offending drug associated with skin related ADRs. Female had experienced 52% ADRs and most commonly affected age group was adult. Based on medDRA and Rawlin and Thomson ADR classification, majority of ADRs were observed from skin system and maximum ADRs belonged to Type A. Causality assessment according to WHO-UMC criteria is reported to be probable. The NCC completeness score was good and this quality reporting ADRs increases the potential for signal generation. Hence, the health system should promote the spontaneous reporting of ADRs. The proper documentation and periodic reporting to AMC is required to ensure drug safety.

Conflict of interest: The authors declare no conflict of interest.
Financial Support: None declared.

TABLE 1 NO OF ADRS ASSOCIATED WITH MOST COMMON CLASS OF DRUGS AS WELL DRUGS

Class of Drug No (%)	Drugs No (%)	No of ADRs	ADRs (No)
Antibiotics 279 (39.02%)	Ciprofloxacin 42 (15.2%)	57	Itching (12), Rash (12), Drug eruption (8), Angioedema (4), Blister (3), Urticaria (3), Loose stools (2), Erythema multiforme (2), Vomiting (2), Thrombocytopenia (1), Dizziness (1), Cyanosis (1), Chemosis (1), Fever (1), Nausea (1), Hypersensitivity Reaction (1), Dermatitis (1), Ulcer (1).
	Ceftriaxone 38 (13,6%)	63	Rash (19), Rigor (5), Chills (5), Itching (5), Fever (4), Dyspnoea (3), Angioedema (3), Nausea (2), Vomiting (2), Dizziness (2), Ulcer (2), Hypotension (2), Anaphylactic Reaction (1), Redness of Eye (1), Abdominal Pain (1), Hypersensitivity Reaction (1), Muscular Pain (1), Drug eruption (1), Erythema multiforme (1), Numbness (1), Tongue Swelling (1).
	Metronidazole 34 (12.1%)	40	Rash (8), Rigor (6), Hypersensitivity Reaction (5), Dyspnoea (4), Abdominal Pain (3), Vomiting (3), Itching (2), Thrombocytopenia (1), Dizziness (1), Tachycardia (1), Anaphylactic Reaction (1), Nausea (1), Weakness (1), Acne (1), Ulcer (1), Urticaria (1).
	Azithromycin 27 (9.8%)	38	Rash (13), Itching (6), Loose stools (4), Muscular Pain (4), Urticaria (2), Hypersensitivity Reaction (2), Drug eruption (2), Injection site swelling (2), Pruritis (1), Angioedema (1),Dyspepsia (1).
	Levofloxacin 23 (8.2%)	36	Itching (10), Rash (9), Dizziness (2), Rigor (2), Vomiting (2), Urticaria (2) Petechial hemorrhages (1), Restlessness (1), Anaphylactic Reaction (1), Gastritis (1), Nausea (1), Chills (1), Muscular Pain (1), Weakness (1), Drug eruption (1).
NSAIDs 85 (11.9%)	Paracetamol 29 (34.1%)	33	Rash (10), Drug eruption (6), Dizziness (2), Angioedema (2), Arrhythmia (1), Auricular swelling (1), Oral candidiasis (1), Hyperbilirubinemia(1), Rigor (1), Dyspnoea (1), Acne (1), Blister (1), Itching (1), SJS (1), SJS-TEN (1), Ulcer (1), Urticaria (1).
	Paracetamol+ Ibuprofen 21 (24.7%)	32	Angioedema (11), Rash (5), Drug eruption (4), Itching (3), Dyspnoea (2), Urticaria (2) Dizziness (1), Hypotension (1), Redness of Eye (1), Dryness of mouth (1), Hypersensitivity Reaction (1).
	Aceclofenac 10 (11.7%)	12	Rash (4), Angioedema (3), Auricular swelling (1), Dyspnoea (1), Drug eruption (1), Itching (1), Urticaria (1).
Antipsychotics 39 (5.5%)	Haloperidol 11 (28.2%)	12	Muscular pain (5), EPS (3), Involuntary movements (2), Pseudoparkinsonism (1), Tremor (1).
	Risperidone 11 (28.2%)	11	EPS (7), Akathisisa (2), Headache (1), Neuroleptic syndrome (1).
	Quetiapine 8 (20.5%)	8	EPS (3), Anemia (1), Tremor (1), Sedation (1), Weight gain (1), Rash (1).
Anti-TB 28 (3.9%)	ATT- Fixed Drug Combination 18 (64.3%)	23	Rash (7), Hepatitis (3), Blurred vision (1), Macular toxicity (1), Vomiting (1), Gastritis (1), Hepatotoxicity (1), Weakness (1), Muscular pain (1), Hyperuricemia (1), Angioedema (1), Dermatitis (1), Erythema multiforme (1), Pruritis (1), Urticaria (1).
	Cycloserine 05 (17.8%)	05	Bipolar disorder (1), Depression (2), Neurotoxicity (1), Suicidal tendency (1).
Corticosteroid 20 (2.7%)	Clobetasol 08 (40%)	09	Tinea incognito (5),Hypersensitivity reaction (1), Acne (1), Erythema multiforme (1), Rash (1).

	Prednisolone 04 (20%)	05	Hypertension (1), Vertigo (1), Chemosis (1), Acne (1), Angioedema (1).
	Betamethasone 03 (15%)	03	Acne (1), Hypertrichosis (1), Itching (1).
Anticonvulsant 14 (1.9%)	Phenytoin 04 (28.6%)	04	Hypersensitivity reaction (2), Rash (1), Ulcer (1).
	Pregabalin 04 (28.6%)	04	Dizziness (2), Confusion (1), Rash (1).

TABLE 2 SYSTEM WISE CLASSIFICATION OF ADRS BASED ON MEDDRA. (TOTAL 877 ADRS)

Sr no	System wise classification, No (%)	ADRs	No (%)
1	Skin 401 (45%)	Rash	171 (42.6%)
		Itching	56 (13.9%)
		Angioedema	46 (11.4%)
		Drug eruption	36 (8.9%)
		Others	92 (22.9%)
2	Musculoskeletal system 112 (12.7%)	Rigors	47(41.9%)
		Chills	28(25%)
		Muscular pain	30(26.7%)
		Weakness	07(6.2%)
3	CNS 96 (10%)	Dizziness	27(28%)
		Extrapyramidal symptoms	16(16.6%)
		Headache	11(11.4%)
		Tremors	08(8.3%)
		Sedation	06 (6.26%)
		Others	28 (29%)
4	GIT 71(8%)	Vomiting	26(36.6%)
		Loose stool	18(25.3%)
		Nausea	09 (12.6%)
		Abdominal pain	09(12.6%)
		Others	09 (12.6%))
5	Immune system 37 (4.2%)	Hypersensitivity reaction	37 (37%)
6	CVS 34 (3.8%)	Tachycardia	08(23.5%)
		Pedal oedema	07(20.5%)
		Anaphylaxis	07(20.5%)
		Hypotension	06(17.6%)
		Others	06 (17.6%)
7	Respiratory system 31 (3.5%)	Dyspnoea	26 (83.8%)
		Cough	03 (9.6%)
		Others	02 (6.4%)
8	General 25(2.8%)	Fever	25(25%)
9	Eye 22 (2.5%)	Redness	07 (31.8%)
		Burning sensation	04(18.1%)
		Blurred vision	03(13.6%)
		Others	08 (36.3%)
10	Metabolic system 15 (1.7%)	Weight gain	05 (33.3%)
		Hypoglycaemia	02 (13.3%)
		Others	08(53.3%)
11	Hepatobilliary system 09 (1%)	Hepatitis	05(55.5%)
		Hyperbillirubinemia	02 (22,2%)
		Hepatotoxicity	02 (22,2%)
12	Blood and lymphatic system 09 (1%)	Anaemia	06 (66.6%)

		Thrombocytopenia	02 (22.2%)
		Leukocytosis	01 (11.1%)
13	Ear 08 (0.9%)	Tinnitus	03 (37.5%)
		Deafness	02 (25%)
		Vertigo	02 (25%)
		Auricular swelling	01 (12.5%)
14	Renal 07 (0.7%)	Urinary Retention	01 (14.2%)
		Urinary Incontinance	01 (14.2%)
		Others	05 (71%)

TABLE 3 DESCRIPTION OF OUTCOME, MANAGEMENT, RECHALLENGE, SERIOUSNESS OF REACTION AND CAUSALITY ASSESSMENT.

Parameter	Informative values	No of ADRs (%)
Outcome	Recovered	528 (60.2%)
	Recovering	265 (30.2%)
	Not recovered	39 (4.4%)
	Fatal	00
	Recovered with sequelae	02 (0.2%)
	Unknown	43 (4.9%)
Management of ADRs	Drug withdrawn	598 (83.6%)
	Dose increased	01 (0.13%)
	Dose reduced	29 (4%)
	Dose not changed	49 (6.8%)
	Not applicable	27 (3.7%)
	Unknown	11 (1.5%)
Rechallenge	No	615 (86%)
	Yes	88 (12.3%)
	Unknown	12 (1.6%)
Seriousness	Not serious	628 (71.6 %)
	Death	00
	Life threatening	44 (5%)
	Hospitalization / prolonged	137 (15.6%)
	Congenital –anomaly	00
	Disability	00
	Other medically important	68 (7.7%)
Causality assessment	Certain	07 (0.9%)
	Probable / likely	513 (71.7%)
	Possible	188 (26.2%)
	Unlikely	06 (0.8%)
	Conditional / Unclassified	00
	Unassessable/ Unclassifiable	01 (0.13%)

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