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# DETECTING AND ANALYZING ADVERSE DRUG REACTIONS IN HOSPITALIZED PEDIATRICS THROUGH INTENSIVE PHARMACOVIGILANCE PROGRAMME TO IMPROVE DRUG SAFETY

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## ABSTRACT

**Background:** Adverse Drug Reactions (ADRs) are the harmful, accidental and unwanted effect of a drug which occurs at the dosages used in humans for prophylaxis, diagnosis or therapy. The pediatric population is one of the most vulnerable groups to ADRs. The WHO Global Individual Case Safety Report (ICSR) database (VigiBase®) reported that the rate of ADRs in 7.7% in children was seen from 0 to 17 years. The aim of this study was to detect and analyze Adverse Drug Reactions (ADRs) in hospitalized pediatric patients through the Intensive Pharmacovigilance programme (IPvP) to improve the drug safety. **Methods:** A prospective cross-sectional study was performed in the pediatric hospital in Nellore in order to assess the hospitalized children from 1 day to 18 years old. Based on the inclusion criteria patients were enrolled. **Results:** From a total of 1083 hospitalized patients, 19 ADR's were recorded. The average age of patients in years was 7.2 (±5.9). The causality assessment in this study showed that most of the ADRs were probable (68.4 %) and 4 certain (8.2 %). The most severe ADR's found were hemolysis and toxic epidermal necrolysis. **Conclusions:** IPvP was an effective tool for ADR prevention, detection, and evaluation of the treatment in hospitalized patients. The intensive monitoring approach in pharmacovigilance amplifies ADR detection and this translates into the improvement of drug safety in children.

**KEYWORDS:** Adverse drug reaction, Intensive pharmacovigilance Programme, Drug safety.

## INTRODUCTION

By the World Health Organization, Adverse Drug Reactions (ADR's) was defined as "Any noxious, unintended and undesired effect of a drug which occurs at the dosages used in humans for prophylaxis, diagnosis or therapy".[1-3] Globally, the presence of ADR's has been increased, showing an incidence of 2.2 million in 1994[4-5] and 10 million in 2014.[6-7] In addition, the prevalence of hospital admissions for Drug-Related Problems (DRP's) has reached up to 28% in the US and the annual cost for this cause is estimated to 170 billion US dollars.[8]

The pediatric population is one of the most endangered group to ADR's.[9] The WHO Global Individual Case Safety Report (ICSR) database (VigiBase®), reported rates of ADR's in 7.7% in children is observed from 0 to 17 years.[10] However, these reports seem to show underestimated rates as other studies with a higher incidence of ADR's reaching >7000 serious or fatal ADR reports in children, mainly ≤2 years old, have been reported.[9,11,12] This susceptibility is due to different factors such as physiological immaturity which determines the changes in pharmacokinetic parameters. As a result, in the pharmacological response, dose modifications in pediatric patients should be calculated based on the weight, body surface area, gestational age, as well as liver and kidney function. Moreover, there is limited scientific evidence on the effectiveness and drug safety in the population since, the standardization of dosage strategies of many drugs is extrapolated from adults, and as a result, children are considered as therapeutic orphans.[11, 13-17]

There is a need to propose valuable methods that can detect the ADRs in an early phase in the pediatric population.[17] In order to reduce the global occurrence of ADRs in hospitals, some strategies have been implemented with the primary objective of diminishing ADR incidence or by reducing patient costs, such as

computerized systems, coded administrations, as well as computerized physician order entries, and clinical decision support systems. In spite of that the spontaneous reporting of possible drug cause adverse drug events.[11,18] While spontaneous reporting underestimates the incidence of ADR's and the use of computerized systems for monitoring provides the best results, there is no single best method to overcome it. However, the use of multiple strategies maximizes the quantification of ADR's.[19]

ADR's represent a significant health problem resulting in the altered therapeutic strategies, increased hospital stay, as well as higher morbidity and mortality rates, and elevated hospital costs. Intensive pharmacovigilance Programme (IPVP) is the systematic monitoring of the occurrence of adverse events resulting from the drug use during the entire length of prescription[1,3,20] and they are considered as a useful tool to prevent, identify, and treat preventable and non-preventable adverse reactions to medications. Furthermore, pharmacovigilance activities in the pediatric population have demonstrated to oblige the assessment of drug safety.[9,20]

However, in order to improve ADR detection, these activities need to be promoted in the hospital pediatric services. In hospitals, there is no specific data about ADR incidence in the pediatric population. Also, studies addressing ADR monitoring activities such as IPVP, are scared especially when related to hospitalized pediatric patients.

## METHODOLOGY

The aim of this study was to detect and analyze the Adverse Drug Reactions (ADR's) in hospitalized pediatric patients through Intensive Pharmacovigilance programme (IPvP) and to enhance the drug safety. A prospective cross-sectional pharmacovigilance study was conducted in the pediatric hospital in Nellore. This study was classified as "no risk"[21] so, only verbal consent was required from the parent or legal guardian of the child in order to participate in the study. For those patients who refused to participate in this study, they were still subject to the corresponding evaluations and treatments before any ADR suspicion. During the evaluation period, gender and reason for admission were asked with and the prescribed medication (indistinct drug group) during the hospital stay was noted. Informed verbal consent for suspecting ADR's and the implementation of relevant tools were obtained. The inclusion criteria were: all genders who are hospitalized with at least one prescribed medication (indistinct drug group). Follow up of the cases was done through medical visits, phone calls, or spontaneous reports. ADR suspicions were assessed with severity scales: Naranjo algorithm, Schumock & Thornton and Hartwig and Siegel. Exclusion criteria were: patients or patients representative declining the doctors prescribed medication given during hospital stay, those who do not answer the questions of verbal consent for suspected ADRs at the time of the interview to detect ADR's.

Initially, the ADR evaluator communicates with the medical team of the pediatric service (attending physician, medical resident, intern, nurse and head nurse). Every 24 h, a visit with each patient was performed. For new admissions, information was provided (including education and suspicions of ADR's). Patients were told to keep in touch with the attending medical personnel or by the evaluator in case of any suspected ADR's. For the identified cases, an assessment of suspected cases was performed by examination and review of the medical and nursing records. In the case of suspecting ADR's, we proceed to collect information and patients were invited to participate in the study. Once, the patient/caregiver/family member gave their verbal consent for the study, we proceed to conduct a review of the medical records to determine age, sex, diagnosis and the characteristics of the prescribed treatment (prescribed drugs, polypharmacy [≥3 drugs], indication, day and dose), affected organs or systems as well as the drug reaction (including severity and progression). Drug-drug interaction analyses were also performed and possible medication errors were evaluated (supra and infra-dose therapy, infusion rate, inadequate route of administration, etc.). After collecting the whole data, the Naranjo algorithm was used to determine the causality.[22,23]

To assess the severity and predictability of ADR's, the Hartwig and Siegel classification[24] and the Schumockn aand Thornton questionnaire[25] forms were used respectively to evaluate the adverse events through a series of questions. In the case of suspected ADR's the official format for suspected ADR's issued by the Federal Commission for the Protection against Sanitary Risks were filed. Once the report was finalized, it was forwarded to the responsible pharmacist of the hospital which in turn forwarded to the Hospital Pharmacy team for its evaluation and for the further corresponding internal registration.

To describe the drugs involved in this study, the Anatomical Therapeutic Chemical (ATC) Classification by the WHO[26] and for affected organs and systems, the System Organ Class (SOC) Classification, proposed by the Uppsala Monitoring Center[27] were used. The following variables were calculated:

1) ADR frequency (based on the total number of hospitalized children within the study period).
2) ADR incidence (ADRs observed in children in the total hospital length of stay in days during the study period × 1000).
3) Percentage of severity (calculated as the level of severity in all ADR's, starting at level 3 Hartwig and Siegel × 100).
4) Percentage of preventable ADR's (all ADR's reported as "preventable" by the algorithm Schumock × 100).[14]

Other results were analyzed using descriptive statistics, which means a measure of central tendency and standard deviation and a measure of dispersion for quantitative data, qualitative data were expressed in absolute frequencies, percentages, and ratios. Results are expressed as averages and percentages. The whole data were analyzed using the Chi-square test or U Mann-Whitney test and p-value <0.05 was considered as significant.

## RESULTS

A total of 1083 hospital admissions were recorded in the study group, the characteristics are shown in Table 1. The male: female ratio was 1.3:1. Registered patients were classified into 2 groups whether they were younger or older than 1 year. The mean age (± SD) observed for all patients was 4.3 (± 0.52) years. A total of 1517 diagnoses were recorded during the study period and the most representative groups were respiratory (457; 30 %) and neurological (161; 11 %), including one obstetrics and gynecology case of asymmetric intrauterine growth restriction.

**Table 1: Pediatric population distribution by age group (<1 year and ≥1 year).**

| Variables | <1 year (age in months) | ≥1 year (age in years) | General [mean (±SD)] |
|---|---|---|---|
| Age | 0.72 (±0.52) | 14.0 (±10) | 4.3 (±0.5) |
| Gender (male/female) | 281/161 | 343/298 | 624/459 |
| Weight (kg) | 11.6 (±7.0) | 49.4 (±35.8) | 61.0 (±42.8) |
| Hospital stay (days) | 11 (+19) | 8 (+12) | 9 (+14) |
| **Diagnostic Group** | | | |
| Respiratory | 272 | 185 | 457 |
| Neurology | 42 | 119 | 161 |
| Blood and Hematopoietic | 67 | 75 | 142 |
| Gastrointestinal | 46 | 86 | 132 |
| Genito-urinary | 27 | 105 | 132 |
| Infectious Disease | 62 | 39 | 101 |
| Development and Nutrition | 36 | 24 | 60 |
| Surgery | 17 | 39 | 56 |
| Legal-Medical | 19 | 18 | 37 |
| Dermatology | 07 | 29 | 36 |
| Soft tissues | 07 | 29 | 36 |
| Metabolic | 12 | 20 | 32 |
| Genetic | 18 | 14 | 32 |
| Head and neck | 12 | 16 | 28 |
| Trauma and Orthopedics | 07 | 16 | 23 |
| Cardiovascular | 06 | 10 | 16 |
| Autoimmune | 00 | 18 | 18 |
| Oncology | 00 | 14 | 14 |
| Toxicology | 00 | 03 | 03 |
| Obstetrics and Gynecology | 01 | 00 | 01 |

The drug delivery groups according to the ATC code are described in Figure 1. The most commonly prescribed drug classes were antibiotics (29.4%) and anti-inflammatory drugs (21%). A total of 19 ADR's were recorded, 18 children developed just one ADR during the hospital stay and 1 presented 2 ADR's with different time periods during the study evaluation (Table 2). The overall estimated incidence of ADR's in children was 17 per 1000 children. The mean age was 7.2 years (± 5.9) with a female predominance (63%). The incidence of ADR's in days was 1.8 per 1000 children days. The average hospital stay (without ADR's) was 9 (+14) days. Lastly, the average for concomitant medications was 3.7(± 2.7) and a significant association with the risk of ADRs ($p < 0.05$; Chi-square), was found.

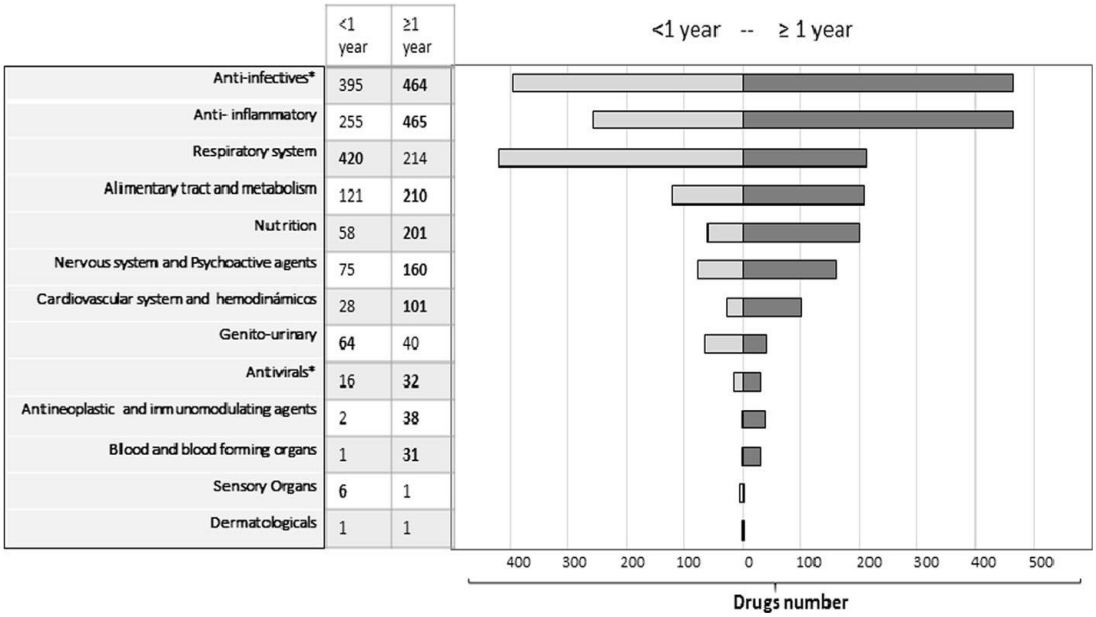


**Figure 1: Pharmacological drug distribution by age groups. In the ATC classification, the antibiotics and antivirals group are together, however, in this figure they are placed separately in order to observe patients of each group individually.**

**Table 2: Characteristics and classification of ADRs.**

| **Variables** | **General [mean(±SD)]** |
|---|---|
| Age (years) | 7.2 (±5.9) |
| Number | **19** |
| Concomitant medications | 3.7(±2.7) |
| Hospital stay (days) | 14 (+17)+ |
| **Naranjo [average points]** | 6.2 (±2) |
| 1–4 points (Possible) | 2 |
| 5–8 points (Probable) | 13 |
| ≥ 9 points (Certain) | 4 |
| **Schumock& Thornton Scale** | |
| Preventable | 4/19 (21%) |
| Not preventable | 15/19 (79%) |
| **Hartwig& Siegel [average level]** | 2.3 (±1.0) |
| Level 1 | **4** |
| Level 2 | **8** |
| Level 3 | **5** |
| Level 4 | **1** |
| Level 5 | **1** |

Considering AB as 1 of the most prescribed drug groups, we found a relationship between the number of AB prescribed with the ADRs reported. There was a high incidence of ADR's caused by antibiotics ($p < 0.05$; Chi-square). After that, we evaluated the relationship between the occurrence of ADR's and the 1st, 2nd, 3rd, 4th and 5th day of AB prescription and we only observed a significant difference in the third day of AB prescription ($p < 0.05$; Chi-square).

Based on the causality determined by the Naranjo algorithm, we observed 2 cases as "possible", 13 patients as having "probable" (68.4%) and 4 cases as having "certain" (21%) ADRs. These 4 cases were attributed to three antibiotics (amoxicillin, amikacin, and penicillin) and the anticonvulsant carbamazepine. The predictability of ADRs, determined by Schumock and Thornton scale was 20%. Hartwig and Siegel severity scale were predominantly in Level 2 (8 cases, 42%). In other words, discontinuation of the drug was required without the administration of an antidote, medicine or an increased length of hospital stay, with an average of 2.3 (± 1) days. The average stay of patients with ADRs in days was 14 (+17) and the percentage of total severity was 36.8%. Furthermore, we found a significant increase in hospital stay compared to the average hospital stay ($p < 0.05$). The more involved drug groups, according to the ATC code, included anti-infective (63%) and nervous system (15.7%) medications. Distribution of ADR's according to organs and systems was mainly skin and annexes (11

cases) characterized by rash and severe itching, followed by the nervous system (5 cases) portrayed by anxiety, headache, and drowsiness (Table 3).

**Table 3 Therapeutic groups and affected organs related to ADRs.**

| n = 19 ADR's | Symptoms | Total |
|---|---|---|
| **Pharmacological groups (ATC code-First level)** | | |
| Antiinfective (J) | | 12 |
| Nervous System (N) | | 03 |
| Blood and blood-forming organs (B) | | 01 |
| Sensory organs (V) | | 01 |
| Alimentary tract and metabolism (A) | | 02 |
| **Distribution by affected organs and systems** | | |
| Nervous system | Anxiety (2), headache(2), drowsiness (1) | 0 |
| Skin and annexes | Rash (9), intense pruritus (2) | 11 |
| Blood and blood-forming organs | Hemolysis (1) | 01 |
| Immunological system | Hypertension (2), hypotension (1) | 03 |
| Gastrointestinal tract | Fever (2), anaphylaxis (1) | 03 |
| Sensory organs | Diarrhea (1) | 01 |
| Muscle-skeletal system | Diplopia (1) | 01 |
| **General effects** | | |
| Paresthesia (1) | | 01 |
| General discomfort (1) | | 01 |

Nevertheless, we observed the appearance of diplopia (by carbamazepine), paresthesia (by diphenidol) and anaphylaxis (by metronidazole). These reactions did not require medical intervention. The most severe ADR's found were hemolysis (1 case) and toxic epidermal necrolysis (classified as skin and annexes, 1 case). For this 2 important severe cases, continuous monitoring was provided during their hospital stay until discharge, both without any consequences. We synthesize the most relevant findings when comparing the pediatric population "with ADRs" against those "without ADR's" in Table 4.

**Table 4 Comparison between pediatric patients with and without ADR's.**

| Variable | Without ADRs n = 1065 [mean(±SD)] | With ADRs n = 18 [mean(±SD)] | P - value |
|---|---|---|---|
| Age (years) | 4.3 (±0.52) | 7.2 (±5.9) | NS |
| Hospital stay (days) | 9 (+14) | 14 (+17) | 0.008 |
| Concomitant medications | 2.3 (±1.95) | 3.7(±2.7) | 0.001 |
| Number of prescribed AB | 0.78 (±0.03) | 1.3 (±0.40) | 0.001 |
| **Relationship with day of AB administration and ADR risk:** | | | |
| 1 day | | | NS |
| 2 days | | | NS |
| 3 days | | | 0.010 |
| 4 days | | | NS |
| 5 days | | | NS |
| 6 days | | | NS |

## DISCUSSION

A total of 19 ADR's were reported with an incidence of 1.7% in relation to hospital admissions. Our study was contrasted with Arulmani et al.,[28] who found an ADR incidence of 11.6%. In the pediatric group. Another study, Telechea et al.,[14] found an incidence of 19.5% in the pediatric intensive care unit. These differences in ADR incidence compared to our studies could be attributed due to ethnic, genetic and dietary factors. Others factors are the disease pattern, socioeconomic status, healthcare infrastructure and the detection method employed.[29] The IPvP monitoring of ADR's in our study, unlike the study by Arulmani et al., was able to discard those suspicions caused by DRP's. Furthermore, we found that the high incidence in the Telechea et al. study may be due to the small group studied in comparison to our study group.

The drug group with the largest number of ADR's was AB and 75% of these were classified as "certain". These findings are consistent with studies reported by Arulmani[28], Murphy, and Suh, even though the percentage caused by AB was higher in our group than those reported by others. For example, Hernández et al., demonstrated that 38% of ADR's were caused by AB in a study conducted in the IMSS (Mexican Institute of Social Security). Similarly, in the review by Ponte, 26.1% of ADRs were attributed due to antibiotics, surpassed only by cardiovascular drugs, which were absent in this study. Moreover, a significant incidence of

ADR's caused by antibiotics and their relationship with the third day of prescription found in our study highlights the importance that it must be given in the surveillance of these drugs, particularly in pediatric patients. Although the average severity of ADR's was "level 2", which establishes: "no increase in the length of hospital stay", there was an increased tendency in our study to favor the length of hospital stay in patients with ADR's compared to the average of all hospitalized patients. Furthermore, an increased length of stay may have an effect on the hospital's economy, described by P.Hernandez[32] as "dollar for dollar", generating an increase of those unscheduled resources in order to handle ADR suspicions.

Polypharmacy observed in this study included 3.7 (± 2.7) concomitant medications, potentially leading to increased risk of interactions or ADR's. Many studies have shown that polypharmacy is an important risk for drug-drug interactions and ADR's.[17, 35, 36] In our study we confirmed that the additive risk caused by the significant increase of ADR's with ≥3 drugs, especially with AB ($p < 0.05$), could be a predictor of ADR's.

The Naranjo algorithm is endorsed internationally as a tool of causality assessment of ADR's. However, it has limitations that hinder the clarification of suspicions and involve ethical implications. For example, it is necessary to perform placebo administration (which may be questioned by the patient's parent/guardian) or the re-administration of the suspected drug when the severity of the reaction is significant (hemolysis, etc.). As a result, a lower causality than expected is established. However, in most pediatric studies, the Naranjo Algorithm is preferred due to its simplicity. Nonetheless, the validity and reliability of this tool have been demonstrated in adults but not in the pediatric population.[9]

The pediatric population is one of the most vulnerable groups to present ADRs. Aagaard et al.,[15] in their review found that >40% of ADR's were seen in the patients aged 1–10 years and in our study we observed 79% of ADR's in this age group of 1–10 years. This increased tendency of ADR's could be attributed to admission diagnoses combined with an increased use of AB, concomitant medications, and an increased hospital stay. In addition, the age group of <1 year (≤ 1 year), we observed an increased susceptibility of the diseases of the respiratory system, urinary system and sensory organs (Table 1). This increased susceptibility could be the result of the pediatric immature immune system. However, further studies are required to clarify the increased rates of ADRs in patients of this age group.

The most affected organs or systems were skin and annexes, as well as the central nervous system (CNS) (Table 3). Our findings are consistent with several studies where a high percentage of clinical manifestations were related to this systems.[15,28]

The most important challenge encountered during the development of the study, was the lack of professional culture in ADR reporting, including the lack of suspicion when a suspected ADR's was present, in addition to the false belief that there are "expected" effects as well as the lack of knowledge in ADR reporting and analysis. These limitations are similar to those described by John et al., study emphasizing the importance of strengthening the education of health personnel in the clinical training of ADR reporting. During this process, we encountered some limitations of this study, described as "Inman's seven deadly sins" characterized by fear, indifference, greed, guilt, complacency, ignorance and timidity.

It is a fact that Pharmacovigilance will eventually develop a secure and coherent utilization of medications.[17] Furthermore, the implementation of IPvP increased the quality of the attention and showed an improvement in the evaluation of drug-related safety by the healthcare team, which was reflected in the overall enhanced patient care. Reasonably, this increased attention is equally reflected as an increase in the occurrence of suspected ADR's and other DRP's, which was well explained by Muehlberger et al., the monitoring of adverse drug reactions provided a higher incidence value in comparison with spontaneous reports. As a result, we have confirmed that pharmacovigilance monitoring of ADR's improved the evaluation and understanding of the drug related safety issues in our study.[9] There are several limitations that must be considered in terms of interpreting the findings of the study. For example, the short implementation period and the use of unlicensed or off-label medications in children was not considered as a potential risk factor in the analysis; another important limitation is the potential selection bias of those patients who did not provide their consent for the study and were not included in the analysis and lastly, the study was only conducted in one hospital and one service area.

## CONCLUSION

We found that IPvP in hospitalized pediatric patients allowed a careful observation of patients during their hospital stay, as well as an increased detection of DRP's and suspected ADR's. As a result, we were able to detect the frequency and the type of drugs which were related to ADR's. By this, we were able to give a rational environment and better patient care through this intensive Pharmacovigilance program.

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