Original Research Article

An intensive monitoring of adverse drug reactions in pediatric hospitalized patients of a tertiary care hospital

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ABSTRACT

Background: Children are at a higher risk of therapeutic failure due to major difference in pharmacokinetic, pharmacodynamics of drugs, off-label use and divergence of their illness from adult. The safety of drugs used in adult patients cannot be extrapolated to a pediatric age group. Hence, this study aimed to evaluate the incidence and overall pattern of adverse drug reactions in pediatric patients hospitalized in pediatric wards at a tertiary care hospital in India.
Methods: Pediatric patients up to 12 years hospitalized in two randomly selected pediatric units were enrolled and followed up daily till discharge. Detailed information of patients and ADRs (adverse drug reactions) if any were recorded from case records. ADRs were assessed for incidence, onset, duration, management, outcome, causality, severity, preventability, seriousness and risk factors. Appropriateness of drug treatment in patients with ADRs was analyzed using Phadke's criteria. Data was analyzed using student's t test, ANOVA and Chi square test.
Results: A total of 700 patients were enrolled (mean age 3.95±0.12 years). A total of 66 ADRs observed in 58 patients. Intravenous (70.4%) being most common route for ADRs. The incidence of ADRs was 8.28%. Majority of ADRs occurred within 1 day, commonly affected skin and appendages followed by (28.78%), GI (25.75%) ADRs were frequently associated with antimicrobials (69.38%) and vaccines and sera (12.24%). Majority of reactions were mild (56%%), non-serious (77.2%), not preventable (95.4%), recovered completely at discharge (83.33%) and had possible (77.2%) causal association with suspect drug. Age group 0-3 years and prescription of ≥5 drugs were risk factors for occurrence of ADRs. Semi rational drug therapy was observed in 65.5% patients.
Conclusions: Clinicians should be vigilant regarding occurrence of ADRs in pediatrics especially during the first week of hospitalization. Risk factors like 0-3 years of age and multiple drugs should be taken into consideration during treatment of these patients to help minimize adverse drug reactions.

Keywords: Intensive monitoring, Pediatric patients, Adverse drug reactions, Risk factors

INTRODUCTION

Pediatric patients are not small adults and so are more prone to develop altered responses to drugs.[1,2] Pediatric patients constitute a vulnerable group with regards to rational prescribing due to lack of adequate clinical trials.

Cost of the studies, responsibility and differences in regulations are major obstacles in performing of a clinic trial in children (Napoleone 2010).[2]

ADR is defined by WHO as a response to a drug that is noxious and unintended and occurs at doses normally used

in man for prophylaxis, diagnosis or treatment of disease, or for modification of physiological function.[3] Adverse drug event (ADE) is defined as any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with the treatment. Moreover, lack of many appropriate pediatric formulations, exposure through maternal, prenatal drug use and breast milk, major difference in pharmacokinetic, pharmacodynamics of drugs, off-label use and also divergence of their illness from adult make them precarious to high risk of ADRs.[4]

Spontaneous reporting plays a major role in the identification of safety signals but it captures only a small fraction of the adverse events that actually take place. Intensive hospital-based monitoring can be done by a group of doctors, nurses or others, screening a defined population which can detect incidence of ADRs and provide detailed and accurate information about type of ADRs, management, outcome, causal drugs and its association with risk factors.[4] Hospital is a complex organization which is treating very ill patient with multiple simultaneous drugs. Intensive hospital based monitoring consists of routine prospective recording of drugs administered throughout their hospital stay to detect ADEs whether or not any association between drugs and events.[5-7] This can shed light on their incidence, extensiveness and pattern of occurrence of ADRs in the local population.

Hence, the present study was conducted to evaluate the incidence, overall pattern of ADRs, associated risk factors, causality, preventability and severity of ADRs and cost of drugs used to treat ADRs in pediatric inpatients, using the intensive method of ADR monitoring.

METHODS

This prospective, observational intensive monitoring of ADR was conducted in pediatric hospitalized patients of two selected pediatric units of a tertiary care teaching hospital in Gujarat after obtaining permission from institutional ethics committee and head of department of pediatrics. The study was carried out over a period of 22 months in which all patients of either gender, up to 12 years and willing to participate in the study were enrolled after taking written informed consent from legally accepted representative (LAR) and informed assent if more than 7 years. Patients not willing to participate and those transferred to other departments after admission were excluded, except if they were transferred for management of an ADR. The two units were selected out of 5 units in pediatrics by convenient sampling method.

The investigator visited the selected units daily and monitored each patient enrolled as per inclusion and exclusion criteria till discharge or for the occurrence of ADR. Details were collected from case records and recorded in a pretested case record form (CRF). Attending doctors and nurses were also informed about the study and were requested to inform any ADR, if any. The patients

who developed the ADRs were monitored daily for the progression of ADRs. The patient who developed ADRs were analyzed for demographic characteristics, cost of drug treatment used for treatment of ADRs and appropriateness of therapy for the prescribed drug by Phadke's criteria.[8] Phadke's criteria assigns a prescription as rational, semirational and irrational. Rational (appropriate) prescribing is that which bases the choice of a drug on its effectiveness, safety and convenience relative to other drugs in a particular patient and takes cost into account only when the above criteria for choice have been satisfied.[8] An irrational drug or irrational drug combination means a drug not recommended in the standard textbook of pharmacology or other evidence-based source, an unnecessary drug or injection is a category of drug or formulation not recommended for that particular condition.[8] Phadke's criteria is a 30 point scale which ultimately 20 points are assigned to main drug and 10 to complementary drug/s. Half points (10 and 5) to the selection of drug and other half point to correctness of dose including route, frequency and duration. The ADRs were analyzed for seriousness, causality, severity and preventability.

Data analysis

Data were represented as frequency, percentages or mean±SEM wherever applicable. Statistical significance was analyzed using student's t test, ANOVA and Chi square test. P value of <0.05 was considered statistically significant. Adverse reactions were analyzed for causality using WHO-UMC scale [9] and Naranjo's score [10], severity using modified Hartwig and Siegel scale [11] and preventability using modified Schumock and Thornton's criteria.[9-12] Appropriateness of drug treatment was analyzed using Phadke's criteria.

Incidence of ADRs, gender, system organ classification of ADRs, occurrence of ADR during hospitalization (Day 1-4), recovered patients, drug groups responsible for ADRs, routes of drug administration responsible for ADRs, ADRs categorization, main drugs and complementary drugs, additional drugs to manage ADRs, causes of ADRs, suspect drug groups, causality, severity, preventability of ADRs were analysed as percentages. Age, comparison of routes of drug administration for ADRs was analysed using Chi square test. While duration of hospital stay, duration of onset of ADRs, time required for recovery of ADR was analysed using means. Onset of ADR compared with body system affecting ADR, time of recovery compared with system affected by ADRs was analysed ANOVA test.

RESULTS

The study aimed to intensively monitor ADRs in pediatric hospitalized patients at a tertiary care teaching hospital. About 19393 pediatric patients were admitted in the study duration of 2 years in 5 units. Out of them a total of 700

patients from 2 units were included in the study as per inclusion and exclusion criteria.

Of the 700 patients included 58 patients developed ADR out of which 33 (8.29%) were boys and 25 (8.27%) girls. 28 ADRs were observed in patients of 0-3 years (48.2%), 15 in 4-6 years (25.86%), 9 in 7-9 years (9, 15.51%) and 6 in 10-12 years (10.34%). The patients belonging to age range of 0-3 years suffered a greater number of ADRs as compared to those of age groups 4-6 years, of 7-9 years and 10-12 years but these difference was not statistically significant (Chi square test; p>0.05). The most common organ systems affected by the ADRs as per system organ classification were skin and appendages disorders (N=19, 28.78%), gastrointestinal system (N=17, 25.75%), body as a whole-general disorders (N=12, 18.18%) and central and peripheral nervous system disorder (N=10, 15.15%). While the other common system affected were respiratory system (5, 7.58%), immunological disorders (1, 1.52%), vascular bleeding and clotting (1, 1.52%) and application site disorder (1, 1.52%). ADRs affecting skin and appendages included itching in 8 patients, rashes 6 patients and redness seen in 5 patients. For ADRs affecting gastrointestinal system, diarrhea (11 patients) was the most commonly observed clinical manifestation followed by vomiting (6 patients). While for ADRs affecting body as a whole-general disorders, fever, sweating, weight gain were

commonly observed. ADRs affecting CNS were 10 which included convulsion (6 ADRs) and headache (2 ADRs).

The mean duration of hospital stay was 3.79±0.13 (mean±SEM) days in the patients who developed ADRs. The mean duration of onset of ADRs in hospitalized patients was 2.93±1.3 days (mean±SEM), 6 patients were admitted due to ADRs. 62.1% ADRs (41 ADRs) occurred within the first day of hospitalization, while 13 (19.7%) ADRs occurred during second day of hospitalization and seven (10.6%) ADRs occurred during third day of hospitalization. A total of 4 ADRs (6%) occurred during 4 or more days after hospitalization. When the onset of ADR was compared with the body system affecting the ADR it was observed that ADRs affecting body as a whole had late onset (days) as compared to ADRs affecting gastrointestinal system (days), central and peripheral nervous system (days), skin and appendages (days) and respiratory system disorders (days), but this difference was not statistically significant (p>0.05) (ANOVA). The mean time required for recovery of ADRs was estimated in patients who completely recovered (55, 83.33%) during their hospital stay and it was found to be 1.83±0.11 days (Mean±SEM). When the time of recovery was compared with system affected by ADR, the duration was significantly longer in ADRs affecting gastrointestinal system, compared to those affecting, body as a whole-general disorders (p<0.05, ANOVA).
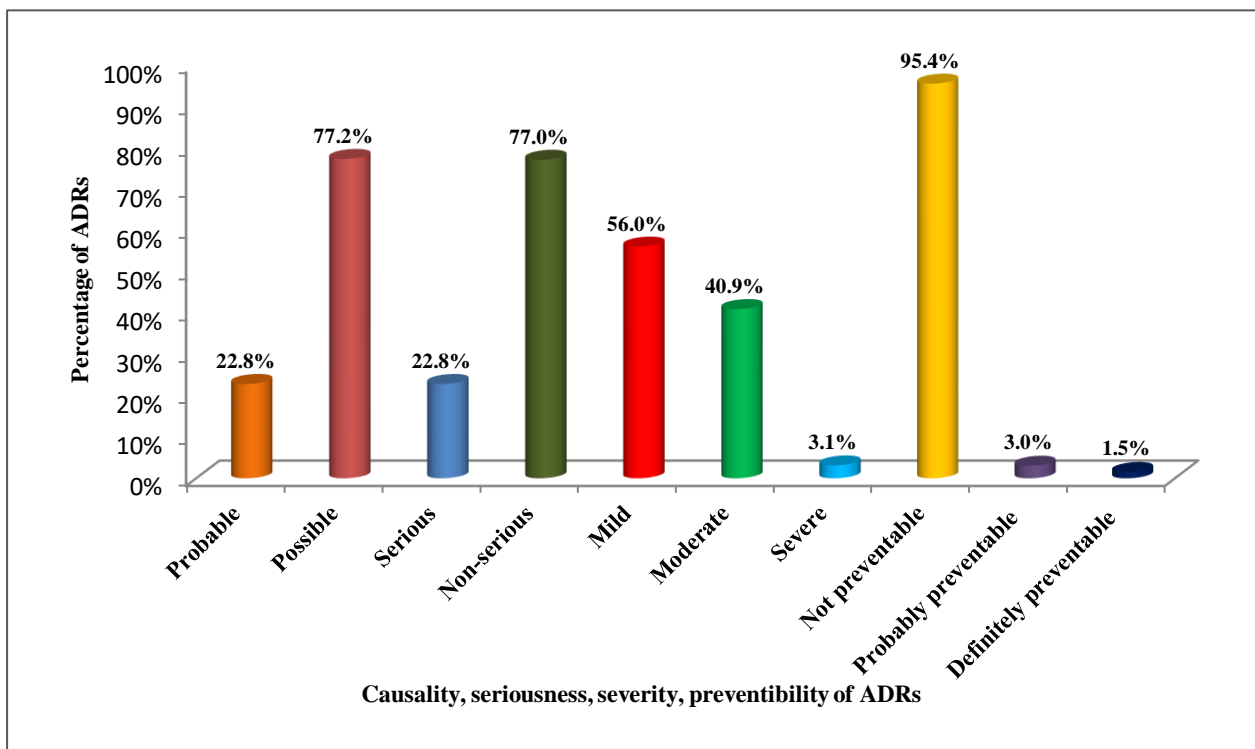

Figure 1: Causality*, seriousness, severity and preventability of ADRs (N=66) among pediatric hospitalized patients at a tertiary care hospital in India; (causality: WHO-UMC scale, severity: modified Hartwig and Seigel scale, preventability: modified Schumock and Thornton's criteria).
*=ADRs due to vaccines were excluded from causality analysis.

Table 1: Clinical manifestations of ADRs as per WHO system organ class (N=66).

WHO system organ class	Number of ADRs (%) (N=66)	Clinical manifestation	Number of ADRs
Skin and appendages disorders	19 (28.78)	Itching	8
		Rash	6
		Redness	5
Gastrointestinal disorders	17 (25.75)	Diarrhoea	11
		Vomiting	6
Body as whole-general disorder	12 (18.18)	Chills	3
		Rigor	3
		Fever	3
		Sweating	1
		Weight gain	1
		Swelling around lips	1
Central and peripheral nervous system disorder	10 (15.15)	Convulsion	6
		Headache	2
		Neuropathy	1
		Dizziness	1
Respiratory disorders	5 (7.58)	Breathlessness	5
Immunological disorders and infections	1 (1.52)	Anaphylactic reaction	1
Vascular bleeding and clotting disorders	1 (1.52)	Swelling at injection site	1
Application site disorders	1 (1.52)	Thrombophlebitis	1
Total	66		

Table 2: Drug groups suspected to cause ADRs in pediatric hospitalized patients.

Drug groups (number of drugs, % of suspected drugs)	Subgroup	Number of drugs prescribed (% of suspected drugs)
Antimicrobials (N=68, 69.38)	Antibacterial	63 (64.28)
	Anti-viral	3 (3.06)
	Anti-malarial	1 (1.02)
	Anti-amoebic	1 (1.02)
Vaccines and sera (N=17, 12.24)	Pentavalent vaccine	9 (9.18)
	Measles vaccine	2 (2.04)
	Intravenous immunoglobulin	1 (1.02)
	Anti-diphtheria serum	5 (5.10)
Drugs acting on blood (N=5, 5.10)	Packed cell volume	5 (5.10)
Drugs acting on central nervous system (N=2, 2.04)	Anti-epileptic	1 (1.02)
	Anaesthetics	1 (1.02)
Others (9, 7.50)	NSAIDS	4 (4.08)
	Corticosteroids	2 (2.04)
Total		98

Table 3: Drugs suspected to cause ADRs in pediatric hospitalized patients.

Name of drug (N=700)	Number of patients with ADRs (%)	ADRs according to system affected (number of ADRs observed)
Amoxicillin+clavulanic acid (N=284)	14 (4.92)	Skin and appendages disorders (6), gastrointestinal system disorders (7), respiratory system disorders (1)
Pentavalent vaccine (N=9)	9	Central and peripheral nervous system disorders (5)
Ceftriaxone (N=243)	9 (3.7)	Skin and appendages disorders (4), gastrointestinal system disorders (3), central

Continued.

Name of drug (N=700)	Number of patients with ADRs (%)	ADRs according to system affected (number of ADRs observed)
		and peripheral nervous system disorders (1), body as a whole-general disorders (1)
Vancomycin (N=28)	6 (21.4)	Skin and appendages disorders (5), gastrointestinal system disorders (1)
Anti-diphtheria serum (N=29)	5 (20.8%)	Skin and appendages disorders (4), immunological disorders and infection (1)
Packed cell volume (N=53)	5 (9.4%)	Body as a whole-general disorders (5)
Meropenam (N=22)	5 (22.8%)	Respiratory system disorders (2), skin and appendages disorders (1), gastrointestinal system disorders(1), vascular bleeding and clotting disorders (1)
Cefotaxime (N=108)	4 (3.7%)	Gastrointestinal system disorders(2), respiratory system disorders (1), body as a whole-general disorders (1)
Azithromycin (N=30)	4 (13.3%))	Gastrointestinal system disorders (3) skin and appendages disorders (1)
Paracetamol (N=570)	4 (0.7%)	Skin and appendages disorders (1)
Amikacin (N=21)	3 (14.2%)	Central and peripheral nervous system disorders (2), gastrointestinal system disorders (1)
Linezolid (N=20)	3(15%)	Skin and appendages disorders (1), gastrointestinal system disorders (1), respiratory system disorders (1)
Oseltamivir (N=18)	3 (16.6%)	Gastrointestinal system disorders (3)
Chloroquine (N=12)	2 (16.6)	Skin and appendages disorders (1), gastrointestinal system disorders (1)
Piperacilin+tazobactum (N=15)	2 (13.3%)	Gastrointestinal system disorders (1), Respiratory system disorders (1)
Prednisolone (N=21)	2 (9.5%)	Body as a whole-general disorders (1), gastrointestinal system disorders (1)
Measeles vaccine (N=2)	2 (100%)	Body as a whole-general disorders (1), gastrointestinal system disorders (1)
Levofloxacin (N=19)	2 (10.5%)	Skin and appendages disorders (1), respiratory system disorders (1)
Cefosulbactum (N=10)	2 (25%)	Skin and appendages disorders (1), gastrointestinal system disorders (1)
Ampicillin (N=36)	1 (2.7%)	Skin and appendages disorders (1)
Benzyl penicillin (N=16)	1 (6.2%)	Immunological disorders and infections(1)
Gentamicin (N=18)	1 (5.5%)	Skin and appendages disorders (1)
Ceftazidime (N=4)	1 (33.3%)	Skin and appendages disorders (1)
Thiopentone sodium (N=2)	1 (50%)	Skin and appendages disorders (1)
Albendazole (N=7)	1 (14.2%)	Gastrointestinal system disorders (1)
Erythromycin (N=2)	1 (50%)	Skin and appendages disorders (1)
Intravenous immunoglobulin (N=2)	1 (50%)	Central and peripheral nervous system disorders (1)
Phenytoin (N=36)	1 (2.85%)	Skin and appendages disorders (1)
Isoniazid (N=6)	1 (16.6%)	Respiratory system disorders (1)

Name of drug (N=700)	Number of patients with ADRs (%)	ADRs according to system affected (number of ADRs observed)
Rifampicin (N=6)	1 (16.6%)	Central and peripheral nervous system disorders (1)
Pyrazinamide (N=6)	1 (16.6)	Central and peripheral nervous system disorders (1)

Table 4: Risk factors for the occurrence of ADRs in pediatric hospitalized patients at tertiary care teaching hospital in India (N=700).

Risk factor	Number of patients with ADR	Number of patients without ADR	P value
Gender			
Male	33	365	>0.05
Female	25	277	
Age (in years)			
0-3	28	371	>0.05
4-6	15	114	
7-9	9	88	
10-12	6	69	
Number of drugs			
≥5	45	149	<0.05
<5	13	493	
Appropriateness of therapy			
Rational	20	414	<0.05
Semirational	38	228	
Irrational	0	0	
Malnutrition			
Normal weight	219	20	>0.05
Under weight	423	38	

A total of 98 drugs were suspected to cause 66 ADRs in 58 patients (Table 1). More than one drug was suspected to cause ADR in 31 (46.97%) patients. The most common drug group responsible for ADRs was antimicrobials (N=68 drugs, 69.38%) followed by vaccines and sera (N=12, 12.24%), ADRs were commonly associated with antibacterials (63 drugs, 64.28%) like amoxicillin with clavulanic acid, ceftriaxone and vancomycin followed by antiviral (3 drugs, 3.06%). For vaccines and sera, pentavalent vaccine (9 drugs, 9.18%) was commonly associated with occurrence of ADRs (Table 1). Intravenous route was most commonly associated with ADRs (N=69, 70.4%) compared to oral route (N=16, 16.32%), however, the difference was not significant (p>0.05, Chi square test).

Fifty five (83.33%) ADRs recovered during the hospital stay. ADRs which were recovering included diarrhoea (4), thrombophlebitis (1), convulsion (1), weight gain (1), dizziness (1), redness around skin (1) at the time of discharge from the hospital. Hospitalization was prolonged in 7 (10.6%) patients due to ADRs like breathlessness, diarrhoea, convulsion. A total of 23 out of 66 (40.9%) ADRs required withdrawal of suspected drugs. ADRs which required withdrawal of drugs were diarrhoea, hypersensitivity, breathlessness, convulsion for which associated drugs with these ADRs were amoxicillin with

clavulanic acid, ceftriaxone, anti-diphtheria serum, amikacin, meropenam. Dose reduction was required in one patient following occurrence of ADR. Death occurred in one patient due to anaphylactic reaction who was prescribed anti-diphtheria serum and test dose of benzyl penicillin diagnosed to have acute tonsillo pharyngitis with diptheria and suspected myocarditis. Seventy seven percent ADRs were non-serious, 56% mild in severity, 95.4% not preventable and 77.2% ADRs were possibly associated with suspected drugs (Figure 1). As per WHO-UMC scale 19 ADRs were probable, 47 were possible while as per Naranjo's scale 20 ADRs were probable and 46 ADRs were possible. ADRs due to vaccines were excluded from causality assessment.

Analysis for correctness of drugs was also carried out in patients with ADRs according to Phadke's criteria. Phadke's criteria include correctness of main as well as complimentary drugs along with correctness of their dosage form, strength and dose. Amongst the 58 patients who developed ADRs, 291 drugs (111 main drugs, 180 complementary drugs) were prescribed to them during their hospital stay. Out of 111 main drugs, 80 (72%) main drugs were correctly prescribed to the patients. While out of 180 complementary drugs only 144 (80%) drugs were correctly prescribed to the patients. The overall 76.9%

drugs were correctly prescribed to 58 patients who developed ADRs. The main drug was correctly prescribed in 28 patients out of 58 patients who developed ADRs with proper dose, formulation, duration as well as strength. Amongst the correctly prescribed drugs, 80 main drugs, 144 complementary drugs the dose, duration, formulation, and strength of the main drug as well as complementary drugs were appropriate. Out of 58 patients who developed ADR 38 patients received semi rational therapy. To identify the risk factors the patients who developed ADRs (N=58) were compared to patients who did not develop ADRs (N=648). There are several risk factors in pediatric population which can lead to development of ADRs. Age, gender, appropriateness of therapy, polypharmacy and malnutrition were analyzed as possible risk factors for occurrence of ADRs in this study. Age 0-3 years, prescription of ≥5 drugs, semi-rational therapy and malnutrition were identified as possible risk factors for occurrence of ADRs in these patients (Table 4). Analysis of cost of drugs to treat the ADRs was carried out in patients who developed ADRs. Additional drugs were required to manage the ADR in 40 (60.6%) out of 66 ADRs in 58 patients. These included use of drugs like, chlorpheniramine, paracetamol, zinc, oral rehydration salt, valproic acid, salbutamol, ondansetron. The overall cost of drugs used for the treatment of ADRs was ₹4040. In patients who required treatment for the ADRs, the average cost of drugs used to treat ADR per ADR was ₹101.

DISCUSSION

Children are considered as therapeutic orphan worldwide. Hence, they are at increased risk of therapeutic failure and ADRs continue to cause unnecessary disability and death among them. Despite efforts being made to reduce the incidence of medication related adverse events, the morbidity and mortality especially in pediatric population due to drug-induced reactions continue to be unacceptably high.[13]

The intensive monitoring of ADRs in pediatric patients was conducted to evaluate incidence, overall pattern, characteristics, management and risk factors of ADRs in pediatric inpatients at a tertiary care teaching hospital in Gujarat, India for a period of 22 months. A total of 66 ADRs were detected in 58 patients, which accounted for an incidence rate of 8.28%. ADRs were more frequent (48.2%) in patients of 0-3 years. The most common suspect drug group was antimicrobials (69.38%) followed by vaccines (12.24%). ADRs involving skin and appendages (28.78%) were most common in paediatrics, which included itching, rashes and redness. Withdrawal of suspected drug was required in 40.9% of cases. The mean time required for recovery of ADRs was estimated in patients who completely recovered during hospital stay and it was found to be 1.83±0.11 days. In 71.2% of cases, the suspect drug had a possible causal relation with the ADR, which was attributed to lack of dechallenge and polypharmacy. Of the 66 adverse reactions, 22.8% were serious, which either resulted in prolongation of hospitalization (10.6%) or required intervention to prevent permanent damage (4.54%). Risk factors identified in the study were polypharmacy, malnutrition, age group of 0-3 years and duration of hospitalization.

It was observed that the incidence of ADR detected in our study was 8.28% in pediatric patients hospitalized to pediatric wards. A study conducted in Germany found incidence of ADRs to be 9.2%.[13] A study conducted by Choonara et al and Martinez-Mir et al found 5.60% and 11.52% incidence of ADRs respectively.[14,15] In adult the incidence of ADR is 4.4% which shows that in the pediatric population the incidence is more as compared to adult. In our study, a little more preponderance to male (57%) for the development of adverse drug reactions was seen as compared to females (43%). A similar study done in pediatric patients where ADRs were more common in male patients (53%). A study conducted in India found that infants less than 1 year of age (60%) were more susceptible for ADRs.[3] It 24.13% ADRs were occurred in patients less than one year of age in our study. Delayed maturation of drug-metabolizing enzymes, lack of many appropriate pediatric formulations, exposure through maternal, prenatal drug use and breast milk and off-label use can also contribute to the greater number of ADRs in this age group.[1,4]

In our study, patients most commonly suffered from respiratory disease (28.57%) followed by infectious diseases (19.85%) and gastrointestinal disorders (12.28%). A study done by Eshetie et al found respiratory diseases while a study done in Germany in pediatric hospitalized patients found infectious and parasitic diseases followed by respiratory diseases as most common diagnosis during study period.[17] This difference may be due to the regional difference in disease pattern in country.

The average duration of hospital stay was 3.79 days. Though longer hospital stay was not found to have any statistical difference in patients who developed ADRs to those who did not, duration of hospitalization is an important risk factor for the occurrence of ADRs as longer hospitalization are exposed to greater number of medications and therefore have higher ADR incidence.[18]

Most common drugs prescribed included vitamins, minerals and nutritional supplement followed by antimicrobials, non-steroidal anti-inflammatory drugs, drugs acting on respiratory system and drugs acting on central nervous system. A significantly higher incidence of ADRs was observed in patients who received 5 or more drugs as compared to patients who received <5 drugs. A study done by Khan et al for adverse drug reactions in hospitalized pediatric patients noticed significantly higher number of ADRs in patients receiving more than 5 drugs.[19] We found that the use of multiple drugs is an important predictor of ADRs. This may be due to the additive risk of an ADR when receiving several drugs or due to drug-drug interactions. Efforts should be made to sensitize the

clinicians for the rational use of medicines as polypharmacy exposed the pediatric patients to unnecessarily a greater number of drugs and thereby more number of ADRs. Uses of multiple antimicrobials for empirical therapy should be minimized as much as possible and it should be only prescribed in appropriate conditions. The reason for intravenous route being most commonly involved with occurrence of ADRs was, intravenous was the most commonly used route for the prescribing drugs due to limitations of pediatric patients to take the drugs orally.

The most common adverse drug reactions seen in our study was diarrhoea (16.7%) followed by itching (12.1%) and maculopapular rash (9%). İn a study conducted in Nigeria in children, two most commonly reported ADRs were diarrhoea (51%) and skin rashes (18%) which is in concordance with our study.[20] A study from North India found maculopapular rash to be most common type of ADR.[21] Diarrhoea is a type A adverse reaction which is directly related to the pharmacological action of the drug. Antimicrobial like amoxicillin and ceftriaxone are commonly associated with adverse drug reactions like diarrhea and also these were the most commonly prescribed antibiotics, uses of this multiple antimicrobials in our study were responsible for the diarrhoea being the commonest clinical manifestation of ADRs.

The most common organ systems affected by the ADRs in our study were skin and appendages disorders (28.78%) and gastrointestinal system (25.75%). This findings matches with similar study done in pediatric patients where most common organ system involved was skin and appendages (91.5%).[16] In our study, skin reactions accounted for 28.78% of total ADRs which involved vaccine induced local site reactions (pain, redness and swelling), drug induced rashes and pruritus. A study conducted by Verma et al also found skin and appendages (37%) as the commonest organ system involved with ADRs followed by gastrointestinal system (30%).[22]

The most common suspect drug group was antimicrobials (69.38%) followed by vaccines (12.24%) and antitoxins drugs (5.10%) and drugs acting on haematological disorders (5.10%). A prospective study conducted by Martinez-mir et al noticed therapeutic group most commonly implicated was anti-infective drugs and vaccines which is similar to our findings.[15] Amoxicillin+clavulanic acid and ceftriaxone were widely prescribed antimicrobials in our hospital setup and the reason for more number of ADRs with these drugs. Pediatric patients are exposed to many vaccines like measeles vaccine, polio vaccine and pentavalent vaccines. These vaccines particularly pentavalent vaccines which is the combination of five vaccines (DPT+HepB+HiB) can lead to many ADRs like convulsion, fever, injection site reations. This fact is also reflected in our study where pentavalent vaccine was responsible for occurrence of ADRs.

Drugs were divided into high risk groups (analgesics, antiepileptics, antibacterial, immunosuppressants, antimycotics and corticosteroids for systemic use) and low risk group (others) according to drug class described in ATC (anatomical and therapeutic classification) by Rashed et al.[23] In the present study, antibacterial were suspected to cause 64.28% ADRs and analgesics were suspected to cause 4.08% of total ADRs, while antiepileptics were associated with 1.02% of ADRs.[23] Additional precautions should be taken while prescribing drugs from such high risk groups. Rational prescribing of drugs should also be promoted. Antimicrobials should be prescribed only when required and usage of multiple antimicrobials should be restricted.

In our study hypersensitivity reactions affecting skin and appendages occurred within the first day of hospitalization. As hypersensitivity reactions being type B reactions, starts early after taking suspected drugs and ADRs affecting skin and appendages can easily and rapidly identified which explains our finding of early onset of ADRs. Short duration (average 1.83 days) and recovery of ADRs during the hospital stay (83.33%%) suggested mild nature and effective management. Of note, ADRs affecting gastrointestinal system specially diarrhoea lasted for longer duration and contributed to increased duration of hospitalization. A longer time required for the recovery of normal gut flora could be the reason for longer duration of recovery of ADRs affecting gastrointestinal system.

According to WHO causality assessment, 19 (28.8%) ADRs were probable. The remaining 47 (71.2%) ADRs were possible. İn the possible cases, ADRs were due to two or more causal drugs associated with occurrence of ADRs. In a study by Mary et al causality was classified as definite (44.1%), probable (49.9%) or possible (6.0%) according to WHO criteria.[24] In our cases, rechallenge was not done so causality was not found in definite category. 56% ADRs were of mild severity in our study. A similar study done in Germany by Oehme et al (2012) found that 90.6% ADRs to be mild.[17] Out of total 66 observed ADRs, a total of 51 (77.2%) ADRs were non serious while 15 (22.8%) were serious. Serious ADRs required prolongation of hospital stay, intensive medical care and 1 ADR was responsible for death due to anaphylactic shock after administration of test doses of benzyl penicillin and antidiphtheria toxin. As antimicrobials like amoxicillin+clavulanic acid, cefotaxime, ceftriaxone amikacin, linezolid were the most commonly involved with the serious ADRs, additional care and monitoring should be carried out while prescribing these drugs. Withdrawal of drugs was done in ADRs like convulsion, hypersensitivity reactions etc to avoid further progression of ADRs. Judicious use of drugs particularly antimicrobials should be avoided as much as possible to prevent such serious ADRs. ADRs due to vaccines were excluded from causality assessment as it requires many details like vaccine product details like cold chain maintenance, method of administration, details of immunization error.

95.4% ADRs in our study were not preventable as hypersensitivity reactions, were not related to dose (type B reactions) hence not preventable. Our finding is in contrast to a study by Sai et al which reported most ADRs to be definitely preventable (61 as these were largely due to vaccines which were responsible for the mild injection site reactions and fever and hence were preventable.[16]

ADRs were significantly higher in patients who received semi rational therapy as compared to patients who received rational therapy (p<0.05). The reason for therapy to be fallen into semi rational category in our study was due to prescription of more than one antimicrobials with similar actions and polypharmacy. Additional drugs were required to manage the ADR and prolonged hospitalization which contributed to the increase the economic burden to the patient and healthcare system.

Various risk factors like prescription of ≥5 drugs, malnutrition, age group of 0-3 years, duration of hospitalization and semi rational therapy though not significant were found to be more in patients who had ADRs. Hence malnutrition and other risk factors like age and longer duration of hospitalization should also be considered for occurrence of ADRs in future studies.

It is highly imperative that more patients can be brought to record, if we explore for the incidence of ADRs with methods like intensive hospital based monitoring which will amplify the coherence of drug therapy and improve drug safety as well.

We found certain difficulties also during our study period. As this was an intensive monitoring, it required more time and efforts with daily visiting the pediatric wards for detection of ADRs and to monitor the course of ADRs found during surveillance. Our population was pediatric age group up to 12 years of age. Therefore, it was further difficult to interact with them and ask details about certain ADRs. We could include only 2 paediatric units for our study therefore we could not get the incidence of ADRs in larger population.

Our study results are important for the Indian scenario since few Indian studies have attempted intensive monitoring of adverse drug reactions in the paediatric population and moreover the study duration, regular follow up of patients and good number of sample size are positive features about our study. The observations and inferences of this study might help to prevent the undesirable drug effects and recommend measures for better and safer drug treatment in this vulnerable population. It is recommended that clinicians should be vigilant regarding occurrence of ADRs in paediatrics especially during the first week of hospitalization as large number of ADRs has occurred during the first week of hospitalization. Increase in number of drugs, semi rational therapy as well as long hospital stay has shown positive correlation with ADRs. Hospital policies about rational use of antimicrobials can also help to decrease the number of semi rational prescription of antimicrobials and hence decrease frequency of ADRs. Risk factors identified in study should be taken into consideration during treatment of these patients to help minimize adverse reactions and thus, prolongation of illness or hospitalization.

CONCLUSION

On the basis of this study, it is recommended that clinicians should be vigilant regarding occurrence of ADRs in pediatrics especially during the first week of hospitalization. Risk factors identified in study like polypharmacy, malnutrition, age group of 0-3 years and duration of hospitalization should be taken into consideration during treatment of these patients to help minimize adverse reactions and thus, prolongation of illness or hospitalization. Precautions should be taken while prescribing drugs from such high risk groups like antimicrobial agents and antiepileptics. We believed that the data generated from the study provides useful information regarding trends associated with adverse reactions in this population and will help to employ adequate preventive measures, to minimize the occurrence of ADRs in this vulnerable population. Further large scale studies involving patients admitted to other units like pediatric intensive care units is recommended to evaluate the overall pattern of adverse drug reactions in the pediatric population.

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