Pediatric pharmacovigilance in an institute of national importance: Journey has just begun

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Abstract:
OBJECTIVE: The objective of this study is to determine the nature and severity of adverse drug reactions (ADRs) in pediatric patients. 

MATERIALS AND METHODS: In this retrospective cohort study, we extracted the data from all the available pediatric ADR forms submitted to ADR monitoring center (AMC) from May 2014 to December 2016. The data including nature, frequency, causality (World Health Organization [WHO] causality scale), and the severity (Hartwig and Siegel scale for severity) of ADR were extracted. We also assessed the preventability of the event on modified Schumock and Thornton scale of ADR preventability. 

RESULTS: There were a total of 20 pediatric ADRs reported during this period. Nearly two-thirds of the ADRs occurred in patients who were receiving multiple drugs (polytherapy). Antimicrobial agents were the most commonly implicated drugs. The most common ADRs were skin rash (maculopapular, erythematous, and urticaria, itching, etc.). The severity and preventability scales indicated that most reactions (18/20) were moderate in nature and all were preventable. Four reactions were “certainly” and ten ADRs were “probably” related to the suspected drug as determined by the WHO causality assessment. 

CONCLUSION: Frequency of ADR increased with number of medications patient was receiving. Health-care providers (HCPs) involved in the care of children must be aware of this fact and should use additional drugs when absolutely necessary. They should be involved in pharmacovigilance program by exchanging and updating each other through sharing constructive information, communication, and education concerning the appropriate use of drugs in children. Pediatric pharmacovigilance is the need of the hour and should be given utmost importance for monitoring the safety of drugs in children. Motivating HCPs for voluntary reporting of ADRs for preventing the morbidity and mortality in this vulnerable population could be of immense importance. 

Keywords: Adverse drug reactions, antibiotics, polytherapy, preventability, severity

Introduction
The World Health Organization (WHO) defines “adverse reactions as harmful and unintended responses to a drug and which occur with doses normally used in humans for prophylaxis, diagnosis or treatment of a disease or modifying a physiological function.”¹ Adverse effects are usually encountered in both

How to cite this article: Sharma PK, Misra AK, Gupta N, Khera D, Gupta A, Khera P. Pediatric pharmacovigilance in an institute of national importance: Journey has just begun. Indian J Pharmacol 2017;49:390-5.
across the country where the information is collected from multiple sources and reported as per standard operating procedure guidelines. The data collected are entered and reported to National Coordination Centre (NCC) through Vigiflow Flow, Version 5.3, (Uppsala Monitoring Centre, Uppsala, Sweden). The aim is to identify and estimate the extent of the problem associated with drug use. Further, efforts are directed to improve the reporting by sensitizing health-care providers (HCPs) to the need of pharmacovigilance to identify and timely reporting of ADRs.

Children are more at risk of having ADRs because many drugs which are prescribed to this population have been marketed with limited or no experience of their efficacy and safety. There are only very few clinical trials which have focused on the efficacy and safety of drugs involving children. Systematic reviews and meta-analysis of drug surveillance in children have shown that the incidence of ADRs could be as high as one in every ten children exposed. The actual incidence may be even higher as the majority of ADRs are either unrecognized or not reported by the health professionals. Therefore, it is the duty of the regulatory authorities to remind health professionals, especially pediatricians about the importance of their contribution toward pediatric pharmacovigilance for safer use of medicine in children. Special care should be given to childhood diseases and disorders that may be qualitatively and quantitatively different from their adult equivalents. This might, in turn, affect the benefit or the risk of therapies. Pediatricians should also be aware that the use of “off-label” drugs, a common practice adopted by pediatricians, increases the risk of ADRs. They should not only pay attention to drugs that are used off label but also to drugs which have clinical studies supporting their safety and efficacy. Thus, an active drug surveillance system is needed to capture drug-related risk information in children.

The aim of the study was to determine the nature and severity of ADRs in pediatric patients based on ADRs received from the Department of Pediatric to our AMC established under PvPI at All India Institute of Medical Sciences (AIIMS), Jodhpur, Rajasthan, India.

**Materials and Methods**

AIIMS, Jodhpur, is an institute of national importance established under Pradhan Mantri Swasthya Suraksha Yojana and is in establishing stage. This is a retrospective cohort study and all the ADRs reported by the department of pediatrics to AMC from the month when AMC was established, i.e., May 2014 to December 2016 were retrieved and analyzed. The ADR form is a simplified version of the Central Drugs Standard Control Organization adopted by the center to facilitate reporting by the HCPs. The HCPs either fill the ADR forms themselves or inform the AMC telephonically. The collected Individual Case Safety Reports (ICSR) are analyzed for patient demography, causality, severity, and preventability of the event. All the ADR reports were verified for their occurrence and crosschecked for completeness by the coordinator, AMC. If deemed necessary, the reporting physician or the parents are contacted and the required information is elicited and captured in the ADR form.

ADRs were classified on the basis of Anatomical and Therapeutic Classification System (ATC 1999). Causality assessment of ADRs was done by causality assessment scale proposed by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO), which classify suspected ADRs as certain, probable, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable. The severity of the ADRs was assessed by modified Hartwig and Siegel scale which gives an impression of the severity of ADRs and tags it as mild, moderate, or severe. Preventability of the ADRs was assessed by modified Schumock and Thornton scale. This scale of preventability classifies ADRs as definitely preventable, probably preventable, and not preventable. Descriptive statistic was used to summarize the data on nature and the frequency of various ADRs.

**Results**

From a total of 20 pediatric patients (aged between 3 months and 17 years), ADR reports were received by AMC until December 2016. The patients who had ADRs, 85% were males and 15% were females. Children <6 years of age (50%), developed more ADRs compared to the higher age group [Figure 1]. Among children <6 years of age, almost two-thirds of them were infants. Polytherapy accounted for more than two-thirds of the ADRs received. The classification of ADRs by

![Figure 1: Distribution of patients according to age group](image_url)
Anatomical and Therapeutic Classification System (1999) showed antimicrobial agents (60%) as the most common drug group involved. Commonly associated agents were vancomycin, meropenem, and ceftriaxone in order of significance [Table 1]. Besides antimicrobial agents, drugs that were involved were from different therapeutic classes [Table 2]. The skin was the most commonly involved organ (80%), and the common manifestations were in the form of rashes and urticaria. Most reactions were moderate (80%) in nature and the remainder being mild as assessed by modified Hartwig and Siegel scale for severity [Figure 2]. Assessment by modified Schumock and Thornton scale of ADR preventability showed that all the ADRs were preventable [Figure 2]. Majority of the reactions were related “probably” to drugs as determined by causality assessment.

Discussion

A total of 20 pediatric ADR reports were collected in AMCs during this period. The use of multiple medications accounted for nearly two-thirds of the ADRs. Antimicrobial agents were the most commonly implicated drugs causing ADRs. Skin is the most affected organ system with common manifestations of rash (mostly maculopapular, erythematous, and urticaria), followed by one each of seizure, dystonia, dryness of mouth, facial edema, and itching. The severity and preventability scales indicated that most reactions (90%) were moderate in nature and all were preventable. Ten ADRs were “probably” related to the suspected drug as determined by the WHO causality assessment.

ADR in the pediatric population is an important health problem. [12] There has been an increase in the incidence of drug-related adverse events, morbidity, and mortality in the pediatric population, and the overall extent of the drug-related events is considerably high. Studies done in the community confirm that at least one in every 500 children will experience an ADR every year. [13] In our study, nearly half of ADRs occur in the age group of 0–6 years, out of which more than two-thirds occurred in infants. The reasons may be due to immature drug metabolizing organ system in newborn and infants that put them at a higher risk of developing an ADR. [14] This is in the correlation with some studies that confirmed that age is also a significant factor that correlates with ADR incidence. Moore et al. [15] conducted a study which also supports the notion that child age had an influence on the incidence of ADRs.

As per results obtained, the potential predictor of adverse events in children was polytherapy. Fattinger et al. suggested an association between a number of drugs received by children and the increased risk of ADRs. [16] Children receiving polytherapy are in general experience up to a threefold higher incidence of ADRs compared to monotherapy because of increase drug-drug interactions or also due to immature drug-metabolizing organ system. [17]

Studies that have been done worldwide estimated that cutaneous ADRs occur in nearly 2.5% of children treated with any drug but frequently with an antimicrobial agent (12%) although the reaction was rarely considered serious. [18] This is in concordance with our observation where antibiotics were the major drug group associated with the ADRs, and cutaneous lesions were the most common manifestations. Although the study analyzed a small number of ADRs and does not warrant such conclusions but it is worth mentioning.

Our study has assessed three different parameters of an ADR, namely the causality, severity, and preventability. The WHO causality assessment scale indicated that 50% of the reactions were “probable” which showed a clear temporal relationship to drug administration and improving on withdrawal of treatment. Furthermore, it cannot be completely ruled out that sign and symptoms of the disease may sometimes simulate as an ADR in these susceptible patients. On the severity scale, most of the reactions were of moderate grades which warrant stopping or changing of the drug. Preventability scale showed that all ADRs were preventable.

AMC was established right from the inception of clinical services and is actively involved not only in collecting ADR data from the hospital but also spreading awareness about the need and importance of pharmacovigilance. This is achieved by sending weekly reminder E-mails; regular sharing of drug safety alerts, newsletter, other advertising materials, running animations on TV panels in inpatient (IPD) and outpatient department (OPD) areas, prescription sheets including patient-centered message emphasising the need for reporting ADR, distributing pamphlets, and sensitization sessions to
| Age/sex       | Primary diagnosis                          | ADR                          | Ongoing drugs                                      | Suspected drug   | Severity | Causality | Preventability |
|--------------|--------------------------------------------|------------------------------|----------------------------------------------------|-----------------|----------|-----------|----------------|
| 15 years/male| Diabetes mellitus with cellulitis          | Erythematous rash           | Amoxicillin/clavulanic acid, piperacillin/tazobactam and carbimazole | Vancomycin       | Moderate | Possible  | Preventable    |
| <1 year/male | Erythematous rash                          |                              | Multivitamins, Vitamin D                            | Meropenem        | Moderate | Possible  | Preventable    |
| 3 months/female| Acute diarrhea with pyrexia               | Facial edema                 | Paracetamol, ondansetron                            | Meropenem        | Moderate | Probable  | Preventable    |
| 8 years/male | Bronchial asthma with exogenous obesity    | Maculopapular rash           | Fexofenadine                                        | Budesonide       | Moderate | Probable  | Preventable    |
| 17 years/male| Pneumonia                                  | Erythematous rash            | Piperacillin/tazobactam, paracetamol, and folic acid | Vancomycin       | Moderate | Probable  | Preventable    |
| 14 years/male| Dengue fever with colitis                  | Dryness of mouth             | Ondansetron, pantoprazole, and paracetamol         | Hyoscine         | Moderate | Certain   | Preventable    |
| 8 years/male | Bronchial asthma with enteric fever        | Urticaria rash               | Paracetamol, ondansetron, and budesonide           | Ceftriaxone      | Moderate | Certain   | Preventable    |
| 5 years/female| Yolk sac tumor left ovary                  | Hypersensitivity reactions   | Ranitidine, metoclopramide, dexamethasone, and mannitol | IV contrast      | Moderate | Certain   | Preventable    |
| 2 years/male | Urinary tract infection                    | Erythematous rash            | Calamine lotion, cotrimoxazole, hydroxyzine and Zytee Gel (Choline Salicylate (9% w/v), Lidocaine (2% w/v)) | Amoxicillin + clavulanate | Moderate | Probable  | Preventable    |
| 1 year/male  | Pneumonia                                  | Urticarial rash              | Paracetamol, hydroxyzine and hydrocortisone        | Vancomycin and meropenem | Mild     | Possible  | Preventable    |
| 8 years/male | Ewing sarcoma                              | Dystonia                     | Dexamethasone, ondansetron, hydroxyzine, etoposide, mesna, ifosfamide, and ranitidine | Metoclopramide   | Moderate | Probable  | Preventable    |
| 5 years/female| Febrile neutropenia                        | Erythematous rash            | Ondansetron, ibuprofen, calcium/Vitamin D and allipurinol | Ceftriaxone      | Moderate | Probable  | Preventable    |
| 6 years/male | Phimosis                                   | Tonic–clonic seizure         | Cefotaxime, tramadol, midazolam, and diclofenac, Haloperidol | Haloperidol      | Moderate | Certain   | Preventable    |
| 1 year/male  | Pleural effusion with pyrexia              | Erythematous rash            | Ceftriaxone, dexamethasone, and paracetamol         | Vancomycin       | Moderate | Probable  | Preventable    |
| 7 years/male | Pyrexia                                    | Papular rash                 | Paracetamol and levofloxacin/ornidazole            | Ibuprofen        | Mild     | Probable  | Preventable    |
| 15 years/male| Pain abdomen                               | Erythematous rash            | Pantoprazole, ondansetron, and multivitamins        | Tramadol         | Moderate | Probable  | Preventable    |
| 17 years/male| Common cold                                | Itching                      | Hydroquinone/mometasone/tretinoin                   | Cetirizine, pseudoephedrine, and paracetamol combination | Moderate | Possible  | Preventable    |
| 16 years/male| Cellulitis                                 | Itching                      | Pantoprazole, diclofenac sodium/serrapeptase        | Vancomycin       | Possible | Probable  | Preventable    |
| <1 year/male | Hypotonia                                  | Erythematous rash            | Vancomycin, piperacillin/tazobactam, cetirizine, and paracetamol | Meropenem        | Moderate | Possible  | Preventable    |
| <1 year/male | Genitourinary congenital anomaly           | Erythematous rash            | Desonide lotion, hydroxyzine, hydrocortisone/fusidic acid cream | Cefotaxime       | Possible | Probable  | Preventable    |

Scales used - Severity=Hartwig and Siegel scale, Causality=WHO causality scale, Preventability=Modified Schumock and Thornton scale, WHO=World Health Organization, IV=Intravenous, ADR=Adverse drug reaction
HCPs and paramedical staff. In addition, the Patient Safety Pharmacovigilance Associate makes a regular visit to OPD and IPD. The collected ICSR was analyzed for patient demography, causality, severity, and preventability of the event. All ADRs were submitted to NCC through “VigiFlow” software.

An important limitation of the study is a fewer number of ADRs that have been reported probably reflecting inadequate workforce, lack of time, and misinformation. Most of the time, pediatricians/physicians usually have misinformation that adverse events that are already known and which have a causal relationship with the offending drug are not to be reported.\(^{19}\) The rechallenge test was not done in any case due to medical and ethical issues.

Ignorance on the part of the faculty in the initial 1st year regarding how to report and no awareness about pharmacovigilance could have also contributed to under-reporting.\(^{20}\) In our country, due to the low ratio of doctor to patient, most of the events are not reported due to lack of time, low motivation, ignorance, and lethargy despite regular reminders through E-mails and short message services. In spite, having trained medical professional in our country, sometimes, doctors are hesitant to report because they fear litigation and think reporting might go against them.\(^{19}\) We expect that in the near future, the reporting of ADRs will improve as the faculty strength of the institute increases.

**Conclusion**

We may conclude that polytherapy probably is the major contributory factor in causing ADRs in children. Many of the patients, in fact, visited pediatric outpatient due to the problem of ADRs and were receiving more than one drug at the time of visit. Physicians should give polytherapy only when necessary, and the maximally tolerated doses of monotherapy are ineffective. It is necessary to amplify active monitoring system and encourages more drug safety initiative by health-care providers to facilitate safe and effective medication in children. Pediatricians, clinical pharmacologists, and other HCPs involved in the care of children must all be involved in pharmacovigilance program by exchanging and updating each other by constructive information, communication, and education concerning the appropriate use of drugs in children.

The methods for ADR detection, evaluation, and monitoring should be strengthened, especially for the pediatric population as many of them may not directly communicate and one has to rely on parent description. The role of pharmacovigilance program in monitoring the safety of drugs in children should be evaluated for detection of newer and rarer ADRs. To improve spontaneous reporting of ADRs by HCPs, emphasis should be given to a regular educational workshop on pharmacovigilance. In addition, increasing awareness in general population to notify anything that they feel is unusual with medication use. The motivation for voluntary reporting of ADRs for preventing the morbidity and mortality in this vulnerable population could be of immense importance.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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