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Pharmacovigilance in Pediatric Population

Roxana De Las Salas and Claudia Margarita Vásquez Soto

Abstract

Pharmacology in pediatric population has specific needs in pharmacovigilance. The lack of studies in children leads mostly to “off-label” prescribing and to an increased frequency of adverse drug reactions. Additionally, younger ages, male sex, prolonged and previous hospitalization, indication of antibiotics, and the number of prescribed drugs are factors associated with a higher risk of ADRs. Consequently, ADRs represent an additional burden of morbidity. This chapter will be focused on the most common adverse drug reactions in children (including infants and newborns), challenges, and new legislative tools in pediatric pharmacovigilance by using the World Health Organization global individual case safety report database (VigiAccess) and results from a Latin American study.

Keywords: adverse drug reaction, child, pharmacoepidemiology

1. Introduction

The safety of medicines in children is a worldwide problem, and the pharmacological characteristics of infants require a specific knowledge by health-care professionals. In other words, to care for children, more training and expertise are necessary. Likewise, the lack of clinical trials in which children are included and the off-label use of medications are determining factors for having more adverse drug reactions than usually. In ambulatory and hospital settings, it is necessary to have personnel with training in taking care of children.

Pharmacovigilance (PV), as was mentioned in the other chapter, “is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem” [1]. It is also proper to ensure that PV was born recently with the thalidomide disaster, with effects on children.

Considering the abovementioned, this chapter shows the main concepts of pharmacovigilance applied to the pediatric population and gives an idea of the main safety concerns of drugs used in the neonatology and pediatric wards and the most frequent adverse reactions. On the other hand, this adds new legislative tools in pediatric pharmacovigilance.

2. A brief history of the beginning of pharmacovigilance in pediatrics

The first example of a safety issue that led to a pharmacovigilance reflection was published in the British Medical Journal in 1877 by chloroform issues. The second problem happened in 1898 with the commercialization of diacetylmorphine, named

as heroin, which started to be addictive at the beginning of the 1910s (500,000 dependent patients reported only in the US) [2]. In 1937, the use of diethylene glycol to solubilize sulfanilamide, without any toxic test previously studied, with a series 34 children deaths from kidney failure (of 103 cases) [3]. The third one was at the beginning of the 1950s (1954), diiododiethyl of tin was added to Stalidon®, a topical skin product, resulting in 102 cases of deaths associated with encephalopathy, and a hundred patients developed severe, irreversible, neurological aftereffects [2].

During the 1960s, many children were born with phocomelia and agenesis of the limbs as a side effect of thalidomide. Thalidomide was marketed in 1957 as an over-the-counter (OTC) hypnotic/sedative and a safe drug, later used in order to manage nausea in pregnant women. In 1961, Widukind Lenz, a German geneticist, linked the serious effects to the use of thalidomide during a congress. This was later confirmed in the same year by William McBride, who established a 20% of rise in phocomelia and agenesis of the limbs malformation. The results were more than 12,000 cases of teratogenic effects in children (not only limbs malformation) [2].

In response to the thalidomide disaster, the World Health Organization (WHO) formerly established its Program for International Drug Monitoring in 1968. In 1978, it is founded the Uppsala Monitoring Centre, a WHO collaborating center created in order to support the mentioned program.

Therefore, a new era of pharmacovigilance was initiated by children's big issues related to teratogenic effects. In other words, PV was born as a result of a disaster in children.

3. Key concepts of pharmacovigilance in pediatrics

According to the World Health Organization (WHO), an adverse drug reaction (ADR) is “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function” [4].

In Spain, the pharmacovigilance system defines an ADR as any harmful and unintentional response to a medication. It not only includes harmful and involuntary effects derived from the authorized use of a medicine in normal doses but is also related to medication errors and off-label terms of the marketing authorization, including misuse, overdose, and abuse of the drug [5]. Terms such as side effect, adverse effect, undesirable effect, and collateral effect are synonymous of ADR.

The variability among pediatric population is associated with higher susceptibility for ADRs. Considering this, whenever there is an ADR, it is necessary to take into account not only the weight, height, and information of the medication but also the exact age of the child. For that reason, it is important to know the pharmacological differences in infants, as shown in **Table 1** [6, 7].

3.1 Challenges of pharmacovigilance in pediatrics

Despite international authorities' efforts to stimulate the notification of adverse drug reactions (ADRs), under-reporting is still quite common [8]. In part, this happens due to the voluntary notification system mainly. Other reasons could be related to problems with the ADR diagnosis, work overload of staff, and possible conflicts of interest [9]. Thereby, the most important challenges in PV are focused on those issues.

Despite the European Medicines Agency, Pharmacovigilance Risk Assessment Committee (PRAC) has a pediatric Committee (PDCO) that revise “all aspects of the risk management of the use of medicinal products”; and generate

Physiologic characteristics	Characteristics
Absorption	
Gastric pH	Lower bioavailability of weak acid drugs Higher bioavailability of weak bases
Gastrointestinal motility	Delayed absorption
Percutaneous absorption	Higher bioavailability
Muscle absorption	Variable (unknown)
Distribution	
Body water	Higher volume of distribution for hydrophilic drugs Less volume of distribution for hydrophilic drugs
Protein binding	Higher free fraction of drugs
Metabolism	
Phase I enzyme (cytochrome (CYP) P450)	Less hepatic clearance
Phase II enzyme (UGT)	Less hepatic clearance. Glucuronidation does not reach adult levels for at least 3 years of age
Elimination	
Renal excretion GFR (tubular absorption and secretion)	Lower renal clearance. Nephrogenesis is complete at 34 weeks of gestation. GFR reaches adult levels by 2 years of age

GFR, glomerular filtration rate; UGT, UDP-glucuronosyltransferase. Source: [6, 7].

Table 1.
 Pharmacological characteristics that can condition the appearance of adverse reactions to medications.

recommendations of safety use of medicine in pediatrics, actually there are many challenges [10].

Intensive pharmacovigilance is needed in pediatric population, due to increased susceptibility to ADRs and predisposing factors [11, 12]. Intensive pharmacovigilance is defined as “the systematic monitoring of the occurrence of adverse events resulting from drug use during the entire length of prescription” [13]. This is the first pharmacovigilance challenge, to achieve integration in health systems in a proactive and routine way. The truth is that pharmacovigilance must function dynamically and based on the fundamental pillars of public health: protection, promotion, and prevention.

Another important challenge is to implement a mandatory reporting system, because in the case of adverse reactions in children, it is always important to analyze the reason for ADR. This is perhaps the most important challenge.

In addition, as shown in **Image 1**, to achieve a benefit-risk balance in pediatric populations, it is necessary to implement a dynamic PV cycle that allows the gain of knowledge and the management of risks associated with medicines in children. That could be an important new legislative tool in pediatric pharmacovigilance.

On the other hand, due to off-label being permitted, authorities have to demand from pharmacy industry the inclusion of children in clinical trial. The main reason for that is that if it is not ethical to include children in clinical trials, much less is to use a medicine that has never been prescribed or used in children population before.

Despite, PRAC-PDCO is constantly communicating about the importance of ADR monitoring and reporting suspected ADR in order to create signals for pediatric population. Some legislative tools for improving pharmacovigilance in pediatric population could be to promote research networks and ADR report in children (including pregnancy), to create networks of pediatric use of medicine and pharmacovigilance, to pilot new approaches to strengthen signal detection, to work on medication error, and to create a PRAC-PDCO collaborative working on benefit-risk worldwide [10] (**Image 2**).

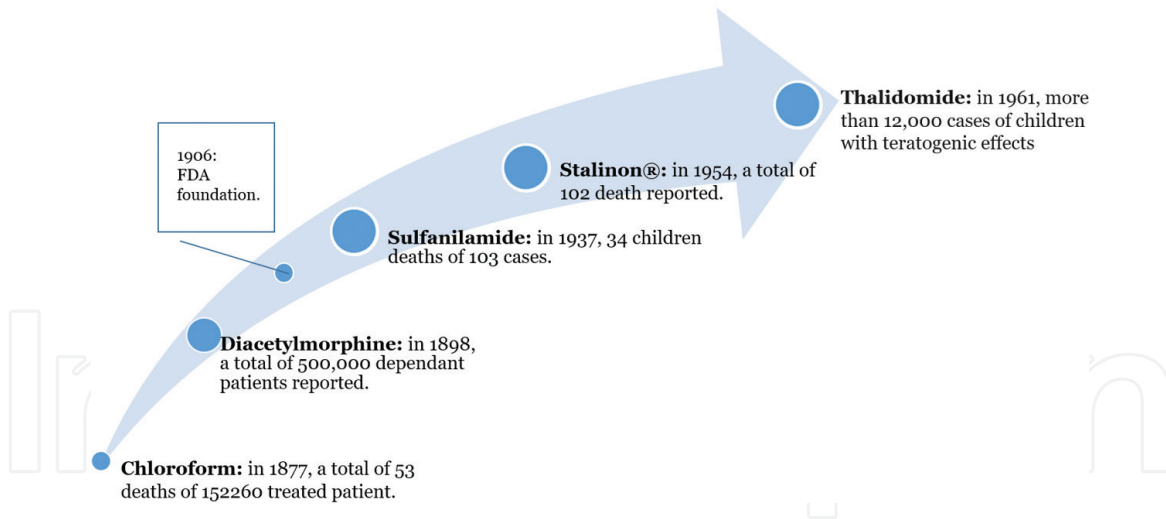


Image 1. Significant milestones of the history of pharmacovigilance in pediatrics.

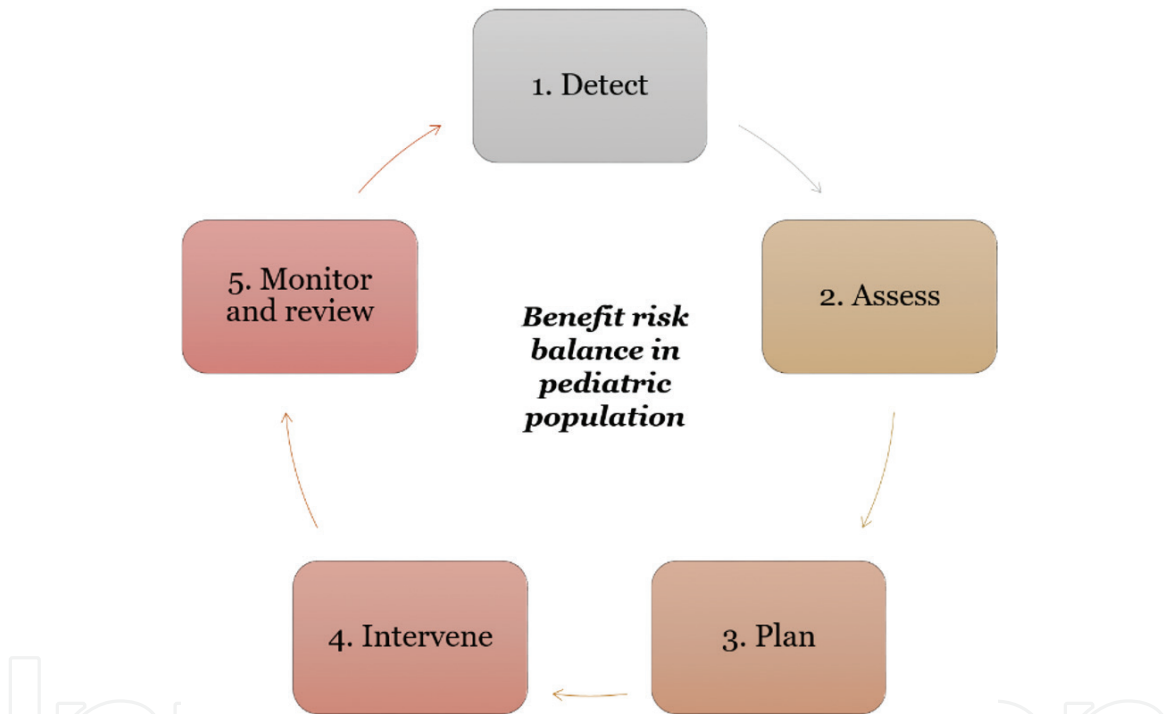


Image 2. Pharmacovigilance cycle. Source: Taken from: Raine J. *Pharmacovigilance in Paediatric Population. The PRAC's perspective EU: EMA; 2014.* (10).

3.2 Importance of pharmacovigilance in children’s intensive care units

Patient safety in child intensive care units is a priority in health care, in which the entire interdisciplinary team has to use guidelines and protocols that attempt to minimize the errors that occur in clinical practice. These controls can be efficient and effective, but sometimes fail, and it produces an error during the prescribing or the administration of medications [14]. Due to complex diseases, critically ill children (newborns and infants) in intensive care units are in a higher risk of developing ADRs [15].

In the neonatal and pediatric intensive care units, efforts have been made to strengthen drug administration processes focused on improving patient identification, drug, and dosage, through a list of checkups with a clear and timely focus on risk management in the use of medications [14].

Therefore, as a component of patient safety policy, in each health institution, this must be effectively coordinated with the pharmacovigilance system; although what this policy is looking for and working for is the patient safety, seen from the integral clinical component and from the pharmacovigilance perspective, the medicine and its use are taken as the central axis. Therefore, the need to efficiently regulate both actions is emphasized, with the aim of not affecting the duplication of efforts and results, in order to achieve maximum patient safety and the most optimal management possible on the safe use of medicines [16].

Due to ADR and inadequate practices on the use of medications which make up a large percentage of hospital admissions and extensive hospital days of stay, it is vitally important to have active pharmacovigilance, improving the education and communication of all risks related to medications. All health teams have to use the same language, and this is possible because the protocols and clinical guidelines established in the institutions, as well as improving the notification of errors in order to analyze and to improve plans [17].

4. Adverse drug reactions in children

The WHO Global Individual Case Safety Report (ICSR) database (VigiBase®), using spontaneous notification system, has reported ADR rates of 7.7% (268.145) in children from 0 to 17 years of age [18]. Nevertheless, ADR prevalence in children can vary due to patient characteristics, methodology used in the evaluation of the suspected ADR, and pharmacological treatments. In addition, ADR only can be classified as definitive if the medication or placebo was readministered and the blood concentration of the drug measured, which is not possible, even for ethical issues in the care of children.

Country/ study	Study ID	ADR incidence	Age	Type of study	Number of patients	Type of service
Spain	Belen 2016 [19]	17.00%	≤29 days (neonates)	Prospective cohort study	332	Neonatal ward
Mexico	Vásquez- Alvarez 2017 [20]	1.75%	≤18 years of age	Prospective cross-sectional	1083	Hospital admissions
Colombia	De las salas 2016 [21, 22]	21.31%	≤5 years of age	Prospective cohort study	1056	Neonatal and pediatrics wards
Brazil	Barbosa 2006 [23]	12.50%	≤16 years of age	Prospective cohort study	265	Pediatric ward
United States*	Sharek 2006 [24]	4.54%	≤29 days (neonates)	Retrospective cross-sectional study	749	NICUs
India	Digra 2015 [25]	0.36%	≤19	Prospective observational study	28,864	Pediatric ward

*Included one Canada neonatal care unit of 15. NICU, neonatal intensive care unit.

Table 2.
 Incidence of ADR in children from different countries around the world.

Age/drug	Ibuprofen	ASA*	Diclofenac	Naproxen	Indomethacin	Piroxicam
0–27 days	416	122	53	36	180	9
28 days to 23 months	3113	533	195	263	107	16
2–11 years	12,428	2196	986	922	144	67
12–17 years	6016	1741	2091	1622	231	184
Total	21,973	4592	3325	2843	662	276

Source: vigiaccess.org. Accessed: 08-15-2018.

*Acetylsalicylic acid. NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 3.
NSAID ADRs in children.

Many studies conducted in different countries, using mostly prospective observational studies, have reported ADR rates ranging from 0.36 to 21.31%. This is described in **Table 2**.

4.1 Individual case safety report

Considering the importance of ADR notifications reported to the Uppsala Monitoring Centre (UMC), some of the drugs with greater frequency of use or with relevant aspects of safety in children have been selected. As nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsant, opioids, and certain cold medicines are frequently used and have relevant issues in medicine safety in children, this section presents the results of the World Health Organization global individual case safety report database (VigiAccess).

The ADR frequency report for NSAIDs is variable. Ibuprofen is the drug with the highest ADR report in children. It could be due to the fact that it is one of the most used drugs in this population. The comparison of other NSAID ADRs is presented in **Table 3**.

Different studies [26, 27] and safety reports [28–30] indicate that cold medicines and opioids may represent risks of ADRs, particularly in younger children. As it is shown in **Table 4**, the majority of UMC reports are associated to diphenhydramine and dextromethorphan. Codeine reports are still growing.

Age/drug	DM	Guaifenesin	Pseudoe	PE	BH	CP	DH	Codeine
0–27 days	9	4	66	13	3	93	25	13
28 days to 23 months	149	103	217	76	13	287	274	136
2–11 years	825	194	502	79	21	703	741	429
12–17 years	600	95	471	37	8	356	604	277
Total	1583	396	1256	205	45	1439	1644	855

DM, dextromethorphan; GUA, guaifenesin; pseudo, pseudoephedrine; PE, phenylephrine; BH, brompheniramine; CP, chlorpheniramine; DH, diphenhydramine. Source: vigiaccess.org

Table 4.
Number of ADRs in children from UMC reports of some cold medicine.

5. A Latin American experience in ADR prospective study

5.1 Study design and participants

A prospective observational cohort study based on intensive pharmacovigilance was conducted from June to December 2013 in two general pediatric wards located in a city of the Colombian Caribbean Coast. One hospital was private and included 20 bed capacity units, from which isolation beds are assigned on a need basis. The other hospital was public with 29 bed capacity units, two of which are used for isolated patients. Both hospitals admit children between the neonatal period and 17 years of age.

This study included 1056 pediatric patients of ≤ 5 years of age (including neonates) without ADRs which were hospitalized at least 24 hours and had at least one prescribed medication. Researchers followed the patients until discharge. All parents authorized children participation and signed a consent. Patients were excluded if they were admitted only for taking diagnostic test or referred from other institutions. In addition, side effects associated with the administration of intravenous solutions, contrast media, nutraceuticals, and topical products were not monitored.

5.2 Data collection

Data collection was conducted by a clinical nurse who was trained in ADR detection. Daily visits to the wards were conducted. The instrument had two sections; the first one contained a sociodemographic variables, medical history, and information about previous medicines. The second one was an adaptation of the Yellow Card Scheme. All data from nursing, medical, and clinical laboratory test records were evaluated in order to detect suspected ADRs. A suspected ADR was defined as “any deviation of the expected clinical status (signs, symptoms and other clinical and laboratory findings)” [31].

The modified Schumock and Thornton criteria [32] were used to evaluate preventability. Naranjo’s algorithm was employed to evaluate the temporal relationship and the biological/pharmacological plausibility between drug exposure and suspected ADR [33], while the severity was judged using modified Hartwig and Siegel Assessment Scale [34]. The team employed for analyzing the aspects was multidisciplinary (a pharmacist, a nurse, a pharmacologist, and a pediatrician).

5.3 Statistical analysis

A descriptive analysis of the variables was conducted. A crude bivariate relative risk (RR) and 95% confidence interval (CI) were estimated between the presence or absence of ADRs (dependent variable) and other variables. A chi-square test ($p < 0.05$) was also done between the dependent variable and the other one.

5.4 Incidence and characteristics of ADRs

Due to physiological and pharmacological differences between neonates and children of other ages, the results of this research are presented in a comparative way.

Two hundred seventy-nine ADRs were detected in 225 children. The cumulative incidence of ADRs was 21.31% (225/1056). Separately, neonate’s incidence was 27.4% (78/284) and ≤ 5 years of age was 19.0% (147/772) [21, 22].

In neonates, 0.81% (1) of the ADRs were classified as definite (certain), 82.93% (102) probable, and 16.26% (20) possible. About 98.37% (121) were not preventable

and 1.63% (2) preventable. About 9.75% (12) of the ADRs were severe, 31.71% (39) moderate, and 58.74% (72) mild.

On the other hand, in children ≤ 5 years of age, 0.64% (1) of the ADRs were classified as definite (certain), 98.08% (153) probable, and 1.28% (2) possible. About 98.72% (154) were not preventable and 1.28% (2) preventable. In terms of severity, 66.03% (103) of the ADRs were mild and 33.97% (53) moderate.

The comparison is shown in **Table 5**, in which it shows higher rates of severe ADRs in neonates. It may be related with the complex treatment established in neonatal intensive care unit (NICU).

The most affected organ system in neonates was the hematologic. In children ≤ 5 years of age, the most affected organ system was digestive. The entire list is detailed in **Table 6**. In all cases, ADR treatment was the responsibility of physicians.

The therapeutic group that most frequently produced ADRs was systemic antibiotics, in both groups, neonates and children. This information is detailed in **Table 7**. This is mainly due to the high use of this group of drugs in children.

5.5 Factors associated with ADRs

The mean gestational age in neonates with ADRs was 34.5 weeks compared with 37.0 ($p = 0.003$) who did not have. Additionally, preterm newborns were 2.30 more likely to have an ADR compare with term (95% CI 1.31–4.01, $p = 0.003$). The mean of days of hospitalization in neonates who had ADRs was 18.5, in comparison with 7.0. Having a hospital stay less than ≤ 8 days is related with the nonappearance of ADR (RR = 0.076, 95% CI 0.037–0.156, $p = 0.000$) [21].

The mean age of children ≤ 5 years of age that developed ADRs was similar between both groups, the ones who had ADRs and the ones did not showed any. However, ADR frequency was higher in children under 2 years of age (12.70%) than in children with 2 or more years of age (6.30%). Male patients were more likely to develop ADRs (RR = 1.66; 95% CI 1.22–2.25, $p = 0.001$) than female [22].

The mean length of hospitalization in children ≤ 5 years of age who had ADRs was higher (7.1 days ± 5.2) than those who did not show ADRs (5.3 days ± 2.6 , $p = <0.001$) [22]. The mean of prescribed medicines in children with ADRs was

Characteristics	Neonatal age n = 284		Children ≤ 5 years of age n = 772	
	N	%	N	%
<i>Imputability (Naranjo's algorithm)</i>				
Definite (certain)	1	0.81	1	0.64
Probable	102	82.93	153	98.08
Possible	20	16.26	2	1.28
<i>Severity (Hartwig and Siegel scale)</i>				
Severe	12	9.75	0	0
Moderate	39	31.71	53	33.97
Mild	72	58.54	103	66.03
<i>Preventability</i>				
Preventable	2	1.63	2	1.28
Not preventable	121	98.37	154	98.72

Table 5.
Characteristics of ADRs in Colombian children.

Organic system affected	Neonatal age n = 284		Children ≤5 years of age n = 772	
	N	%	N	%
Hematologic	42	34.15	2	1.28
Digestive	41	33.33	100	64.1
Renal	12	9.76	4	2.56
Integumentary	6	4.88	19	12.19
Cardiovascular	3	2.44	21	13.46
Others	19	15.44	10	6.41
Total of ADR	123	100	156	100

Table 6.
 Organic system affected in neonates and children with ADRs.

ATC code	Neonatal age n = 284		Children ≤5 years of age n = 772	
	N	%	N	%
Anti-infectives for systemic use	99	80.49	110	70.51
Respiratory system	9	7.31	25	16.03
Systemic hormonal preparations*	1	0.81	7	4.49
Nervous system	2	1.63	8	5.13
Cardiovascular system	3	2.44	1	0.64
Blood and blood-forming organs	2	1.63	1	0.64
Alimentary tract and metabolism	0	0	4	2.56
Others	7	5.69	0	0
Total	123	100	156	100

ATC, anatomical therapeutic chemical classification.

*Excluding sex hormones and insulins.

Table 7.
 ADRs presented by children.

higher than those who did not show any (mean 5.0 ± 2.5 vs. 3.9 ± 2.4 drugs) ($p = <0.001$). Similarly, the number of prescribed systemic antibiotics in children with ADRs was also higher than in those who were not prescribed any (mean 2.0 ± 0.5 vs. 1.0 ± 0.5) ($p = <0.001$). The use of systemic antibiotics was correlated with a higher risk of ADRs (RR = 1.82 (95% CI 1.17–2.82, $p = 0.005$)) than those who did not use an antibiotic (Table 4). About 1.5% (12) of patients with ADRs reported previous ADRs [22].

6. Discussion

We followed a cohort of 1056 hospitalized patients, among neonates and children ≤5 years of age. We identified an ADR incidence of 21.3%, which is higher than Jimenez et al. [35]. These results demonstrate that children are particularly susceptible to ADRs. A Cuban Research which included patients under 18 years of age found that the age range most affected by ADRs was between 2 and 11 years

of age [36]. But we only included patients ≤ 5 years of age. Children ages were divided as < 2 years and ≥ 2 years of age, due to biological variability. Males were more often affected by ADRs than females, similar to the WHO ICSR database (VigiBase®), in which ADRs were primarily presented in males [18]. However, other studies have revealed higher ADRs rate in females [36, 37].

The mean of days of hospitalization in neonates who had ADRs was 18.5, in comparison with 7.0. The average length of hospitalization in older children was 7.1 days. This difference might be due to differences in neonates and children patients. The mean number of prescribed medicines in children with ADRs was similar to European and non-European countries who have reported an average number higher than 5 [33].

Respiratory drugs and systemic antibiotics were the therapeutic groups mostly associated with ADR incidence in both neonates and children. As noted, respiratory drugs and systemic antibiotics are not only the most prescribed class of drugs for hospitalized children but also the ones that usually cause ADRs. The most common ADRs linked to systemic antibiotics were digestive for older children, while hematologic were for neonates. Similar findings were reported by Belen-Rivas et al. [19].

Most of the ADRs found in our study were mild. These results differ with the findings of Shamna et al. [39], who found that moderate ADRs were the most common. According with Naranjo's algorithm, the majority of ADRs were classified as probable; also Belen-Rivas [19] reported that the majority of ADRs were probable. The evaluation of ADRs is predisposed by the definitions, the methodology of detection, classification, and the study setting included.

The main limitation of this study was the determination of imputability of adverse events. Regardless of patient daily visits, only 0.81% of neonates and 0.64% of older children were categorized as definite ADRs. Naranjo's algorithm determines an ADR as definite when the drug is readministered or a placebo is administered and the drug serum level lab tests are carried out. In most cases, for ethical reasons, these are not feasible. Likewise, if a suspected ADR is detected, in most of the cases, the drug is ceased, which limits the ability to evaluate all the criteria for imputability. This study was purely observational, and no intervention was conducted on patient's treatment.

Even though we did not estimate a sample size due to difficulties in establishing the general population, an observation period of 6 months permitted us to measure an ADR incidence.

7. Conclusion

ADRs are common among inpatient neonates and children. In neonates, having less than ≤ 8 days of hospitalization is linked with the nonappearance of ADRs (RR = 0.076, 95% CI 0.037–0.156, $p = 0.000$). In children, males are more likely to develop ADRs (RR = 1.66; 95% CI 1.22–2.25, $p = 0.001$) than females. Even when in neonates, it is not a significant RR; males have higher rates of occurrence than females. Systemic antibiotics are correlated with a higher risk of ADRs (RR = 1.82 (95% CI 1.17–2.82, $p = 0.005$) in children. All these findings mean that ADR represents an additional burden of morbidity and risk for pediatric patients, particularly in those who used several medicines.

Pharmacovigilance in pediatric population needs to be reinforced. It is necessary to develop a proactive pharmacovigilance and patient safety programs with a focus in risk analysis and management, in which ADR reporting should be mandatory. This measure might help us make our health-care systems safer, especially for children, in which this topic must be further investigated.

For succeeding in ADR detection, it is important to have a team conformed by physicians, nurses, pharmacists, and others (according to the health service). In addition, it should be noted that, due to the role nurses play in the administration and monitoring of therapy, they have a privileged position to detect drug effects, including ADRs.

In order to prevent ADRs, it is advisable to generate strategies that are aimed at improving drug administration safety protocols.

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Conflict of interest

The authors declare no conflict of interest.

Ethical considerations

The protocol was approved by the Research Ethics Committee of the Health Care Division of the “Universidad del Norte” and was declared as minimal risk by the researchers. Likewise, the protocol was conducted under the human research ethical criteria defined as the Declaration of Helsinki.

Appendices and nomenclature

ADR	adverse drug reaction
OTC	over the counter
WHO	World Health Organization
NICU	neonatal intensive care unit
UMC	Uppsala Monitoring Centre
NSAIDs	non-steroidal anti-inflammatories

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