

DOI: <https://dx.doi.org/10.18203/2319-2003.ijbcp20205127>

## Original Research Article

# Adverse drug reactions or events in children with assessment of causality and severity: a retrospective analysis from Bhavnagar

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**Received:** 19 October 2020

**Accepted:** 19 November 2020

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### ABSTRACT

**Background:** Objective was to study the occurrence of adverse drug reactions in pediatric age group in a tertiary care hospital setting.

**Methods:** A retrospective study was undertaken to analyze adverse drug events in pediatrics wards of a tertiary care hospital. Any event marked as 'suspected adverse drug reaction' was included in the study and ADR forms were analyzed for causality and severity. Other parameters like age and sex, class of drug, types of ADR, commonly involved systems and polypharmacy were studied.

**Results:** Total 74 cases of admitted patients (13 deaths: 11 infants, 6 neonates) with severe ADR were studied of whom 39% were females. Antimicrobials were the commonest drug class (54%) with Skin most commonly involved. 77% cases were of probable category according to Naranjo's scale of causality assessment. 11% cases were prescribed polypharmacy.

**Conclusions:** Antibiotics were the class of drug causing maximum ADRs. The commonest system involved was skin. Redness, itching & rashes were the common symptoms. Antimicrobials should be used judiciously. Polypharmacy should be avoided. ADR reporting should be strengthened. Extra vigilance is required for infants and neonate's prescriptions.

**Keywords:** Adverse drug reaction, Adverse drug event, Children, Naranjo scale, Pharmacovigilance

### INTRODUCTION

An adverse drug reaction (ADR), also known as adverse drug event (ADE), is defined as any noxious, unintended and undesired effect of a drug which occurs at a dose used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions.<sup>1</sup> WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects; or any other drug related problems. ADR burden the health system by not only increasing the mortality & morbidity but also the expenses and length of hospital stay. Pharmacovigilance is used to identify, appraise, comprehend and avert ADRs with the eventual aim to develop secure and coherent utilization of medications.<sup>2</sup> It gives a measure of the

burden of drug induced morbidity. More than half of ADRs could be averted with better prescription care.<sup>3</sup>

Data in adults cannot be relied upon to predict ADRs in children. Some ADRs have shown exclusivity to pediatric age group. Recent examples of ADRs detected exclusively in the pediatric age group include: greenish discoloration of teeth following ciprofloxacin in neonates; gastric outlet obstruction due to prostaglandin infusion in neonates; fatal hepatic dysfunction following valproic acid in developmentally delayed, mentally retarded & children with congenital anomalies of less than 2 years of age; benign intracranial hypertension due to recombinant growth hormone therapy in children; isotretinoin causing depression in adolescents.<sup>4-8</sup>

The safety profile of a drug thus marketed with its testing done on adults can vary significantly when used in children.<sup>9</sup> Due to these difficulties ADR reporting is one method to get information regarding adverse drug reactions occurring in children based on which changes in dose adjustments, withdrawal of drug usage in children or other such measures may be undertaken to ensure safety.

### Aim and objectives

Aim and objectives were to analyze retrospectively ADR forms for studying its patterns, common drug classes involved, causality assessment (assessed by Naranjo's algorithmic scale) and severity and, orienting clinicians towards the ADRs occurring in pediatric age group and help them ensure optimal drug usage in children safely.

### METHODS

A retrospective analysis study was undertaken by reviewing the ADR forms from pediatrics department. Data was analyzed for the ADRs that were reported in the period of 1 year and 2 months interval (1 August 2015 to

30 September 2016). Discretion of information acquired was secured & confidentiality was maintained during the study.

### Inclusion criteria

Any undesirable and unintended event that was marked as suspected ADR and reported from inpatients between the ages 0-12 years.

### Exclusion criteria

Tuberculosis drugs, non-infectious adverse transfusion reactions (NIATR), blood transfusion reaction (BTR), and adverse events following immunisation (AEFI).

This was analysed as per Naranjo probability scale, (Table 1) as it is easy to apply, though it is not that sensitive or specific as to be called an excellent method of certainty. The Roussel Uclaf causality assessment method (RUCAM) is another scale for evaluating the likelihood that a medication has caused drug induced liver injury.

**Table 1: Naranjo ADR probability scale.<sup>10</sup>**

Question	Yes	No	Don't know	Score
Are there previous conclusive reports on this reaction?	+1	0	-	+1
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
Did the adverse event reappear when the drug was re-administered?	+2	-1	-	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	-	-1
Did the reaction reappear when a placebo was given?	-1	+1	-	+1
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	-	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	-	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1

Scoring:  $\geq 9$  Definite ADR, 5-8 Probable ADR, 1-4 Possible ADR, 0 Doubtful ADR

### RESULTS

Total 74 cases of ADRs were reported in the study duration of 1 year and 2 months, of which 61% occurred in males and 39% in female. More than one drug was prescribed in about 11% cases (polypharmacy). Class of drug causing ADRs, adverse effects, systems involved and severity of ADRs are as in Tables 2 to 4.

Antibiotics were the most common drug to cause adverse events as it is widely prescribed. Anti-convulsants was next as acute empiric therapy has to be followed by a long time (Table 2). Most adverse events were related to the skin and gastrointestinal system as expected, followed by

respiratory, blood, cardiovascular, thermal, and nervous system (Table 3).

**Table 2: Class or group of drugs.**

Drug class	N
Antibiotics	40
Anti-convulsants	18
Immunoglobulin	4
Antiviral	4
NSAIDS, steroids	4
Surfactant	4
Anti-emetic	3
Immunosuppressant	1

**Table 3: Adverse events (number).**

Symptoms/signs	N
Redness, itching, urticaria facial flushing, alopecia	18
Abdominal pain, distension loose stool, nausea, vomiting	17
Bronchospasm, shallow respiration pulmonary hemorrhage	9
Pancytopenia, thrombocytopenia blood in stool, hematuria	7
Anaphylaxis, shock	6
Fever, rigors,	5
Headache, eye pain, photophobia	4
Tremors, head nodding, hypotonia,	4
Edema face, eyelid; neck rigidity	4
Hepatitis	3
Metabolic, arrhythmia, weight gain*	6*
Lupus, hirsutism, acute kidney injury (AKI), gum hyperplasia #	4#

\*2 each, # 1 each

The gastrointestinal system was most commonly affected as opposed to the expected skin involvement, as this study looked at admitted patients and therefore serious condition and severe events where skin was not the only manifestation. No case of Steven Johnson syndrome or erythema multiform was there, probably due to high awareness leading to lesser use of sulpha or other drugs (Table 4).

**Table 4: System involved in adverse drug event.**

System	N
Gastrointestinal	22
Skin	19
Respiratory	17
Central nervous	10
Thermoregulatory	6
Blood	5
Genitourinary/ Renal	4
Cardiovascular*	4

\*Does not include anaphylaxis 6 cases.

**Table 5: Severity assessment.**

Seriousness of reaction	N
Hospitalization-initial or prolonged	39
Required intervention to prevent permanent impairment/ damage	11
Life threatening	14
Death	13
Disability	0
Congenital anomaly	0
Non serious-no intervention	7

Table 5 shows that according to Naranjo's scale (Table 1) of causality assessment, 77.3% cases were of probable

causality score, possible score was for 13.6% cases and 9.1% cases had definite score. This assessment merely shows the probability of occurring and does not mean cause and effect; but rather an association, whether strong or weak, between an adverse event and a drug or drugs.

Beside this, 13 (17 %) death associations were reported (Table 6). 83 % patients recovered.<sup>11,12</sup>

**Table 6: Association of adverse events with deaths.**

S. no.	Age	Drug	Complication
1	Neonate	Surfactant	Pulm haemorrhage
2	Neonate	Surfactant	Pulm haemorrhage
3	Neonate	Amikacin	Renal
4	Infant	NSAID	Bleeding
5	Infant	Phenobarbitone	Resp failure
6	3 years	anti-snake venom	Resp failure
7	Neonate	Midazolam	Resp failure
8	Neonate	Midazolam	Resp failure
9	Neonate	Midazolam	Resp failure
10	Infant	azithromycin iv	Cardiac arrest
11	Infant	Levetiracetam	Neutropenia <sup>11</sup>
12	8 years	Midazolam	Cardiac arrest <sup>12</sup>
13	Infant	Piperacillin	NEC

Out of 13 deaths only 2 were above 1-year-age, others were all neonates or infants <1-year age. We need to be more careful and vigilant while using drugs in first year and first month of life. And be on the lookout for ADR or an Adverse Event all the time with a high degree of suspicion.

## DISCUSSION

Higher incidence is found in males (61%). Contrary finding was depicted in a study where 67% females were found to be affected.<sup>13</sup> Number of drugs used increases the risk of ADRs. In our study we found 11% cases were prescribed more than one drug. A decrease in ADRs was noticed with decrease in number of drugs. Drug interactions may add up the adverse effects.

In one study it is reported that 30% of neonates receiving more than 10 drugs get no less than one ADR and, in our study, we found that all five (11%) neonates with ADR were receiving more than 4 drugs. Exponential rise of ADRs in neonates has been seen when exposed to four or more medications as also new-born and infants are at a higher risk due to immature metabolizing system.<sup>14</sup> However it is unavoidable sometimes in a neonate as sepsis markers are not well-defined.<sup>15</sup> It is recommended to avoid poly-pharmacy if it is not essential and to report the drug intake by each child to discover potential sources of heterogeneity between studies. As such it is a long-advocated practice to use drugs as judiciously as possible,

may it be the number of drugs or classes of drugs used. In our study antibiotics drugs were responsible for maximum of about 54% cases of ADRs, which has also been reflected in various studies. In India, antibiotics are used in a high number of prescriptions, so this may be one reason for this class of drugs to appear as major class responsible for causing ADRs. One study has reported similar findings; about 67% cases were because of antibiotics. Most of the drugs used in adult patients are not commonly used in pediatric age group such as anti-hypertensive, lipid lowering agents, anti-diabetics, etc. So, antibiotics were common class of drugs causing ADRs in children.

In our study anaphylactic reactions were seen in 8.4% of which antibiotics, sodium valproate and anti-diphtheritic serum were contributing, in contrast to one study in which antibiotics were the major group contributing to anaphylaxis.<sup>16</sup>

Also, fever, abdominal pain and respiratory depression altogether accounts for 18.3% of cases. Vomiting, nausea, diarrhea, chills and rigors were other common manifestations found apart from other ADRs. Skin was the most common system involved (28.2%) with next GIT (21.1%). Most of the pediatric studies frequently use Naranjo's algorithm for ADR assessment. It is simple and brief, its validity and reliability have been demonstrated in adults but not in children.<sup>10,17</sup> According to Naranjo's scale of causality assessment, in our study 77.3% cases were of probable causality score, 13.6% had possible score and 9.1% had definite score. Classification and evaluation of ADRs in terms of severity can recognize the root cause of ADRs and appropriate steps by healthcare providers can improve paediatric pharmacovigilance.

## CONCLUSION

Antibiotics were the class of drug causing maximum ADRs. The commonest system involve was skin. Redness, itching and rashes were the common symptoms. Thirteen deaths (11 infants including 6 neonates) had association with a potential ADE. Polypharmacy was seen with more reactions including in neonates.

Antimicrobials (including antibiotics) should be used judiciously. Polypharmacy should be avoided. ADR reporting should be strengthened.

## Recommendations

We need to strengthen the ADR monitoring, reporting and awareness programs. Avoidance of indiscriminate use of drugs especially antibiotics, polypharmacy, including in neonates and early recognition of ADRs will decrease associated morbidity and mortality and drug resistance due to suboptimal ADR reporting practices. As neonates and infants are a very high-risk group for deaths, we need to be vigilant for infant's prescriptions.

## ACKNOWLEDGEMENTS

We thank the pharmacology department for the guidance.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Gohil JR, Sarwad AB, Chauhan HR, Jasani JR, Gujarati HR. Adverse drug reactions or events in children with assessment of causality and severity: a retrospective analysis from Bhavnagar. *Int J Basic Clin Pharmacol* 2020;9:1883-7.