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Adverse drug reactions in neonatal intensive care unit: Characteristics and risk factors

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Abstract

Adverse drug reactions (ADRs) in neonates can significantly affect expected clinical outcomes. The aim of this study was to analyze the prevalence and characteristics of ADRs and identify the risk factors involved in a neonatal intensive care unit (NICU). A prospective cohort study based on intensive pharmacovigilance was carried out in NICU of a public teaching hospital in the south of Mexico. Neonates admitted to the NICU who had between 1 and 90 days of age, with at least 24 hours of hospitalization, and a confirmed suspicion of ADRs were included. The prevalence and characteristics of ADRs were analyzed. Relative ratios (RR) were estimated with 95% confidence intervals (CI) to evaluate the risk factors of ADRs ($p<0.05$). 998 newborns were included, 109 ADRs were detected in 75 newborns, the cumulative incidence was 7.51% and the ADRs were mainly probable imputability and moderate severity. The therapeutic group most frequently related to the development of ADRs was anti-infectives for systemic use and the blood and lymphatic system was most affected by the ADRs. Identified risk factors were: female sex (RR 1.58; 95% CI 1.01-2.47), prematurity (RR 5.6; 95% CI 3.45-9.11), low birth weight (RR 2.52; 95% CI 1.63-3.91), length of hospitalization >15 days (RR 12.95; 95% CI 7.89-21.25) and drugs administered >5 (RR 5.92; 95% CI 2.6-13.48). These results should be considered and studied in greater depth, which will allow the prevention of the development of ADRs in this group of patients.

Keywords: Adverse Drug Reactions; Newborn; Intensive Care Units; Risk Factors

1. Introduction

Neonates are a special group that is usually exposed to a large number of drugs, which increases the risk of developing adverse drug reactions (ADRs) [1]. This is due to the fact that they present significant differences with respect to other age groups in terms of pharmacokinetic and pharmacodynamic processes, which in turn affects the safety margin of the drugs used and can significantly affect the expected clinical results [2, 3].

In previous investigations, a high frequency of ADR has been reported in neonates, and they have been characterized with respect to its type, imputability and severity. Currently there are reports that have studied the risk factors that may be associated with the development of ADR in neonates [4-6] however, there are no studies in the Mexican hospital setting.

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In order to identify the possible risk factors associated with the development of ADRs, we have carried out a prospective cohort study through the active pharmacovigilance method, where ADRs were identified and characterized. Using this approach, we were able to identify the associated risk factors to the development of ADR in neonatal patients in a NICU.

2. Material and methods

2.1. Study design and population

A prospective cohort study based on active pharmacovigilance was carrying out for six months in the Neonatal Intensive Care Unit (NICU) of a public teaching hospital in the south of Mexico. The patients were monitored from admission to discharge, to identify the presence of ADRs. Neonates admitted to the NICU between 1 and 90 days of age, with at least 24 hours of hospitalization, at least one medication administered, and who had a confirmed suspicion of ADR were included. Patients with an incomplete information in their medical records were excluded.

2.2. Patient data

The patients´ files were analyzed to obtain demographic characteristics (age, sex, gestational weeks, birth weight), and length of hospitalization. According to the gestational weeks, the patients were classified as preterm infants (< 37 weeks of gestation) and term infants (37-42 weeks of gestation); World Health Organization (WHO) growth charts were used to categorize patients as low birth weight (below the 10th percentile) and adequate birth weight (between the 10th to the 90th percentile) considering their gestational age. The registration was done electronically.

2.3. ADR identification and evaluation

We defined ADR according to the WHO definition [7]. Pharmacotherapy data related to suspected ADRs included: name of the drug, dosage, route of administration, dosage form, and days of treatment. The MedDRA® System Organ Classes (SOC) was employed by classified the system or organ affected by the ADRs and, the drugs were classified according to the WHO Anatomic Therapeutic Chemical (ATC) classification.

Confirmed ADRs were evaluated concerning

- Imputability: It was assessed using the Naranjo´s algoritm [8]. It consists of assigning a level according to the association of ADR with the suspected drug, based on the score obtained in a questionnaire (maximum score is 13 points). The imputability levels are:
  - Definitive (≥9 points): A clinical event, including alterations in laboratory tests, that manifests with a plausible temporal sequence in relation to the administration of the drug, and that cannot be explained by concurrent disease, or by other drugs or substances. The response to drug withdrawal (dechallenge) must be clinically plausible. The event must be definitive from a pharmacological or phenomenological point of view, using, if necessary, a conclusive re-exposure (rechallenge) procedure.
  - Probable (5–8 points): A clinical event, including alterations in laboratory tests, that manifests with a reasonable temporal sequence in relation to the administration of the drug, that is unlikely to be attributable to concurrent disease, nor to other drugs or substances, and that upon dechallenge of the drug presents a clinically reasonable response. No rechallenge information is required to meet this definition.
  - Possible (1–4 points): A clinical event, including alterations in laboratory tests, that manifests with a reasonable temporal sequence in relation to the administration of the drug, but that may also be explained by concurrent disease or by administration of other drug, but which may also be explained by concurrent disease, or by other drugs or substances. Information regarding drug withdrawal may be missing or unclear.
  - Doubtful (0 points): A clinical event, including alterations in laboratory tests, that manifests with an unlikely time sequence in relation to the administration of the drug, and that may be more plausibly explained by concurrent disease, or by other drugs or substances.
- Severity was assigned as mild (signs and symptoms easy to tolerate, do not require treatment, do not prolong hospitalization), moderate (do not directly threaten the life of the patient, require pharmacological treatment, and may require discontinuation of treatment), severe (directly threatening the patient's life, prolonging hospitalization, can cause disability or disorders and malformations in the newborn) and fatal (directly or indirectly contribute to the death of the patient) [9].

2.4. Statistical analysis

Descriptive statistics was used to summarize data. Bivariate comparative analysis between patients with and without ADRs was performed by $\chi 2$ test for qualitative variables and by comparison of means for quantitative variables. Relative ratios (RR) were estimated with 95% confidence intervals to evaluate the risk of ADRs based on patient's characteristics and pharmacotherapy. All results were considered to be statistically significant at $p < 0.05$. Data management and statistical analysis were carried out using IBM SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA).

2.5. Ethical implication

This study was performed with the prior approval of the Ethics and Research Committees of the hospital. In addition, informed consent was obtained from the legal guardians of all individual participants in the study. All information collected for the study was used for scientific purposes only and confidentiality was strictly guaranteed at all times.

3. Results

A total of 998 newborns were included in the cohort study, the proportion between males and females was similar. The mean age was 30.08 ± 17.4 days and birth weight was 2349.71 ± 0.70 grams. Table 1 shows the demographic and clinical characteristics of patients.

Table 1 Demographic and clinical characteristics of patients in the study cohort

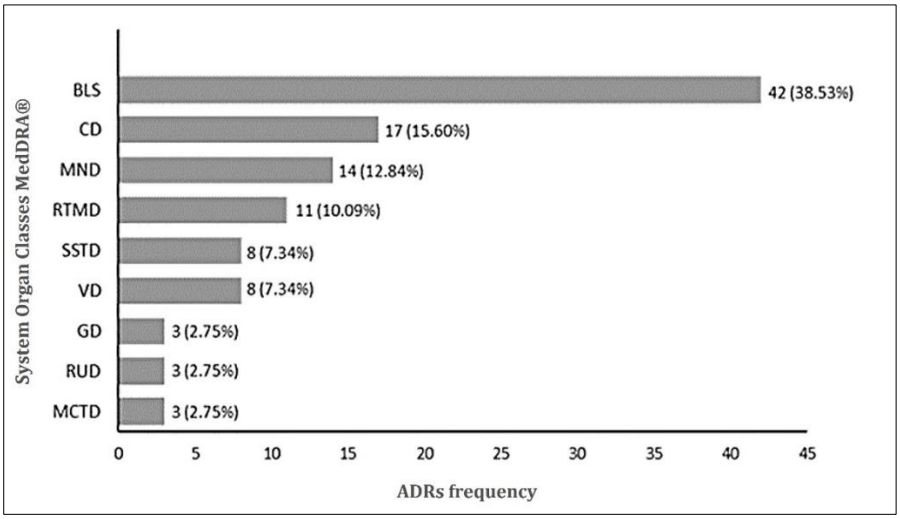
Variable	Characteristics	n (%)
Sex	Female	486 (48.7%)
	Male	512 (51.3%)
Gestational weeks	Preterm infants (26-36 weeks)	314 (31.46%)
	Term infants (37-41 weeks)	684 (68.54%)
	Mean ± SD (weeks)	37.55 ± 2.39
Birth weight	Low birth weight	347 (34.77%)
	Adequate birth weight	651 (65.23%)
	Mean ± SD (grams)	2349.71 ± 0.70
Number of drugs by patient	≤ 5	339 (33.97%)
	> 5	659 (66.03%)
	Mean ± SD	5.9 ± 1.6
Age	Mean ± SD (days)	30.08 ± 17.4
Length of hospitalization	Mean ± SD (days)	18.78 ± 12.6
Diagnostics – (ICD-10 code), n=2196	Congenital pneumonia – (P23)	534 (24.3%)
	Newborn respiratory distress – (P22)	441 (20.1%)
	Urinary infection – (P39.3)	318 (14.5%)
	Risk of sepsis during labor – (O75.3)	264 (12.0%)
	Meconium aspiration – (P24)	195 (8.9 %)
	Others	444 (20.2%)

Abbreviations: ICD-10 code, code of International Classification of Diseases 10th revision; SD, standard deviation.

In 75 newborns were detected 109 ADRs, represented an average of 1.45 RAM per newborn. The cumulative incidence of ADR was 7.51% (75/998) and an incidence density of 11.56 ADRs /1000 patients-day. The therapeutic group most frequently related to the development ADRs was anti-infectives for systemic use (n=51 ADRs, 46.80%); Table 2 and, the blood and lymphatic system was the most affected (n= 42 ADRs, 38.53%); Fig. 1.

Table 2 Therapeutic groups related to ADRs

ATC – main anatomical/pharmacological groups / Total ADRs in the group, n (%)	**Drug ATC code**	**ADRs n (%)**	**ADRs description (n)**
J- anti-infectives for systemic use / 51 (46.80)	Ampicillin J01CA01	28 (25.69)	Thrombocytopenia (14), leukopenia (5), alteration of bleeding times (9).
	Gentamicin J01GB03	12 (11.01)	Thrombocytopenia (12).
	Meropenem J01DH02	5 (4.59)	Tecreased hematocrit or hemoglobin levels (3), apnea (2).
	Cefotaxime J01DD01	2 (1.83)	Thrombocytopenia (2).
	Vancomycin J01XA01	2 (1.83)	Phlebitis (2).
	Amikacin J01GB06	2 (1.83)	Apnea (2).
N- nervous system / 19 (17.02)	Caffeine N06BC01	12 (11.01)	Tachycardia (5), hyperglycemia (5), food intolerance (1), polyuria (1).
	Midazolam N05CD08	4 (3.67)	Cyanosis (2), bradycardia (1), fasciculations (1).
	Phenytoin N03AB02	2 (1.83)	Bradycardia (2).
	Nalbuphine N02AF02	1 (0.92)	Bradycardia (1).
C- cardiovascular system / 30 (27.65)	Furosemide C03CA01	14 (12.84)	Decreased hematocrit or hemoglobin levels (5), hypocalcemia (9).
	Dobutamine C01CA07	8 (7.34)	Hypertension (8).
	Norepinephrine C01CA03	4 (3.67)	Hypertension (4).
	Hydralazine C02DB02	4 (3.67)	Edema (4).
R- respiratory system / 9 (8.26)	Salbutamol and ipratropium bromide R03AL02	9 (8.26)	Tachycardia (5), oxygen desaturation (2), increased respiratory rate (2).



Abbreviations: BLS = blood and lymphatic system; CD = cardiac disorders; GD = gastrointestinal disorders; MCDT = musculoskeletal and connective tissue disorders; MND = metabolism and nutrition disorders; RTMD = respiratory, thoracic and mediastinal disorders; RUD = renal and urinary disorders; SSTD = skin and subcutaneous tissue disorders; VD = vascular disorders

Figure 1 System Organ Classes affected by the ADRs

The ADR imputability was mainly "probable" (68.81%) and in terms of severity, 61.47% were "moderate". (Table 3)

Table 3 Assessment of ADRs

Characteristics		**n (%)**
Causality	Probable	75 (68.81%)
	Possible	34 (31.19%)
Severity	Mild	67 (61.47%)
	Moderate	42 (38.53%)

Table 4 Factors associated to ADRs

Variable	**Characteristics**	**With ADR (n= 75)**	**Without ADR (n=923)**	**RR (95% CI)**	**p-value**
Sex	Female	30	482	1.58 (1.01-2.47)	0.042*
	Male	45	441		
Gestational weeks	Pi (28-36 weeks)	54	260	5.6 (3.45-9.11)	< 0.001*
	Ti (37-41 weeks)	21	663		
Birth weight	LBW	43	304	2.52 (1.63-3.91)	< 0.001*
	ABW	32	619		
Length of hospitalization	> 15 days	56	129	12.95 (7.89-21.25)	< 0.001*
	≤ 15 days	19	794		
Drugs by patient	> 5	69	590	5.92 (2.6-13.48)	< 0.001*
	≤ 5	6	333		

Abbreviations: Pi = preterm infant, Ti = term infant, ABW = adequate birth weight, LBW = low birth weight; * statistically significant, p-value < 0.05

Sex, prematurity (gestational weeks < 36 weeks), low birth weight, length of hospitalization >15 days, and more than 5 prescribed medications were correlated with the risk to develop ADRs. (Table 4)

4. Discussion

For our best knowledge, this is the first prospective cohort study with an active ADRs monitoring and ADRs risk factors identification in neonate patients from a NICU of a public teaching hospital in Mexico. The main findings of our study are that the ADRs identified were mainly probable imputability and moderate severity. The therapeutic group most related to ADRs was anti-infectives for systemic use, and the blood and lymphatic system was the most affected. Likewise, we identified the factors related to ADRs in newborns in the NICU, such as female sex, being premature, low birth weight, length of hospitalization> 15 days, and drugs administered> 5.

ADRs in the neonatal population are an essential public health problem, and the existing data in this regard are not yet sufficient. We analyzed the ADRs in a cohort of 998 neonatal patients. The cumulative incidence of ADRs identified was of 7.51%, similar findings have been published by several authors. Morales et al. [10] reported an estimated frequency of 2.12% to 8.07% in a descriptive study in a tertiary care pediatric hospital in Mexico. Kurian et al. [11] reported an incidence of 4.99% in a prospective study in 1082 pediatric patients in India, Smyth et al. [12] in a systematic review, reported an incidence of 0.6% to 16.8% in hospitalized pediatric patients. However, others studies have reported high scores compared with our results, Rivas et al. [13] reported an incidence of 44.4% of ADRs in NICU patients, and De Las Salas et al. [14] reported a cumulative incidence of 27.4% in 78 neonates, the possible explanation for these differences could be the fact that the estimation of the incidence of ADR is influenced by different factors, such as the definition of ADR, the detection and evaluation methods used, as well as the under-reporting of ADRs [15-17].

In agreement with others reports, the therapeutic group mostly associated to the development of ADRs was anti-infectives for systemic use (46.80%), related to alterations in the blood and lymphatic system [13, 18, 19]. Ampicillin and gentamicin were predominant. Anti-infective drugs are frequently used in NICUs to treat life-threatening situations. However, the fact that they have a narrow therapeutic profile and are commonly used off-label indication suggests that they should be closely monitored, as they pose a risk for the development of ADRs in neonates [20-23].

The second group related to ADRs were drugs for the cardiovascular system. where furosemide was the most common (12.84%), this drug is approved in term neonates to treat edema associated with congestive heart failure, cirrhosis, and renal disease. However, it is often administered off-label in premature newborns, to treat respiratory conditions, and in higher than recommended doses, which has been documented by several authors as a risk factor for ototoxicity and sensorineural hearing loss [24,25], which is consistent with the results of our study where the ADRs associated with this drug were identified mainly in preterm newborns.

Other group related to ADRs was the drugs for the nervous system (17.02%), which mainly caused cardiac disorders and where caffeine citrate was the most involved in the events. Caffeine citrate is the drug of choice for the treatment of apnea of prematurity and presents few side effects, however, there are reports of cardiac, gastrointestinal and nervous system disorders, as well as acute kidney damage related to the administration of overdose of this drug, which could explain the ADRs associated with caffeine citrate identified in this study [13, 18, 26, 27].

The most affected SOC was blood and lymphatic system (BLS); these data differ with those of other reports, in which gastrointestinal disorders (GD) and skin and subcutaneous tissue disorders (STD) were the most reported [14, 28, 29]. The discrepancy may be due to the heterogeneity of the information used to identify the affected SOC. In our study, the information was obtained from the patient's written medical history, which can sometimes be limited for this purpose. Some authors have proposed the use of electronic medical records or electronic registries to avoid this limitation [30, 31].

The imputability assigned with the Naranjo algorithm showed that most of the ADRs were classified as probable (68.81%) and the rest as possible, which is consistent with other studies [11, 32].

Other limitation of our study was that despite the follow-up of the patients, we did not identify ADRs with definite imputability, since in order to classify an ADR as definitive, it is necessary to re-administer the drug, or to quantify serum levels of the drug. This was not carried out due to the ethical and safety protocols of the hospital that indicate the suspension or non-re-administration of the drugs in case of suspected ADR, since there is no infrastructure for monitoring drug serum levels. In addition, some authors suggest that the Naranjo algorithm used for the assessment of ADRs in the hospital setting is not a consistent tool, so they suggest the use of more valid and reliable algorithms to identify ADRs, specifically in the NICU population [33, 34].

Previous studies have documented age, sex, comorbidities, polypharmacy, and days of hospitalization as risk factors associated with the development of ADRs [35, 36]. We identified female sex, prematurity (preterm infant), low birth weight, length of hospitalization >15 days, and drugs administered >5, as risk factors associated with the development of ADR (Table 4), findings that coincide with those reported in the literature. Prematurity and low birth weight have been previously described as risk factors for developing ADRs, both related to physiological immaturity, which may affect pharmacokinetic and pharmacodynamic processes [18], De las Salas et al. [14] reported in a study conducted in a NICU in Colombia, that being premature presented an increased risk of developing ADR (OR=2.30; 95% CI: 1.31-4.01; p=0.003). On the other hand, Smyth et al. [12] reported in a systematic review of ADRs in children that the risk increases with the number of drugs taken (OR=1.49; 95% CI: 1.14-1.94; p=0.01) and females are more prone to ADRs (OR=1.13; 95% CI: 0.91-1.4; p=0.23). It has also been described that the likelihood of ADRs is higher as the duration of hospitalization increases, which may be related to increased exposure to multiple drugs [37].

5. Conclusion

Neonates in the NICU are exposed to the development of ADRs, the incidence of ADR identified in our study was 7.51% and mainly related to systemic anti-infective drugs, with the blood and lymphatic system being the most affected. Neonatal characteristics, polypharmacy and prolonged hospital stay were identified as risk factors for ADRs in a NICU. This indicates the need to take these factors into account when establishing drug therapy and to closely monitor patients with these characteristics in order to prevent the development of ADRs and promote the safe use of drugs in this group of patients.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have declared that no competing interests exist.

Statement of ethical approval

The study was approved and authorized by the hospital's Research Committee and by the Research Ethics Committee under registry number CEI-006-1-17.

Statement of informed consent

Informed consent was obtained from the legal guardians of all individual participants included in the study.

References

[1] Allegaert K, Van den Anker JN. Adverse drug reactions in neonates and infants: a population-tailored approach is needed. Br J Clin Pharmacol 2015; 80: 788–795. https://doi.org/10.1111/bcp.12430.

[2] Ruggiero A, Ariano A, Triarico S, Capozza MA, Ferrara P, Attinà G. Neonatal pharmacology and clinical implications. Drugs Context 2019; 14: 212608. https://doi: 10.7573/dic.212608.

[3] Allegaert K, van de Velde M, van den Anker J. Neonatal clinical pharmacology. Paediatr Anaesth 2014; 24: 30-38. https://doi:10.1111/pan.12176.

[4] Aranda J, Seliske P, Horton L, Collinge J, Outerbridge EW. Risk factors in neonatal adverse drug reactions. Pediat Res 1984; 18, 149. https://doi.org/10.1203/00006450-198404001-00334

[5] Rashed AN, Wong IC, Cranswick N, Tomlin S, Rascher W, Neubert A. Risk factors associated with adverse drug reactions in hospitalised children: international multicentre study. Eur J Clin Pharmacol 2012; 68: 801-810. https://doi: 10.1007/s00228-011-1183-4.

[6] Santos PH, Fraga IM, da Silva W. Risk factors for adverse drug reactions in pediatric inpatients: A cohort study. PLoS One 2017; 12: e0182327. https://doi.org/10.1371/journal.pone.0182327.

[7] World Health Organization (WHO)-Uppsala Monitoring Centre (UMC). Glossary of terms used in Pharmacovigilance. 2011. Available at http://who-umc.org/Graphics/24729.pdf. Accessed July 3, 2021.

[8] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239–245.

[9] Official Journal of the Federation. Official Mexican Standard NOM-220-SSA1-2016, Installation and operation of pharmacovigilance. 2016. Available at: http://www.dof.gob.mx/nota_detalle.php?codigo=5490830&fecha=19/07/2017. Accessed July 5, 2022.

[10] Morales-Ríos O, Cicero-Oneto C, García-Ruiz C, Villanueva-García D, Hernández-Hernández M, Olivar-López V, et al. Descriptive study of adverse drug reactions in a tertiary care pediatric hospital in México from 2014 to 2017. PLoS One 2020; 15:e0230576. https://doi.org/10.1371/journal.pone.0230576.

[11] Kurian J, Mathew J, Sowjanya K, Chaitanya KR, Ramesh M, Sebastian J, et al. Adverse drug reactions in hospitalized pediatric patients: a prospective observational study. Indian J Pediatr 2016; 83: 414-419. https://doi.org/10.1007/s12098-015-2002-1.

[12] Smyth RM, Gargon E, Kirkham J, Cresswell L, Golder S, Smyth R, et al. Adverse drug reactions in children—a systematic review. PLoS One 2012; 7:e24061. https://doi.org/10.1371/journal.pone.0024061.

[13] Rivas A, Arruza L, Pacheco E, Portoles A, Diz J, Vargas E. Adverse drug reactions in neonates: a prospective study. Arch Dis Child 2016; 101: 371-376. https://doi.org/10.1136/archdischild-2015-309396.

[14] De las Salas R, Díaz-Agudelo D. Adverse drug reactions in neonates hospitalized in neonatal intensive care units in Barranquilla, Colombia. Biomedica 2017; 37: 33-42. Available at https://revistabiomedica.org/index.php/biomedica/article/view/3192. Accessed June 18, 2022.

[15] Roberts EK, Hawcutt DB, Turner MA. Prospective identification and causality evaluation of suspected adverse drug reactions in neonates. Br J Clin Pharmacol 2021; 87: 1541–1546. https://doi.org/10.1111/bcp.14485.

[16] Morales O, Jasso L, Talavera J, Téllez-Rojo M, Olivar V, Garduño J, et al. A comprehensive intervention for adverse drug reactions identification and reporting in a Pediatric Emergency Department. Int J Clin Pharm 2016; 38: 80-87. https://doi.org/10.1007/s11096-015-0209-x.

[17] Morales-Ríos O, Jasso-Gutiérrez L, Garduño-Espinosa J, Olivar-López V, Muñoz-Hernández O. Do pediatricians identify adverse drug reactions even when they do not report them? Bol Med Hosp Infant Mex 2015; 72: 106–111. https://doi.org/10.1016/j.bmhimx.2015.04.003.

[18] dos Santos DB, Coelho HL. Adverse drug reactions in hospitalized children in Fortaleza, Brazil. Pharmacoepidemiol Drug Saf 2006; 15: 635–640. https://doi.org/10.1002/pds.1187.

[19] Oshikoya KA, Chukwura H, Njokanma OF, Senbanjo IO, Ojo I. Incidence and cost estimate of treating pediatric adverse drug reactions in Lagos, Nigeria. Sao Paulo Med J 2011; 129: 153-164. https://doi.org/10.1590/s1516-31802011000300006.

[20] Kent A, Turner MA, Sharland M, Heath PT. Aminoglycoside toxicity in neonates: something to worry about?. Expert Rev Anti Infect Ther 2014; 12: 319-331. https://doi.org/10.1586/14787210.2014.878648.

[21] Rivera-Chaparro ND, Cohen-Wolkowiez M, Greenberg RG. Dosing antibiotics in neonates: review of the pharmacokinetic data. Future Microbiol 2017; 12:1001-1016. https://dx.doi.org/10.2217%2Ffmb-2017-0058.

[22] de Souza AS, dos Santos DB, Rey LC, Medeiros MG, Vieira MG, Luna HL. Off-label use and harmful potential of drugs in a NICU in Brazil: A descriptive study. BMC pediatrics 2016; 16. https://doi.org/10.1186/s12887-016-0551-8.

[23] Laforgia N, Nuccio MM, Schettini F, Dell'Aera M, Gasbarro AR, Dell'Erba A, et al. Off-label and unlicensed drug use among neonatal intensive care units in Southern Italy. Pediatr Int 2014; 56: 57-59. https://doi.org/10.1111/ped.12190.

[24] Manfredini, V.A., Cerini, C., Clavenna, A. et al. Furosemide use in Italian neonatal intensive care units: a national survey. Ital J Pediatr 2020; 46: 86. https://doi.org/10.1186/s13052-020-00851-2

[25] Chant K, Bitner-Glindzicz M, Marlow N. Cumulative risk factors contributing to hearing loss in preterm infants. Archives of Disease in Childhood - Fetal and Neonatal Edition 2022. https://doi.org/10.1136/archdischild-2022-324331

[26] Nicole R. Dobson, Carl E. Caffeine Use in Neonates: Indications, Pharmacokinetics, Clinical Effects, Outcomes. Neo Reviews 2013; 14:e540-e550. http://dx.doi.org/10.1542/neo.14-11-e540.

[27] Harer MW, Askenazi DJ, Boohaker LJ, Carmody JB, Griffin RL, Guillet R, et al. Association between early caffeine citrate administration and risk of acute kidney injury in preterm neonates: results from the AWAKEN study. JAMA Pediatr 2018; 172:e180322. https://doi.org/10.1001/jamapediatrics.2018.0322.

[28] Star K, Edwards IR. Pharmacovigilance for children's Sake. Drug Safety 2014; 37: 91–98. https://doi.org/10.1007/s40264-013-0133-8.

[29] Sepahi M, Movahed Z, Heydari H, Shirkhodai M, Shokrollahi M. Surveillance of adverse drug reaction in hospitalized children, a cross sectional study from Qom Province, Iran. Life Sci J 2013; 10: 122–125.

[30] Feng C, Le D, McCoy AB. Using electronic health records to identify adverse drug events in ambulatory care: a systematic review. Appl Clin Inform 2019; 10: 123-128. https://dx.doi.org/10.1055%2Fs-0039-1677738.

[31] Foreman C, Smith WB, Caughey GE, Shakib S. Categorization of adverse drug reactions in electronic health records. Pharmacol Res Perspect 2020; 8:e00550. https://doi.org/10.1002/prp2.550.

[32] Priyadharshini R, Surendiran A, Adithan C, Sreenivasan S, Sahoo FK. A study of adverse drug reactions in paediatrics patients. J Pharmacol Pharmacother 2011; 2: 277–280. https://doi.org/10.4103/0976-500x.85957.

[33] Varallo FR, Planeta CS, Herdeiro MT, Mastroianni PC. Imputation of adverse drug reactions: Causality assessment in hospitals. PLoS One 2017; 12:e0171470. https://doi.org/10.1371/journal.pone.0171470.

[34] Du W, Lehr VT, Lieh-Lai M, Koo W, Ward RM, Rieder MJ, et al. An algorithm to detect adverse drug reactions in the neonatal intensive care unit. J Clin Pharmacol 2013; 53: 87-95.

[35] Jose J, Rao PG. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res 2006; 54: 226–233.

[36] Rashed AN, Wong IC, Cranswick N, Tomlin S, Rascher W, Neubert A. Risk factors associated with adverse drug reactions in hospitalised children: international multicentre study. Eur J Clin Pharmacol 2012; 68: 801-810. https://doi.org/10.1007/s00228-011-1183-4.

[37] Smyth RL, Peak M, Turner MA, Nunn AJ, Williamson PR, Young B, et al. ADRIC: Adverse Drug Reactions In Children – a programme of research using mixed methods. Programme Grants for Applied Research. 2014; 2: 1-184. https://dx.doi.org/10.3310/pgfar02030.