Original Research Article

Pattern of adverse drug reactions in paediatric patients reported to adverse drug reaction monitoring centre in a tertiary care hospital

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ABSTRACT

Background: Adverse drug reactions (ADRs) are an important cause of morbidity and mortality across the world and contribute to a significant economic burden on healthcare resources and community. In children, monitoring ADRs is essential as adequate clinical trials are lacking in this group. So, this study was undertaken to assess the ADR pattern in a paediatric population in a tertiary care hospital.

Methods: A cross sectional, retrospective study was done at ADR monitoring centre (AMC) for a period of 3 years in a tertiary care hospital. All the ADRs reported by the Department of Paediatrics to AMC were collected and analyzed for age group affected, demographic profile, ADR pattern, drug group, systems affected, causality and severity of the ADR.

Results: During the study period, a total of 102 ADRs were reported to the AMC from the paediatric department. Out of 102 ADRs reported, males represented 60.8% and females represented 39.2%. Maximum number of ADRs were seen in the age group of 1-5 years (43.3%). Most common ADR reported was maculopapular rash (27.5%) followed by diarrhoea (14.7%). The most common drug class causing ADRs are antibiotics (36.3%) followed by anticonvulsants (18.6%). Vaccines contributed to 14.7% of all reported ADRs. Majority of the ADRs were of probable (70.6%) causality and moderate (52%) in severity.

Conclusions: ADRs were reported more among under 5 years of age and antibiotics were the common implicated causative agents. Most of the reactions were of moderate severity. Information acquired through ADR reporting may be useful in identifying and minimizing preventable ADRs and augmenting the knowledge of the prescribers to deal with ADRs more efficiently.

Keywords: Adverse drug reaction, Causality, Paediatric, Pharmacovigilance

INTRODUCTION

Adverse drug reactions (ADRs) are a common cause of hospital admissions, prolongation of hospital stays and a major cause of morbidity and mortality in both adults and

children. ADRs constitute a major cost factor in public health care. Almost 5% of hospital admissions in the paediatric setting and 10% of hospitalized paediatric patients are presumably due to drug related problems.¹ ADRs account for 4.2-30% of hospital admissions in the

USA and Canada, 5.7-18.8% of admissions in Australia, and 2.5-10.6% of admissions in Europe.² In another study, incidence of ADRs causing hospital admission in children ranges from 0.4-10.3% (pooled estimate of 2.9%) and their occurrence in hospitalized children is 0.6-16.8%.³ These statistics reflect the magnitude of problem necessitating the need for early detection, treatment and reporting of ADRs.

WHO defines ADR is a response to a drug that is noxious and unintended, and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.⁴ Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.⁵

In Indian population, the median incidence of ADRs that lead to hospitalization and that developed during hospitalization were 2.85% and 6.34% respectively.⁶ Another study showed that hospital admissions due to ADRs accounted for 0.7% of total admissions and deaths due to ADRs accounted for 1.8% of total admissions in a tertiary referral center in South India.⁷ This ADR burden scenario in India stresses upon more effective pharmacovigilance activities.

Government of India has started a nationwide Pharmacovigilance Programme of India (NCC-PvPI) under the aegis of Ministry of Health and Family Welfare, in the year 2010 and Indian Pharmacopeia Commission, Ghaziabad, Uttar Pradesh, India serves as National Coordination Centre (NCC). The National Pharmacovigilance Programme aims to cultivate the culture of adverse event notification and to generate ADR data on the Indian population and share the information with global health care community through World Health Organization Monitoring Centre (Uppsala monitoring centre). The signals generated are used to recommend regulatory interventions in the form of banning a drug or revised drug labels, issuing drug safety alerts and communicating the same to healthcare professionals. NCC-PvPI issued 56 drug safety alerts from March 2016 to June 2017.⁸

Paediatric patients are a vulnerable group as many new drugs are marketed without sufficient clinical trials in this age group, thereby increasing the risk of drug toxicity.³ Knowledge of drug safety is limited in the paediatric population due to ethical considerations, with the exceptions of paediatric oncology and vaccinations. Pharmacodynamics and pharmacokinetics in children differ from adults and therefore the spectrum of adverse reactions also differ.⁹ Neonates are prone to a high risk of ADRs due to their immature hepatobiliary and renal system. Thus, an active drug surveillance system is required to capture drug-related risk information in children. The present study would indicate ADR pattern and burden in paediatric patients in this region, which

would be helpful in orienting paediatricians towards the problem of ADRs occurring in this paediatric age group to help them ensure safe usage of drugs in children. So, the present study was undertaken to assess the clinical pattern, causality, and severity of ADRs and the causative drugs in a tertiary care teaching hospital.

METHODS

A cross sectional, retrospective and analytical study was conducted at Adverse drug reaction Monitoring centre (AMC) for a period of 3 years i.e. January 2016 to December 2018 in a tertiary care teaching hospital in Guntur, Andhra-Pradesh, India, after obtaining prior permission from the Institutional Ethics Committee and from Indian Pharmacopeia Commission (IPC), Ghaziabad, Uttar Pradesh, India. Our AMC is actively involved not only in collecting ADR data from the hospital but also spreading awareness regarding the need and essence of pharmacovigilance.

Inclusion criteria

Inpatients of both sexes between the ages of 0-12 years who developed ADRs to drugs and vaccines that were reported to ADR monitoring centre.

Exclusion criteria

- Cases with ADRs due to blood transfusion therapy
- Cases with intentional or accidental poisoning of drugs
- Cases with inadequate information regarding the ADR and its details.

Study population

Patients aged 0-12 years of either gender with suspected ADRs to drugs and vaccines that were reported to ADR monitoring centre includes the study population.

All the ADRs reported by the Department of Paediatrics to AMC during the study period were collected and analyzed. Data includes demographic details, details about ADR onset, duration, severity and outcome of the reaction, suspected drug, its dose, its route and any other concomitant medication. The reported ADRs were analyzed for the clinical nature, severity, systems affected and causative drugs.

Causality assessment of ADRs was done by WHO causality assessment scale which classifies suspected ADRs as certain, probable, possible, unlikely, conditional/unclassified, and un-assessable/unclassifiable.¹⁰ The severity of the ADRs was assessed by Modified Hartwig and Siegel Scale which assess the severity of ADRs and classifies them as mild, moderate, or severe.¹¹

Mild category includes level 1 and 2. Level 1: The ADR requires no change in treatment with the suspected drug. Level 2: The ADR requires the suspected drug to be withheld, discontinued or otherwise changed. No antidote or other treatment is required, and there is no increase in length of stay.

Moderate category includes level 3 and 4(a), 4(b). Level 3: The ADR requires the suspected drug to be withheld, discontinued or otherwise changed, and/ or an antidote or other treatment is required. There is no increase in length of stay. Level 4(a): Any level 3 ADR that increases length of stay by at least one day. Level 4 (b): The ADR is the reason for admission.

Severe category includes level 5, 6 and 7. Level 5: Any level 4 ADR that requires intensive medical care. Level 6: The ADR causes permanent harm to the patient. Level 7: The ADR either directly or indirectly leads to the death of the patient.

Data obtained was analysed using descriptive statistics (SPSS 16.0) and the values were expressed in numbers, percentages. MS Excel was used to generate graphs and tables, wherever necessary.

RESULTS

During the study period, a total of 102 adverse drug reactions were reported from the paediatric department to AMC. Sixty-two (61%) represented males and 40 (39%) represented females. The results are graphically represented in Figure 1. In the present study, most common presenting condition/ diagnosis for the reported ADRs was epilepsy (18.6%) followed by immunization (13.7%), upper respiratory tract infections (13.7%) respectively.

Figure 1: Gender wise distribution of ADRs.

Out of total (102) reported ADRs, 13 (12.7%) children were of less than 1 year, 44 (43.3%) children were of 1-5 years age group, 28 (27.4%) children of 6-10 years age group and 17 (16.6%) children were greater than 10 years. This indicates that occurrence of ADRs were more common in children less than 5 years age. The distribution of ADRs in various age groups is given in Table 1. Reported adverse drug reactions which affected various organ systems was shown in Table 2. Of the total ADRs reported, 45.1% of ADRs affected the skin and subcutaneous tissue, 33.3%, 8%, 6.9% affected the gastrointestinal system, immune system and central nervous system respectively.

Table 1: The distribution of ADRs in various age groups.

Age group	Number of ADRs	ADRs (%)
<1 year	13	12.7
1-5 years	44	43.3
6-10 years	28	27.4
>10 years	17	16.6

Table 2: Organ systems affected and ADRs reported.

Organ system involved	ADRs reported N (%)	Distribution/type of ADRs
Skin and subcutaneous tissue disorders	46 (45.1%)	Maculopapular rash (28), urticaria (11), Injection site rash (2), Gingival hyperplasia (3), hypersensitivity (1), Steven Johnson syndrome (1)
Gastrointestinal system	34 (33.3%)	Diarrhoea (15), vomiting (9), constipation (2), abdominal pain (3), Drug induced hepatitis (2), pancreatitis (1), malena (1), dry mouth (1)
Central nervous system	7 (6.9%)	Hyperactive behaviour (2), Ataxic gait (1), Tremors(1), Irritability (1), Convulsions (1), somnolence (1)
Immune system	9 (8%)	Lymphadenitis (3), Fever (2), Injection site abscess (2), Injection site induration (2),
Musculoskeletal system	2 (2%)	Arthralgia (1), Rigors (1)
Metabolic disorders	2 (2%)	Hyperglycaemia (2)
Eye disorders	1 (1%)	Nystagmus (1)
Blood/circulatory system	1 (1%)	Thrombocytopenia (1)

Most common reported ADR was maculopapular rash (27.5%) followed by diarrhoea (14.7%), urticaria (10.7%) and vomiting (8.8%). ADRs related to nervous system include hyperactive behaviour, irritability, ataxic gait, somnolence, nystagmus and tremors. Other less frequent ADRs include gingival hyperplasia, hyperglycaemia, constipation, malena, fever and rigors, arthralgia, thrombocytopenia, abdominal pain, dry mouth, and pancreatitis. A single case of steven Johnson syndrome was reported with phenytoin. Other Serious ADRs include severe lymphadenitis with BCG vaccine and an episode of convulsions with DPT vaccine.

Antibiotics (36.3%) were the frequent cause of ADRs reported followed by anticonvulsants (18.6%), NSAIDs (5.9%), antimalarials (3.9%), immunoglobulins (3.9%) and antitubercular drugs (3.9%) respectively. Very few ADRs were reported with other drugs which includes hormones, antacids, anticoagulants, antihelminthics, antivirals, hematinics, steroids and minerals (Figure 2). Vaccines contributed to 14.7% of all ADRs. Lymphadenitis, injection site abscess, injection site rash, injection site induration and urticaria were the ADRs produced with vaccines.

Figure 2: Distribution of ADRs according to drug class involved.

Among antibiotics fixed dose combination of amoxicillin and clavulanic acid contributed to 9.8% of all ADRs followed by ceftriaxone (6.9%). Ampicillin, piperacillin tazobactam, ceftriaxone, cefotaxime, cefpodoxime, ceftazidime was the betalactam antibiotics associated with ADRs. Other antibiotics associated with ADRs of low incidence include ciprofloxacin (flouroquinolones), amikacin (aminoglycosides), cotrimoxazole, vancomycin. Among anticonvulsants, phenytoin contributed to 10.7% of all ADRs followed by Sodium valproate (6.8%) and carbamazepine (1%) (Table 3).

Most of the ADRs occurred after parenteral administration (56.2%) of drugs, followed by oral route (40.8%) (Figure 3). For all the ADRs, causal relationship with the drug was assessed using WHO causality

assessment scale. According to WHO causality assessment, 70.6% were assessed as probable and 29.4% as possible in nature. The severity of ADRs was assessed using Modified Hartwig and Siegel Scale. Majority of the ADRs were of moderate severity (52%), followed by mild (43.1%) and severe (4.9%). On assessing the outcome of the reported ADRs, 82.4% were recovered and 17.6% were recovering either with stopping the drug/changing the dosing schedule or other treatment modalities (Table 4).

Table 3: Distribution of ADRs according to common individual drugs causing them.

Individual drugs	Frequency of ADRs N (%)
Amoxicillin clavulanic acid	10 (9.8%)
Ceftriaxone	7 (6.9%)
Piperacillin tazobactam	4 (3.9%)
Chloroquine	4 (3.9%)
MR vaccine	5 (4.9%)
Rabies antiserum	5 (4.9%)
Phenytoin	11 (10.7%)
Sodium valproate	7 (6.8%)

Figure 3: Route of administration of drugs of the reported ADRs.

Table 4: Distribution of ADRs based on WHO Causality scale, Modified Hartwig severity scale and outcome of the reaction.

Parameter	No. of ADRs	ADRs (%)
WHO causality assessment scale		
Probable	72	70.6
Possible	30	29.4
Severity Assessment Scale		
Mild	44	43.1
Moderate	53	52
Severe	5	4.9
Outcome of ADRs		
Recovered	84	82.4
Recovering	18	17.6

DISCUSSION

Drug safety is an important issue in all medical disciplines but in paediatrics this is still more essential by the fact that adequate clinical trials are lacking in this area. ADRs have a major impact on healthcare system by increasing financial burden on society. In India, Ramesh et al. estimated the cost associated in treating all reported ADRs to be Rs 76,564 (US \$1595), with the average Rs. 690 (US \$15) per ADR (12).

The information regarding reporting of ADRs may be useful in identifying and minimizing preventable ADRs. Pharmacovigilance is the programme conducted worldwide to report various adverse reactions occurring due to drugs that are already being marketed.

In the present study, 61% male and 39% female children had ADRs. These are comparable to the study done by Murthy SN et al, where 59.52% males and 40.48% females had ADRs.¹³ In the present study, out of total (102) reported ADRs, 13 (12.7%) were of less than 1 year, 44 (43.3%) were of 1-5 years age group, 28 (27.4%) were of 6-10 years age group and 17 (16.6%) were greater than 10 years. This indicates that occurrence of ADRs were more common in children less than 5 years age. This is similar to a study done by Digra et al.¹⁴

In the present study, the dermatological system was found to be involved in 45.1% patients. Similar observations were made by Digra et al, and Priyadharsini et al, who reported rashes as the major presentation of ADR in 67.30% and 37% patients, respectively.^{14,15}

In the present study, antibiotics were responsible for (36.3%) of the ADRs, whereas anticonvulsants contributed to (18.6%). In India, antibiotics are used commonly, so this might be the reason for this class to appear as major class responsible for causing ADRs. These observations are consistent with the studies done by Reena V et al, Priyadharsini et al, and Arulmani et al, reported antibiotics (68%), (67%) and (33.5%) as the most common drug class implicated respectively.¹⁵⁻¹⁷

WHO defines an adverse event following immunization (AEFI) as a medical incident that takes place after an immunization causes concern, and is believed to be caused by the immunization. The goal of vaccine pharmacovigilance is the early detection and timely response to adverse events following immunization. Vaccines contributed to 14.7% of all ADRs in the present study. Lymphadenitis, injection site abscess, injection site rash and injection site induration and urticaria were the ADRs produced with vaccines. BCG, DPT, MMR, pentavalent and MR vaccines were the vaccines involved in producing ADRs. Another study by Staltari O et al, on vaccines reported 3.9% ADRs were probably related to vaccination.¹⁸ Three cases of serious ADRs (severe lymphadenitis) were reported with BCG vaccine and an episode of convulsions with DPT vaccine were reported.

According to WHO causality assessment, 70.6% were assessed as probable and 29.4% were possible in nature. The causality assessment of ADRs has a pivotal role in drug development as it establishes a causal relationship with the drug. Present study observations were consistent with the other studies who reported 80%, 76.56%, and 62.2% of ADRs as probable by Priyadharsini et al, Reena V et al, and Arulmani et al.¹⁵⁻¹⁷

The present study documented 52% ADRs as moderate, 43% ADRs as mild and 4.9% ADRs as severe in nature which was consistent with the studies carried out by Ramesh M et al, Shamna et al, and Singh et al, who reported 47%, 63.26% and 35.7% of ADRs were moderate in severity.¹⁹⁻²¹ In the present study, five cases were recognized as severe type. A single case of Steven Johnson syndrome was reported with phenytoin. Other Serious ADRs include severe lymphadenitis with BCG vaccine and an episode of convulsions with DPT vaccine. These cases recovered eventually. There were no cases of death reported due to ADRs.

CONCLUSION

ADRs were reported more among under 5 years of age. The present study highlighted antibiotics as the main therapeutic drug class causing ADRs. Clinical spectrum ranged from the more common reactions like rash to severe Steven Johnson syndrome requiring immediate management. The present study has provided insight into the burden of ADRs in paediatric patients of GGH, Guntur. The awareness and sensitisation programmes regarding spontaneous reporting of ADRs among health care professionals should be considered and improved.

Detection and prevention of ADRs at the earliest is very important, as they not only reduce morbidity and mortality but also prevent the health care cost in their management. Information acquired through ADR reporting may be useful in identifying and minimizing preventable ADRs and augmenting the knowledge of the prescribers to deal with ADRs more efficiently and effectively.

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Ethical approval: The study was approved by the Institutional Ethics Committee and from Indian Pharmacopeia Commission, Ghaziabad, Uttar Pradesh, India

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