ADVERSE DRUG REACTION PATTERN IN HOSPITALIZED CHILDREN OF A SOUTH INDIAN TEACHING HOSPITAL

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Summary

Infancy and childhood is a period of rapid growth and development. Although important advances have been made in pediatric clinical pharmacology, there is still a dearth of information on many aspects of Adverse Drug Reactions (ADRs) in children.

The aim of the present study was to implement an ADR reporting and monitoring system in the department of pediatrics, to categorize and analyze the most common drugs and various predisposing factors attributed to the occurrence of ADRs, and to assess the causality of the same.

A six months period between November 2002 and April 2003. All children aged 0- 16 years and under drug treatment, hospitalized during the study period were included in the study. A clinical pharmacist was posted in the pediatric department. Different promotional activities were carried to increase the awareness of ADR reporting among the physicians. All the ADRs were reported and documented with the help of clinicians. Documented ADRs were accessed and analyzed for different parameters like incidence, age-related variation, attributed drug class, individual drug, type of reaction, probability, severity and the outcome of the ADRs.

All together 1161 patients were admitted during the study period. The number of ADRs reported was 17. The frequency of ADRs in these patients was 1.46%. The system most commonly affected was gastrointestinal (59%), hematological (12%), and the endocrine systems (12%). Prednisolone, aspirin, co-trimoxazole, erythromycin, L-asparaginase and vincristrine were the most common drugs associated with ADRs. Distributin of the ADRs according to the gender showed a female preponderance (1.4:1). According to causality, 65% of the ADRs were regarded as probable, 29% as possible and 6% as definite as per the WHO causality assessment scale. Most of the ADRs were moderate (46%), 42% were mild and 12% were severe as per the Hartwig etal scale. In most of the cases suspected drug was withdrawn. Most of the patients were recovered from the ADRs whereas 18% of the patients had their ADR continuing at the time of the study.

ADRs were not common in pediatric patients, and most of them were usually mild in severity. Gastrointestinal system was the most frequently associated system and the commonly involved drugs were antibiotics and analgesics.

Key words: Adverse drug reactions, Causality assessment, Pediatrics, Severity assessment

Introduction

Drugs no matter how safe and efficacious are always coupled with inescapable risk of Adverse Drug Reactions (ADRs). ADRs are a cause of significant morbidity and mortality in patients of all arenas of healthcare today. It has been estimated that from one third to as high as half of ADRs are believed to be preventable. Cost of morbidity due to drug related event was estimated to be USD 76.6 billion [1]. The World Health Organization (WHO) defines an ADR as a response to a drug which is noxious, unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function [2].

The incidence and severity of ADRs can be influenced by patient related factors like age, sex, disease, genetic factors another drug related factors. Infancy and childhood is a period of rapid growth and development. The various organs, body systems and enzymes that handle drugs develop at different rates and present a challenge to pediatrician, since drug dosage, formulations, response to drugs and ADRs vary throughout childhood. Al though important advances have been made in pediatric clinical pharmacology, there is still a dearth of information on many aspects of ADRs in children. The ADRs could produce new illnesses that slow the cure of the underlying illness and increase the cost of health. The frequency of ADRs in pediatric inpatients is reported to be between 5.6 and 16.8% [3].

There are some similarities between ADRs in adults and children. But there are special problems that are specific to children. For example tetracycline causing teeth staining, chloramphenicol causing grey baby syndrome etc are specific to children alone [4]. These defects make it difficult in extrapolating the ADR pattern of the adult to children thus making ADR monitoring in children mandatory. In general drugs safety is one of the neglected areas in developing countries like India. Most of the studies on ADR pattern in pediatrics are from the developed countries. There are only limited studies from India carried out in pediatric population [5,6]. Hence the present study was carried out.

Objectives: The objectives of the present study were to

1. implement an ADR reporting and monitoring system in department of Pediatrics of Kasturba hospital, Manipal

2. categorize and analyze the most common drugs and various predisposing factors attributed to the occurrence of ADRs in the study group

3. access the causality and severity of the reported ADRs

4. increase the awareness about ADR reporting and monitoring program among the healthcare professionals in the pediatrics department

Materials and Methods

Definition adopted: All ADRs considered into the study fulfils the WHO definition of ADRs. [2]

Study site: The study was conducted in the pediatric department of Kasturba Hospital (KH), Manipal. One of the pediatrics units, which is situated in the TMA Pai Hospital, Udupi was also included in the study. KH is a 1400 bedded tertiary care teaching hospital with different specialty and super specialty departments. It provides healthcare to all strata of people covering various parts of Karnataka State as well as people from the neighbouring states of Kerala and Goa.

Study type: Prospective, spontaneous reporting study.

Study duration: November 2002 to April 2003.

Inclusion and exclusion criteria: All the hospitalized children up to 16 years of age under drug treatment, during the study period were included.

Study tools: The following tools were used in the study.

ADR reporting form: This form was developed by the Department of Pharmacy Practice, Kasturba Hospital, Manipal.

ADR documentation form: This form was developed by the Department of Pharmacy Practice, Kasturba Hospital, Manipal.

Naranjo scale [7]: It was the scale used to carryout the causality assessment.

Hartwig et al. scale [8]: It was the scale used to carryout the severity assessment.

Operational modality: A clinical pharmacist was posted in the pediatric department. Different promotional activities were carried to increase the awareness of ADR reporting among the physicians. These activities included awareness notifications, which were placed in the wards and Out-patient departments (OPDs) and personal discussion with the clinicians. Promotion was also carried out by publishing ADR reporting related information in the Quarterly newsletter published by the Department of Pharmacy Practice.

The Clinical Pharmacists reported all the suspected ADRs by filling the ADR reporting form and documented with the help of clinicians in recognizing them and documented in the ADR documentation form.

The filled ADR reporting form and the ADR documentation forms were accessed and analyzed for different parameters like incidence, age-related variation, attributed drug class and individual drug, type of reaction, probability, severity and the outcome of the ADRs.

Results: Altogether 1161 patients were admitted during the study period. The number of ADRs reported was 17. The overall incidence was 1.46%.

Purpose of visit: It was found that 2 patients visited the hospital due to ADRs. The remaining ere related to ALL (4), Respiratory tract infections (2), aplastic anemia (1), Arthritis (1), CMV (1), cervical adenitis (1), Diabtes (1), gastritis (1), Nephrotic syndrome (1), cardiac failure (1) and UTI (1).

Month wise distribution of the ADRs: The highest number of ADRs were reported in the month of November 6 (37%), followed by March 5(31%), January 3(19%) and December 2 (13%). There were no ADR reported in the months of February and April.

Classification of the ADRs: ADRs were categorized according to Wills et al classification. It was found that 9 ADRs belonged to the class U, 7 belonged to type A and 1 type H.

Gender wise distribution of ADRs: Seven (41%) of the ADRs were reported in males and the remaining 10 (59%) were reported in females. A female preponderance was observed in the study (1.4:1).

Age wise distribution of the ADRs: The distribution of ADRs based on the age group at which it occurs, demonstrated the highest incidence in patients between 4-8 years (34%) of age followed by 8-12 years (24%), 12-16 years (24%) and 0-4 years (18%) of age.

System involved in the ADRs: Gastrointestinal system was affected in 59% of the patients followed by blood (12.55), endocrine (12%), skin, bone and central nervous system (6% each).

Drug class associated with ADRs: Anticancer drugs and antibiotics accounted for 4 (23.52%) each of the total ADRs followed by corticosteroids and analgesics 3 (17.65%) each, antidiabetics, antiviral and immunosuppressants 1 (5.88%) each.

High risk drugs associated with ADRs: The association of ADRs with particular drugs is listed in Table 1.

Predisposing factors for the suspected ADRs: In 15 of the total cases, there were no predisposing factors. Intercurrent disease and allergy to the drug were found to be responsible in 1 each of the patients.

Management of the ADRs: In 9 (53%) of the cases, the suspected drug was withdrawn, in 7 (41%) no change was made in the drug therapy and dose reduction was done in 1 (6%) patient.

Outcome of the ADRs: Twelve (76%) patients recovered from the ADR, incase of 3 (18%), the ADRs were continuing at the time of the study and the outcome of 1(6%) ADR was not known.

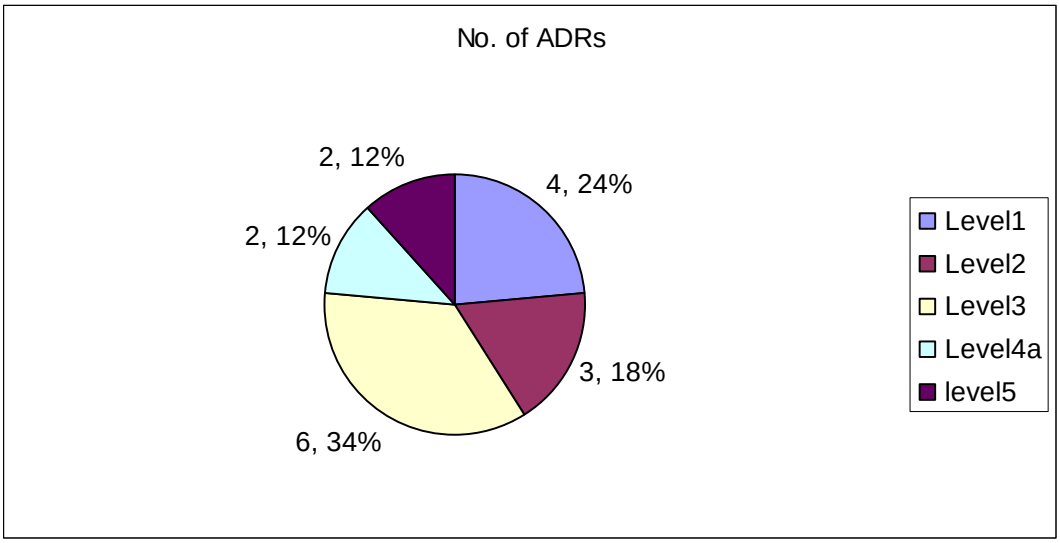
Causality assessment of the ADRs: The causality assessment of the ADRs as per the Naranjo algorithm revealed 13 ADRs to be probable, 3 to be possible and 1 to be definite.

Severity assessment of the ADRs: The severity assessment of the ADRs as per the Hartwig et al scale is mentioned in the Figure 1.

Table 1. High risk drugs and the adverse drug reactions

Adverse drug reaction	Suspected drug	Number of ADRs
Avascular necrosis	Prednisolone	1
Erythematous skin rash	Ibuprofen	1
Gastric irritation	Aspirin	1
Gastric irritation	Metronidazole	1
Gastritis	Cyclophosphamide	1
Headache	Co-trimoxazole	1
Hypoglycemia	Insulin	1
Neutropenia	Gancyclovir	1
Pancreatitis	L-asparaginase	1
Paralytic ileus	Vincristine	2
Tenderness	Co-trimoxazole	1
Thrombocytopenia	Gancyclovir	1
Vomiting	Metronidazole	1
Vomiting	Erythromycin	2
Weight gain	Prednisolone	2

Figure 1. Severity of the reported adverse drug reactions



Discussion

The present study evaluated the pattern of ADRs in the pediatrics departments in South India. The incidence of ADRs was 1.46%. This value is consistent with two Indian studies [5,6]. However, most of the studies conducted in different part of the world show a much higher incidence of pediatric ADRs [3,9,10]. The lesser incidence of ADRs in our study might be related to the prudent use of drugs in these patients.

In our study, female children had a higher preponderance to the ADRs. Another Indian study identifies a ratio of 1.2:1 (females:males) [6]. Some studies have shown a female preponderance [6,11] whereas other shows a male preponderance [3,12,13].

There is a wide range of discrepancies between the correlation of age and drug reactions in pediatric patients. Different studies showed different results. A study by Gonzalez-Martin G and coworkers in hospitalized pediatric patients has demonstrated an increase in ADRs with age [3]. Whereas Morales-Olivas et al has shown that age group of 1-4 has the highest incidence of ADRs [14]. An Indian study reported a higher incidence of ADRs among pediatric patients in the age group of 6-10 years [5]. In our study higher number of ADRs was seen in patients with the age group 4-8 years. The exact reason for this pattern is not known.

In our study a higher number of ADRs were related to the GIT (59%). Our finding is supported by Gonzalez-Martin G and coworkers [3]. In our study, anticancerous drugs and antibiotics accounted for a higher number of ADRs. Several studies have reported antibiotics as the most common classes causing the ADRs in pediatric population [5, 13, 14]. This is because antibiotics are the most widely used drugs in pediatric patients. In most of the cases of the ADRs, no risk factor was involved except is two cases where incurrent disease and allergy to the drug were found responsible. The management of the ADRs depends upon the type and the severity of the ADRs. In our case, in 53% of the cases, the suspected drug was withdrawn. In our case, 76% of the cases, the patients recovered from the ADR.

Carrying out the causality assessment using standard methods is one of the best ways to establish the causal relationship between drug and effect. The Naranjo algorithm [7] is used widely in carrying out the causality assessment of ADRs. It is based on the score calculated on the basis of points given for each of ten questions that comprises the table. On a scale of 13, if the score is greater than 9, then the adverse reaction is categorized as definitely caused by the particular drug. A score of (5-8) is categorized as probably caused by the drug while a score of (1-4) is categorized as possibly caused by the drug. In our case, 13 (76.47%) of the total cases, there was a ‘probable’ association between the suspected drug and the ADR.

In order to take appropriate initiatives towards management of the ADR, it is necessary to study the severity of the ADRs. Hartwig scale [8] is widely used for the purpose. This scale categorizes the reported adverse drug reactions into different levels as mild, moderate or severe based on the treatment and whether or not hospitalization was required for the management of the ADRs. In our patient, the ADR was found to be of moderate type. In our case most of the ADRs were mild in nature. However, two of the ADRs were of severe (level 5) suggesting that these ADRs required an intensive medical care.

Limitations: Since our study is a spontaneous reporting type, there can be good chances that some of the ADRs might have gone under noticed and hence not reported. Under reporting of ADRs is a well known limitation for the spontaneous reporting of ADRs. Our study has not included the OPD patients and hence cannot be generalized to the entire pediatric population.

Conclusion: Our study identified that ADRs were not common in pediatric patients and most of the ADRs occurred were mild in nature. Gastrointestinal system was the most commonly affected system and the commonly involved drug classes were antibiotics and analgesics. It was also found that dose related ADRs were common in children suggesting that a fairly good amount of ADRs can be prevented by using appropriate dose of the drugs in them.

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