ADVERSE DRUG REACTION CAUSING HOSPITAL ADMISSION IN CHILDHOOD: A PROSPECTIVE OBSERVATIONAL, SINGLE CENTRE STUDY

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ABSTRACT :

A serious ADR is any untoward medical cause at any dose: leads in death; is life threatening; needs or prolongs hospital admission; needs medical or surgical intervention to preclude permanent destruction of a body function or permanent damage to a body structure; is a congenital anomaly; or is any medical event that would be regarded as serious if it is not responding to immediate therapy. The aim of this study was to ascertain the incidence of ADR-related hospital admissions in children and to determine the proportion of the drug groups involved and the types of syndromes. Admissions were assessed in the hospital information system on a daily basis. The trail team gathered the following data from the case notes: age, sex, presenting complaint, clinical history, diagnosis and medication including OTC drugs taken previously. Suspected ADRs were eventually assessed in detail, and causality assessment was undertaken to determine whether each suspected reaction was unlikely, possible, probable or definite. The reactions classified as unlikely were excluded from the analysis. In our trail, females were identified as a statistically notable risk factor for ADRs. Causes for this elevated risk are not entirely clear but involved gender-associated differences in pharmacokinetic, immunological and hormonal elements as well as changes in the utilization of medicines by women likened with men. Women usually have a lean body mass, a decreased hepatic clearance, have changes in action of cytochrome P450 enzymes and metabolize medicines at different rates equated with men.

Key words: Intervention, immunological, cytochrome P450 enzymes

I.INTRODUCTION

The WHO defines an adverse reaction[1] as any noxious, unintentional and disagreeable effect of a drug which occurs at doses used in humans for prophylaxis, diagnosis or therapy. Adverse drug reactions (ADRs) are important cause of morbidity, hospitalization, increased health expenditure and even death[2,3]

Drug allergies are estimated to account for <10% of all adverse drug reactions, with drug intolerance accounting for the other 90%. ADRs usually predict risk from accepting the drug in the future and warrant prevention[4,5], specific therapy, changes of the dose regimen, or withdrawal of the product. They range from common irritant eruptions to rare, life-threatening drug-induced disorders. A serious ADR is any untoward medical cause at any dose: leads in death; is life threatening; needs or prolongs hospital admission; needs medical or surgical intervention to preclude permanent destruction of a body function or permanent damage to a body structure; is a congenital anomaly; or is any medical event that would be regarded as serious if it is not responding to immediate therapy[6, 7, 8]. The most common skin drug eruptions typically present as pruritus, maculopapular eruptions, urticaria, angioedema, phototoxic and photo allergic reactions, fixed drug reactions, and exfoliate lesions. These manifestations clinically resemble an allergic response and are considered drug hypersensitivity reactions (DHRs). Drug reactions can be solely restricted to the skin, or they may be part of a systemic reaction. Examples of systemic reactions include: toxic epidermal necrolysis (TEN); DRESS (drug reaction with eosinophilia and systemic symptoms; also called dry not life-threatening and recovery is rapid.

Adverse drug reactions (ADR) are rated as the fifth leading cause of death among all diseases. Approximately 5e8% of all hospitalization worldwide is due to ADR. Cutaneous adverse drug reactions (CADR) are the commonest ADR (30-45%) and responsible for about 2% of hospital admissions. Approximately 2-7% of these may be severe. In India,[9, 10] CADR account for 2e5% of all inpatients, while it affects 2.6% of outpatients. CADRs are defined as undesirable changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug. They range from minor exanthematous skin rashes to severe, life threatening ones like

Toxic epidermal necrolysis[11]. It can affect all ages and is a global phenomenon. Female sex, increasing age, more number of drugs, immunosuppressed patients and autoimmune disorders are implicated risk factors. We herein describe the common severe cutaneous adverse drug reactions (SCAR) seen in clinical practice[12, 13]. It is important that all medical fraternity be aware of these adverse reactions to correctly diagnose them at an early stage and prevent complications and thereby improve morbidity and mortality due to these conditions.

EPIDEMOLOGY:

Many studies have attempted to determine the incidence of adverse drug reaction in a variety of settings. The estimation of incidence vary widely and this reflects the methods used to detect and define suspected reactions. One of the key study is. In 1960s the Boston Collaborative drug surveillance program was pivotal in establishing the epidemiological basis of drug induced disease. Data were collected on over 50000 consecutive patients admitted to medical wards over a 10 year period, allowing much original research on the association between short term drug exposures and acute ADRs. In a interim analysis of 19000 patients monitored, the adverse reaction rate was 30%. Many ADRs were however, minor and it was concluded that drugs were remarkably non-toxic. Detailed analysis of the data provided much information on patient characteristics predisposing to ADRs and allowed some established adverse effect of drug such as excessive drowsiness with Flurazepam to be quantified.

The world health organization defines an adverse reaction as any noxious, unintentional and undesired effect of a drug which occurs at doses used in humans for prophylaxis, diagnosis or therapy. Adverse drug reactions (ADRs) are important cause of morbidity, hospitalization, increased health expenditure and even death. A meta-analysis found serious ADRs accounting for 6.7% of hospitalized admissions in USA. ADRs accounted for 0.7% of total admissions and 1.8% of total deaths in a South Indian hospital. Cutaneous ADRs (CADRs) are among the most frequent ADRs. Studies have found the incidence of CADRs in developed countries as 1-3%, while the incidence in developing countries is supposed to be higher between 2 and 5%. " ADR reporting leads to an increased general vigilance and may influence the recommendations for drug use through regulatory authorities

AETIOLOGY:

It is mostly caused by drugs (80-95%). The drugs commonly implicated are antibacterial, anticonvulsants, non-steroidal anti-inflammatory drugs and allopurinol. Rarely infections (especially Mycoplasma pneumonia), graft versus host disease (GVHD) and vaccinations have been reported to cause this condition. Risk factors include concomitant Human immunodeficiency virus (HIV) infection, radiotherapy, lymphomas, leukaemias and systemic lupus erythematosus. HIV patients are three times more prone to develop TEN compared to the normal population. Women are more affected than men for unspecified reasons (Clinical features

The aim of this study was to ascertain the incidence of ADR-related hospital admissions in children and to determine the proportion of the drug groups involved and the types of syndromes. To compare the results obtained by the use of three different scoring systems for ADR causality. To assess the causality (possible/probable/definite) of ADRs using three different algorithms

II.MATERIALS AND METHODS

STUDY TYPE: Observational.

STUDY SITE: Study is conducted at PRIME HOSPITALS (AMEERPET)

SAMPLE SIZE: 64 Subjects

STUDY DURATION: study will be of 8 months. From Dec 2016 to July 2017.

All patients younger than 19 years of age admitted to the Department of Pediatrics were included in the study. Surgical cases were included as well. This department is the only pediatric facility in the region. Admissions possibly caused by ADRs were further evaluated. The study period was from December 2016 to July 2017.

INCLUSION CRITERIA:

1. Age Younger than 19.
2. Cases were collected from IP; OP and Surgical cases were also included in the study.
3. 9-month period, including weekends and holidays, were prospectively screened.

EXLUSION CRITERIA:

1. Patients who were admitted because of intentional drug overdose were excluded.
2. Patients of age above 19 were excluded from the study.

METHOD:

The definition of ADR is 'an appreciable dangerous or unpleasant response, originating from an intervention associated to the use of a medical product, which predicts risk from future ingestion and warrants prevention or specific therapy, or changing of the dosage regimen or withdrawal of the product'. This definition was chosen because it describes only clinically notable ADRs that cause harm and involves the concept of preventive action. Sufferers who were admitted because of intentional drug overdose were excluded.

Admissions were assessed in the hospital information system on a daily basis. The trail team gathered the following data from the case notes: age, sex, presenting complaint, clinical history, diagnosis and medication including OTC drugs taken previously.

Suspected ADRs were eventually assessed in detail, and causality assessment was undertaken to determine whether each suspected reaction was unlikely, possible, probable or definite. The reactions classified as unlikely were excluded from the analysis. The assessment of causality in each patient admitted due to an ADR was performed using the Naranjo algorithm, the Liverpool ADR Causality Assessment Tool, an algorithm developed by Gallagher *et al*., and the Edwards and Aronson causality assessment method. Two investigators (PL and JV) independently assessed causality for all ADR cases using the above-mentioned algorithms. Agreement on the classification result between the two investigators was taken as accepted consensus. Where the investigators did not achieve consensus, a third investigator (KU) assessed the cases to decide on causality. The categories obtained by all three algorithms were compared.

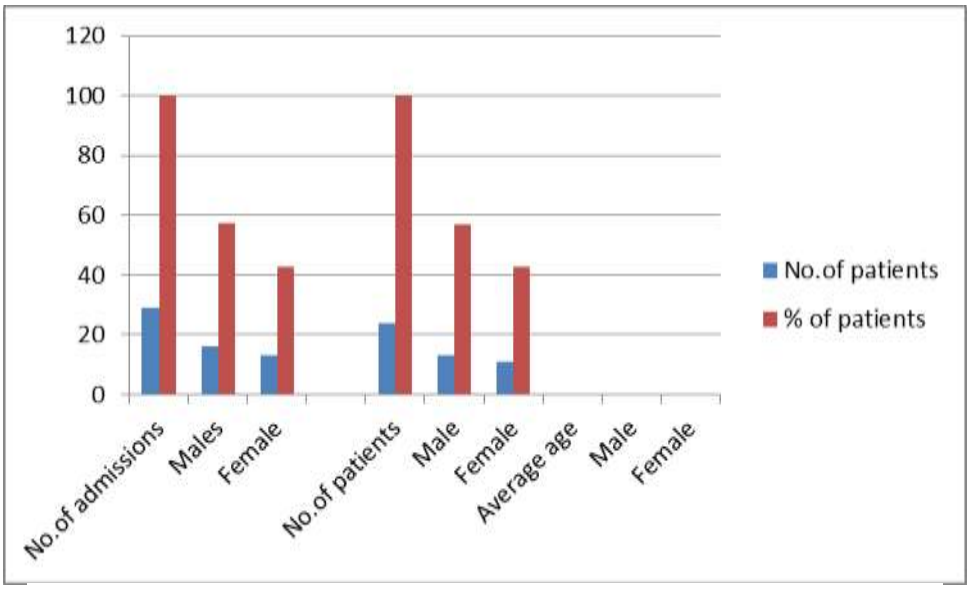
Analyses of ADR rates were based on the number of admissions with the rate expressed as the number of admissions caused by ADR per 100 admissions, together with 95% CIs. Multivariate logistic regression was used to calculate odds ratios (ORs) for possible risk factors for ADRs. Univariate analysis was conducted using the Mann-Whitney *U*-test for the evaluation of age-related ADR distribution. Frequency data were analysed by chi-square test.

III.RESULTS

Over the study period, there were 49 admissions (26boys and 23 girls). Some patients were admitted repeatedly and some of them had more than one ADR. The average age of the patients admitted was 7.1 ± 5.7 years (for demographic data, see table 1).

Table 1: Demographic data of the study cohort, age expressed in years

	No. of patients	**% of patients**
No. of admissions	29	100
Males	16	57.3
Female	13	42.7
No. of patients	24	100
Male	13	57.1
Female	11	42.9
Average age	7.1±5.7	
Male	7.0±5.5	
Female	7.2±5.9	



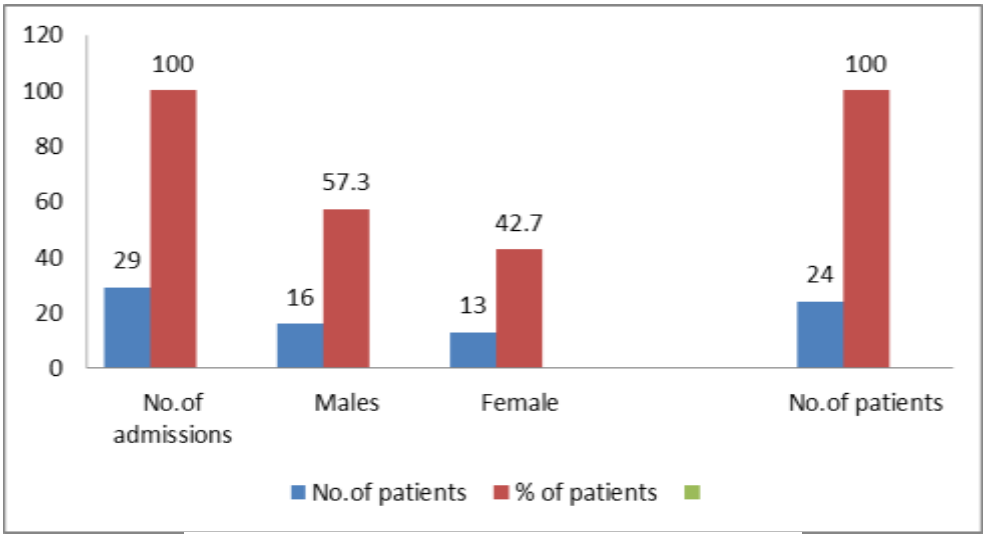
Graph.No.1: No. of patients according to admissions, gender and average

Sixty-four admissions (2.2%) were caused by the ADR (28 girls and 36 boys). This gives an incidence of 2.2 ADRs per 100 admissions. ADRs were divided into subgroups of drugs causing ADRs (fig. 1) and organ systems affected by ADRs (fig. 2). Twenty-eight admissions (43.1%) caused by the ADR were found in children suffering from oncological diseases. Sixteen of them were due to an infectious complication. Among the effects of anticancer chemotherapy, the most common ADRs were febrile neutropenia (12 admissions) and mucositis (five admissions)

The other aim of this study was to assess the causality (possible/probable/definite) of ADRs using three different algorithms. The results are shown in table 2.

Table 2: The probability of adverse drug reactions (ADRs) as assessed by the Naranjo algorithm, the Liverpool ADR Causality Assessment

	Naranjo	Liverpool	Edwards
Definite/certain	21	20	17
Probable	40	44	39
Possible	3	0	8
Total	24	24	24



Graph.No.2: Liverpool causality assessment scale

By means of multivariate analysis (table 3), female sex was identified as a statistically significant risk factor for ADRs ($p < 0.05$) as was oncological diagnosis which had an OR of 9.8 ($p < 0.001$). The effect of age was not significant. Univariate analysis showed that patients with identified ADRs were significantly older than those without, 6.3 and 5.7 years, respectively ($p < 0.05$); this difference was more pronounced in the non-oncological diagnosis group (8.7 *versus* 5.5, respectively, $p < 0.05$), but it was non-significant in the oncological patient group (6.1 *versus* 5.8, NS).

Table 3: Multivariate logistic regression analysis for risk factors for occurrence of adverse drug reactions (ADR) admission

	Odds ratio	95% cl for OR	p-value
Female	1.583	1.37,1.80	0.034
Age	1.030	0.99,1.07	0.101

IV.DISCUSSION

In a previously mentioned study, the top three drugs causing ADRs were phenobarbital, aspirin and phenytoin, all of which are now used in children much less because of safety concerns and better available alternatives . On the contrary, in the most recent study by Gallagher *et al.*[13], the absolute majority of ADRs were caused by anticancer drugs (44.2%). Substantially fewer ADRs were caused by corticosteroids (41%), NSAIDs (12.4%) and vaccines (8.8%). Our study shows a somewhat different sequence: anticancer chemotherapy caused 35% of the cases, followed by antibiotics (18%), immunosuppressant and vaccines (both 9%). Glucocorticoids caused 5% of the cases. NSAIDs were involved in two cases only; another two were caused by paracetamol, with all of them classified as antipyretics and accounting for 6%.

The majority of ADRs seen in our study occurred in patients with an oncological disease, a finding similar to that in the study by Gallagher *et al.*[13] Oncological patients are very often exposed to medications that cause ADRs, including febrile neutropenia, nausea, vomiting, thrombocytopenia and others, all of which require admission. These ADRs may be unavoidable. Although several trails have assessed a potential preventative strategy for neutropenia, no definite evidence presents about the utilization of granulocyte colony-stimulating factors to prevent such ADRs[14]

Antibiotics account for 18% of all admissions due to an ADR; 55% of them were caused by beta-lactams. Antibiotics are the most frequent drugs prescribed in children worldwide, and beta-lactam antibiotics are the most commonly prescribed group of antibiotics in children. In children managed with beta-lactams, skin rashes are often recorded. Such rashes are repeatedly assumed to be a drug-associated allergy, although viral infection is also often deemed in the differential diagnosis. It has been advised that most of these rashes are actually not allergic in origin. However, in clinical practice, the large majority of these children are labelled 'penicillin-allergic' without appropriate testing, mostly for fear of a more severe allergic reaction. This diagnosis often exists until adulthood. As a result, they may be denied the optimal antimicrobial therapy. Alleged penicillin allergies are likely to be treated with more toxic, broad-spectered and more expensive antibiotics, with effects on microbial resistance patterns and public economy as an outcome. [15, 16.]

The diagnosis of a beta-lactam allergy is usually determined by skin tests, and in the case of a negative skin test, an oral challenge test (OCT) is occasionally performed . One of the limitations of our study is that none of the patients underwent a skin test to confirm beta-lactam allergy. None of them underwent an OCT either. None of the skin ADRs caused by beta-lactams was assessed as definite/certain[17, 18], so we admit the possibility that some of the skin reactions may not have been due to beta-lactams.

Cyclosporine may be associated with a number of potentially serious ADRs. In this study, three different patients were admitted due to probable cyclosporine toxicity. One of the patients was treated for myelodysplastic syndrome (MDS), the treatment of which is based on immunosuppressive therapy that includes cyclosporine. This patient was admitted because of nausea and vomiting probably caused by toxic plasma levels of cyclosporine. The treatment with cyclosporine had been started 11 days before the admission, and the plasma levels were measured regularly. When the patient was admitted, the levels were higher than recommended (396 μg/l). Cyclosporine treatment was temporarily stopped and then administered in lower doses.

It is well known that cyclosporine has a narrow therapeutic window. In clinical practice, the pharmacokinetic profile can provide an indicator of the appropriate dose to obtain an optimal effect and to try to avoid an ADR. In children, there is a lack of conformation about the best schedule that should be adopted. Optimal strategies with the least toxicity remain to be determined. Cyclosporine plasma levels should be measured regularly, and therapeutic drug monitoring in cooperation with clinical pharmacologists might be the best strategy[19].

Steroid-induced hyperglycaemia, insulin resistance, diabetes mellitus, osteoporosis, anxiety, depression, etc., are among the most repeatedly recorded corticosteroid SEs. In the paediatric population, corticosteroids as well remain the key therapy responsible for medication-induced growth impairment. Although they can cause a number of severe ADRs, they are still considered as one of the most potent and consistently effective long-term treatments for a variety of conditions[20]

V.CONCLUSION

In our trail, females were identified as a statistically notable risk factor for ADRs. Causes for this elevated risk are not entirely clear but involved gender-associated differences in pharmacokinetic, immunological and hormonal elements as well as changes in the utilization of medicins by women likened with men. Women usually have a lean body mass, a decreased hepatic clearance, have changes in action of cytochrome P450 enzymes and metabolize medicines at different rates equated with men. Other important elements include conjugation, absorption, protein binding and renal excretion, which may all have some gender-related differences. However, how these differences shows an elevated risk of ADRs is not clear. Indeed, all these conditions can be present in child age. Trails focusing on these differences in children are almost entirely lacking.

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