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Research Article

A Prospective Study of Adverse Drug Reactions in 1 Month–12 Years Old Pediatric Patients

Asawari Raut[1], Vijay Kalrao[2], Roja Rani[1], Ravi Kumar[1]
[1]Bharati Vidyapeeth Deemed University, Poona college of Pharmacy, Pune, India
[2]Bharati Vidyapeeth University Medical College, Pune, India

Abstract
Adequate controlled clinical trials in pediatric population, especially in oncology and vaccinations are still insufficient due to ethical considerations. Certain conditions in children in general and in Indian children in particular, suggested the need for Adverse Drug Reaction (ADR) monitoring. Thus this study was aimed to investigate the incidence of ADRs in pediatric populations. A prospective spontaneous reporting study was conducted over a period of six months from October 2012 to March 2013 in pediatric inpatients ward of Bharati Hospital in Pune. Reported ADRs were assessed for its causality by using WHO causality assessment scale, and its severity by using Hart wig Severity Scale. A total of 107 suspected ADRs were reported and evaluated from 54 patients, showing an overall incidence of 4.75%. Incidence rate of ADRs during hospitalization was 4.13%, while ADRs induced hospitalization was 0.62%. The gastrointestinal system (48.59%) was the most affected, and antibiotics was the most common the drug class associated to ADRs. In term of causality, 55.14% of the reactions were classified as possible, while in term of severity, 64.49% were classified as moderate. Most patients (60.75%) recovered from the incidence. Although the prevalence and severity of ADRs in pediatrics populations is reported to be higher than those of in adults, the incidence of ADRs in our study was only 4.75% which is lower than those of reported in adults, this may due to the spontaneous reporting system that used in this study.

Key words: Adverse drug reaction, causality, prospective spontaneous reporting system, severity

Studi Prospektif Reaksi Obat yang Merugikan pada Pasien Anak 1 Bulan–12 Tahun

Abstrak
Uji klinik pada anak khususnya onkologi dan vaksinasi masih kurang memadai karena pertimbangan aspek etik. Kondisi tertentu pada anak secara umum dan khususnya di India memerlukan pemantauan Rekasi Obat yang Merugikan (ROM). Penelitian ini bertujuan untuk mengetahui insidensi ROM pada pasien anak. Studi pelaporan spontan prospektif dilakukan selama enam bulan pada Oktober 2012–Maret 2013 di bangsal anak Rumah Sakit Bharati di Pune. ROM yang dilaporkan dinilai kausalitasnya dengan WHO *causality assessment* dan keparahan dengan skala *Wig Hart Severity*. Sebanyak 107 suspek ROM dilaporkan dan dievaluasi dari 54 pasien menunjukkan insidensi sebesar 4,75%. Tingkat kejadian ROM selama rawat inap sebesar 4,13% sementara ROM yang menyebabkan pasien dirawat inap sebesar 0,61%. Sistem pencernaan (48,5%) paling sering dilaporkan dan antibiotik sebagai obat yang berasosiasi dengan ROM. Berdasarkan kausalitas, 55,14% reaksi obat diklasifikasikan *possible* (55,14%) sementara dalam aspek kepaharahan, 64,49% diklasifikasikan moderat. Mayoritas pasien sembuh dari ROM (60,75%). Prevalensi dan keparahan ROM pada anak dilaporkan lebih tinggi dibandingkan dewasa, akan tetapi insiden ROM pada penelitian ini hanya 4,75% yang lebih rendah daripada yang dilaporkan pada orang dewasa, dimungkinkan karena penelitian ini merupakan sistem pelaporan spontan.

Kata kunci: *Causality*, keparahan, reaksi obat yang merugikan, sistem pelaporan spontan prospektif

Correspondence: *Asawari Raut, M Pharm, PhD, Department of Clinical Pharmay, Bharati Vidyapeeth* Deemed University, Poona college of Pharmacy, India, email: asawari.raut@gmail.com
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Introduction

According to World Health Organization Collaborating Centre for International Drug Monitoring, Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems. Recently, its concerns have been widened to include herbals, traditional and complementary medicines, blood products, biological, medical devices, and vaccines.[1]

Early detection of unknown adverse reactions, interactions, and the detection of ADRs have increase the prevalence of known ADRs. Identification of risk factors and possible mechanisms underlying ADRs, estimation of quantitative aspects of benefit or risk analysis needed to improve drug prescribing and regulation.[2]

Before a new drug is marketed, clinical trials are conducted to detect ADRs in adult patients. These pre-marketing trials can be inadequate to detect the full range of ADRs that can occurs.[2] Children constitute a vulnerable group. Adequate controlled clinical trials in children, with the notable exceptions of pediatric oncology and vaccinations, are insufficient due to ethical considerations. Only a vigilant post marketing surveillance detects ADRs occurring uniquely in children, for example, sulfonamide induced Kernicterus in premature infants,[3] Chloramphenicol induced "Grey baby syndrome"[4] and Phenytoin induced movement disorders.[5]

Certain conditions in children in general, and in Indian children in particular, highlight the need for ADR monitoring. Children may not voice any complaints and ADRs may easily go unnoticed, for example, Ethambutol induces visual deficit, and Phenobarbitone causes drowsiness. These drugs can lead to impaired learning and deterioration in school performance. Growth potential may get inhibited by drugs, for example, corticosteroids used for Nephrotic syndrome.[6] Ethnic and socio cultural variables are known to influence the frequency of ADRs, children in India represent a wide variety of ethnic and socio cultural groups.[7] The disease spectrum in Indian children is quite different to those of in developed countries. Several diseases including tuberculosis, malaria, typhoid fever, recurrent infective diarrhea, scabies, chronic epilepsy, kala-azar, are common in India. Therefore, it is necessary to identify ADRs in the treatment of diseases which are endemic in Indian children.[8]

Malnutrition affects drug pharmacokinetics and thus influences the frequency of ADRs. More than 50% of Indian children are malnourished.[9] Irrational multiple drug prescriptions are common in pediatric practice. Patients taking a new drug along with other drugs may experience ADRs that not revealed during the pre-marketing trials, for example, ventricular arrhythmias can occur when Terfenadine, an antihistamine, is taken in combination with the antifungal agent Ketoconazole.[10]

Certain drugs (e.g. Ciprofloxacin) that is not recommended for pediatric use, are in fact being widely used in Indian children. On account of its possible adverse effect on growing cartilage, ciprofloxacin is not recommended for routine use in children.[11] Since 1990 with the advent of multi-drug resistant typhoid fever, Ciprofloxacin is being widely used. Such clinical situations offer an opportunity to gather unique data on ADRs in children. ADR surveys need to be done for drugs not routinely recommended but still being used in Indian children, for example, Norfloxacin, Mefloquine, Enalapril etc.[12] Additives such as colorings, flavorings and sugars are being widely used in liquid formulations prescribed in pediatric practice. These so-called "inactive" ingredients may also cause adverse reactions such as rhinitis, urticaria, headache, asthma, gastrointestinal

dysfunction, and even anaphylactic shock. In India, this problem has received little attention. Manufacturers either do not provide clear-cut information of all additives used or they use synonyms making it difficult to identify them.[13] Present study is conducted in Pediatric inpatients of tertiary care teaching hospital to assess incidence and severity of ADRs in Pediatric patients.

Methods

A prospective spontaneous reporting study, that approved by the Bharti Vidyapeeth Deemed University Medical College Institutional Ethics Committee, was conducted over a period of six months from October 2012 to March 2013. Pediatric patients aged from 1 month to 12 years were included in the study. Patients admitted other than pediatric ward, neonatal patients, adolescent patients and patients with intentional or accidental poisoning, were excluded from the study.

WHO definition of an ADR was adopted. Spontaneous reporting system was the method followed for monitoring ADRs. Medical staff, medical post graduates, nursing staff and patient's care takers were educated and encouraged to report ADRs. ADR notification forms were kept in the nursing stations of pediatric wards and the PharmD students played a crucial role in monitoring through daily participation in ward rounds and encouraging the physicians to report.

Any reaction observed by the student was brought into the notice of the physician, who if convinced enough that drug is responsible cause of reaction filled the notification form. Informed consent was taken from the patient care taker for suspected ADR before documentation. The demographic details of the patient were collected along with the current concern and drug therapy details in a systematically designed patient profile form. All relevant data including the drugs patient received prior to the onset of reaction, respective dose, and route of administration with frequency, date of onset of reaction and the patient's allergic status were noted. In addition to this patient's medication history and other co-morbidities were identified to assess causality relationship between the suspected drug and reaction. The medication order and records were reviewed on daily basis throughout the stay of patient in the hospital. Any drug treatment and/or supportive therapy given for management of the reactions were also noted.

Causality assessment was carried out using WHO scale which categorizes the causality relationship into certain, probable, possible, conditional/unclassified, unlikely, un-assessable/ unclassifiable.[14, 15]

1. Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenological, using a satisfactory rechallenges procedure if necessary.
2. Probable/Likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
3. Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.

Information on drug withdrawal may be lacking or unclear.

4. Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
5. Conditional/Unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination
6. Unassessable/Unclassifiable: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Severity of ADR was graded as per scale developed by Hart wig as mild, moderate and severe. The most common class of drugs causing ADRs were identified and documented.[16]

1. Mild: The ADR requires no change in treatment with the suspected drug. The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required, and there is no increase in length of stay.
2. Moderate: The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/ or an antidote or other treatment is required. There is no increase in length of stay or any ADR that increases length of stay by at least one day. The ADR is the reason for admission.
3. Severe: Any ADR that requires intensive medical care. The ADR causes permanent harm to the patient. The ADR either directly or indirectly leads to the death of the patient.[16]

A total of 1137 patients were admitted in pediatric ward in the duration of 6 months, among which 633 were male and 504 were female patients. From this total population, 54 patients were identified with ADRs; demographic details were mentioned in (Table 1).

Results

A total of 107 suspected ADRs were reported and evaluated from 54 patients (35 males, 19 females) during the study period. The percentage of ADRs observed in male (64.81%) was greater than female (35.19%). Out of 54 patients, 21 (38.89%) developed more than one ADR.

Majority of ADRs 61 (57%) were reported in the patients aged <1 year followed by 16 (14.95%) in 6–9 years patients, 14 (13.08%) in 1–3 years patients, 11 (10.28%) in 3–6 years patients. Whereas, least number of ADRs 5 (4.68%) were reported in patients aged between 9–12 years. (Figure 1).

The overall incidence rate was 4.75%. Male experienced a significantly higher incidence of ADRs (5.53%) than female (3.76%). Incidence rate of ADRs during hospitalization (4.13%) was higher than those of ADRs induced hospitalization (0.62%).

Table 1 Demographic Details

Gender	Patients Admitted (%)	Patients With ADRs (%)
Male	633(55.67)	35(64.81)
Female	504(44.33)	19(35.19)
Total	1137	54

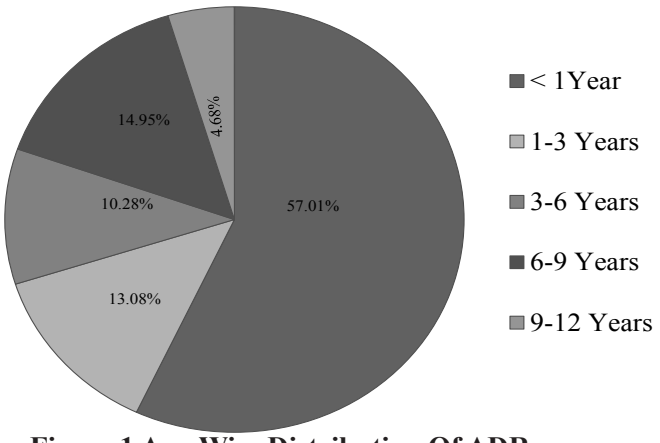

Figure 1 Age-Wise Distribution Of ADRs

The drug class most commonly associated with ADRs was Antibiotics (67.28%) followed by anticonvulsants (9.34%) while least affected class was found to be vitamin supplements and diuretics (0.93%) as given in (Figure 2). Cephalosporins (33.3%) were the antibiotics responsible for greater proportion of ADRs, followed by Penicillins (29.2%) and Aminoglycosides (16.7%), whereas the least number of antibiotics responsible for ADRs were Fluoroquinolones (1.45%) Carbapenems (1.4%) (Table 2).

Antibiotics were responsible for major percentage of ADRs, the types of ADRs for which antibiotics were responsible are mentioned in the following Table 3.

Accordingly, the organ systems most commonly affected by an ADR was the gastrointestinal system (48.59%) followed by immune system (25.23%) and the least effected system was nervous system (4.67%) (Figure 3).

Assessment of ADRs is given in (Figure 5). Causality assessment of suspected ADRs

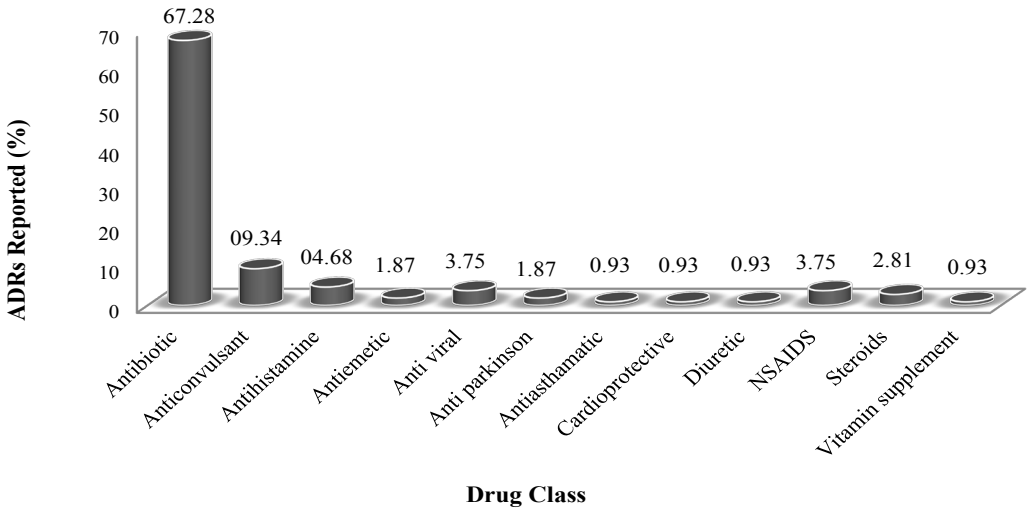

Figure 2 Drug Class Responsible for ADRs

Table 2 Antibiotic Class Responsible for ADRs

Antibiotic Class	ADRs Reported n (%)
Penicillins	21 (29.2)
Cephalosporins	24 (33.3)
Aminoglycosides	12 (16.7)
Macrolides	2 (2.8)
Sulphonamides	4 (5.6)
Fluoroquinolones	1 (1.4)
ß Lactamase Inhibitors	6 (8.3)
Carbapenems	1 (1.4)
Nitrobenzene derivative	1 (1.4)

shows out of 107 reported ADRs 59 (55.14%) were assessed to be "Possible", 27 (25.23%) as "Probable", 19 (17.75%) as "Certain" and 2 (1.87%) as Unclassifiable. Reported reactions were found to be "Mild" 38(35.51%) followed by "Moderate" 69(64.49%). No single ADR was found to be severe as per Hart wig's severity assessment scale.

In majority of ADRs (60.75%), "Complete recovery" was achieved, 22.43% ADRs were found to be "recovering" and 2.80% ADRs were of "unknown" outcomes in which the outcomes could not be assessed as the patients sought voluntary discharge from the hospital. No fatal reactions were reported (Table 4).

Reporting of ADRs was dominated by the PharmD students (Table 5) of Department of Clinical Pharmacy (81.30%). This was followed by medical post graduates who reported about 13.08% ADRs. Physician reporting was found to be 5.62%.

Discussion

Studies have been performed in different parts of the world on ADRs among pediatric patients. Most studies evaluating pediatric ADRs were conducted in US and Europe. The need for more studies evaluating ADRs in children is evidenced by the lack of published clinical studies specifically in India and our limited knowledge of the safety of many pharmacologic agents that are currently in the market. It has been found that ADRs were associated with 243 reported deaths among young children in

Table 3 Distribution of Antibiotics Causing ADRs

Antibiotic	ADR
Ampicillin, Cloxacillin, Amoxicillin, Clavulanic Acid, Vancomycin, Levofloxacin, Ceftriaxone	Rash
Ceftriaxone, Ampicilin, Cloxacilin, Amikacin, Cephradine,	Fever
Ampicillin, Cloxacillin, Clavulanic Acid, Amoxicillin, Ceftriaxone, Vancomycin, Meropenam, Amikacin, Trimethoprim, Sulfadoxin	Vomiting
Amoxicillin, Clavulanic Acid, Ceftriaxone, Ampicillin, Cloxacillin, Amikacin, Piperacillin, Tazobactam, Azithromycin,	Diarrhoea
Chloramphenicaol, Sulphadoxin, Pyrimethamine	Anemia
Amoxicillin, Clavulanic Acid	Swelling
Piperacillin	Thrombocytopenia
Vancomycin	Facial Puffiness
Amikacin	Hypokalemia

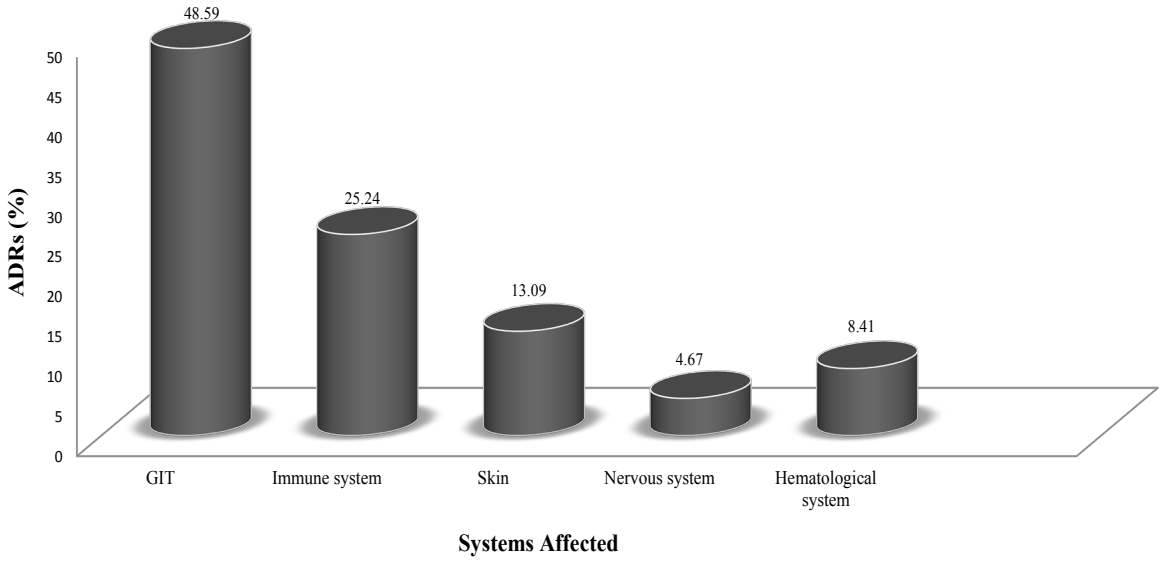

Figure 3 Organ System Affected Due to ADRs

the age groups of newborn to 2 years of age each year.[17] Intensive monitoring of patients (1137) admitted in Pediatric ward for 6 months duration has provided the following information i.e. 54 patients were identified with 107 ADRs. The percentage of ADRs observed in male (67.28%) was greater than female (32.72%), the reason behind this may be, in the total number of patients admitted in pediatric ward, male population was more when compared to female. Meanwhile in a study conducted by Inocencia Martinez-Mir,[18] it was found that the percentage of ADRs developed in females was high (68.97%) compared to males (31.03%), which was quite opposite to our study. Around 60% of population has experienced single ADR and remaining 40% has developed more than one ADR. If the number of prescribed drugs is more than 6 drugs which are used for chronic purposes, the possibility of multiple ADRs is higher. In the present study patients

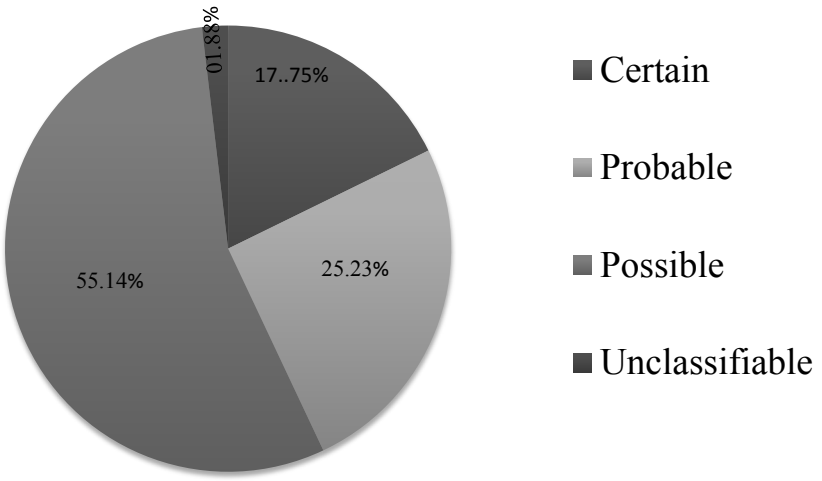

Figure 4 Causality of ADRs

Table 4 Severity of Adverse Drug Reactions

Outcomes of ADRs	ADRs Reported n (%)
Fatal	0
Continuing	15 (14.02)
Recovering	24 (22.43)
Recovered	65 (60.75)
Unknown	3 (2.80)
Others	0

aged less than 1 year old (50%) were more predominantly more in number, followed by 6–9years (14.95%). These findings coincide with a pilot study carried out in Boston by Martinez-Mir, M García-Lopezet et al[19] and the work of Whyte & Greenan.[20] The main reason for observing more number of ADRs in patients below one year age group are due to less developed physiological conditions, so their drug pharmacokinetic parameters are varied and immunity are weaker compared to other age groups.[20]

The cumulative incidence rate of total ADRs was found to be 4.75%. The incidence rate of ADRs during hospitalization was 4.13% and incidence rate of ADRs induced hospitalization was found to be 0.62% which was less than the results of a meta-analysis conducted by Clavenna et al,[21] published during 2001–2007 period in which estimated incidence rate of ADRs among hospitalized children was 10.9% and an incidence of ADRs leading to admission to a pediatric hospital was 1.8%. In both the studies, the incidence rate of ADRs during hospitalization was higher compared to ADRs induced hospitalization. This is because the number of patients admitted due to ADRs are less compared to patients with ADRs during hospitalization.

Antibiotics were found to be most common class of drugs causing ADRs, in which antibiotics were responsible for 67.28% of ADRs. This is in accordance with the results of Priyadarshini et al[22] (67%) in India and Jennifer le et al[23] (33%) in California where antibiotics are the major class of drugs responsible for most of the ADRs. The reasons for this may be because antibiotics are more prescribed in developing countries like India, in turn more prescribed in pediatrics as they commonly have infectious conditions like URTI, LRTI, UTI, sepsis, and to prevent nosocomial infections, more over the study period was mostly winter which is also an underlying cause for various infections. Lack of rationality in use of drug therapy is also a reason. Antibiotics not only kill harmful bacteria but also destroy the useful bacteria present in the body. Among antibiotics, Cephalosporin's (33.3%) were most common class of drugs associated

Table 5 ADRs Reported

Profession	ADRs Reported n (%)
Clinical Pharmacist	87 (81.30)
Residents	14 (13.08)
Physician	6 (5.62)
Nurse	0
Patient	0

with ADRs followed by Penicillin's (29.2%) and Amino glycosides (16.7%) as they are most commonly prescribed antibiotics and presented complaints were fever, diarrhea, vomiting etc. Cephalosporins are more associated with ADRs as they are generally prescribed for nosocomial infections in our hospital. Next to antibiotics, anticonvulsants (9.34%) were more number of drugs associated with ADRs which were prescribed for febrile seizures, epilepsy conditions, and various syndromes.

The most common system affected due to ADRs in our study was gastrointestinal (48.59%) followed by immune system (25.24%), skin (13.09%), hematological (8.41%) and nervous system (4.67%) which was similar to studies conducted by Kramer et al[24] and Inocenica Martinez et al.[18] The may due to the most of the drugs primarily act on gastrointestinal tract and results in irritation of mucous membrane. Drugs like antibiotics kill useful bacteria when they are intended to kill harmful bacteria, this may hamper the digestion of some substances which may lead to diarrhea or vomiting. This can be avoided by following proper prescribing guidelines and considering administration of drug with or without food, dose, and dosing frequency.

Causality assessment was done by using WHO Causality Assessment Scale, which revealed that 58% of ADRs were possible, 19% were certain, 19% were found to be probable and remaining 4% were classified under other categories. Meanwhile in a study conducted by Jennifer le et al[23] 44% of the ADRs were found in possible and probable categories and only 8% of ADRs fall into certain category. Severity assessment was carried out by using Hartwig's Severity Assessment Scale, resulting 35.51% of ADRs were assessed as mild, and 64.49% of ADRs were assessed as moderate, and no severe reactions were identified. These results are little contrast to the observations of Priyadarshini et al,[22] in which 77% of ADRs were reported as moderate and 23% as severe. Whereas in a study by Inocenica Martinez et al,[18] 52.9% reactions were severe, 39.7% were moderate, and only 4.4% were mild.

When reporting of ADRs by different healthcare professionals is seen, the Clinical Pharmacist has reported around 81.30% of ADRs, followed by Resident Doctors (13.08%) and Physicians (5.62%). The study of Le et al[23] on ADR reporting, also showed similar results to our study in which 89% ADRs were reported by pharmacists. The reason behind the results is PharmD students have ADR reporting as part of their curriculum so that has reflected in the reporting. Drug therapy monitoring was intensive by PharmD students than other healthcare professionals which helped better screening of adverse effects of drugs.

Conclusion

Incidence of ADRs in our study was found to be 4.75% which is lower than the previous report, this may due to the spontaneous reporting system that used in the present study. It is well known fact that ADRs do occur at normal doses in children as well as adults, they are inevitable, but the impact of these ADRs in pediatrics is high when compared to adults. Though no severe reactions were encountered in our study, the study was conducted for short term, long term studies would be beneficial to provide better screening for severe ADRs.

Hospitalized children are administered with more than one drug, which is also one of the reasons for developing ADRs in pediatrics. In our study patients were administered at least 4 and up to 10 drugs in therapy.

The study results revealed that there is a need of implementing pharmacovigilance programs to ensure the safety of drugs

in children. Pediatricians and clinical pharmacists could be the key players in recognizing, evaluating, monitoring, communicating, and documenting ADRs.

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