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Temporal profile of adverse drug reactions and associated clinical factors: a prospective observational study in a neonatal intensive care unit

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ABSTRACT

Objective Although adverse drug reactions (ADRs) are quite common in hospitalised neonates, pharmacovigilance activities in this public are still incipient. This study aims to characterise ADRs in neonates in a neonatal intensive care unit (NICU), identifying causative drugs, temporal profile and associated factors.

Design Prospective observational study.

Setting NICU of a public maternity hospital in Natal/Brazil.

Participants All neonates admitted to the NICU for more than 24 hours and using at least one medication were followed up during the time of hospitalisation.

Primary outcome measures Incidence rate and risk factors for ADRs. The ADRs were detected by an active search in electronic medical records and analysis of spontaneous reports in the hospital pharmacovigilance system.

Results Six hundred neonates were included in the study, where 118 neonates had a total of 186 ADRs. The prevalence of ADRs at the NICU was 19.7% (95% CI 16.7% to 23.0%). The most common ADRs were tachycardia (30.6%), polyuria (9.1%) and hypokalaemia (8.6%). Tachycardia (peak incidence rate: 57.1 ADR/1000 neonates) and hyperthermia (19.1 ADR/1000 neonates) predominated during the first 5 days of hospitalisation. The incidence rate of polyuria and hypokalaemia increased markedly after the 20th day, with both reaching a peak of 120.0 ADR/1000 neonates. Longer hospitalisation time (OR 0.018, 95% CI 0.007 to 0.029; p<0.01) and number of prescribed drugs (OR 0.127, 95% CI 0.075 to 0.178; p<0.01) were factors associated with ADRs.

Conclusion ADRs are very common in NICU, with tachycardia and hyperthermia predominant in the first week of hospitalisation and polyuria and hypokalaemia from the third week onwards.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to characterise adverse drug reactions (ADRs) during the length of stay of neonates in the neonatal intensive care unit.
⇒ This study prospectively analysed ADRs in a large group of neonates undergoing daily intensive care during the hospitalisation period, employing clear and robust detection methods.
⇒ However, the data were obtained from a single institution, which may have compromised the generalisability of the findings.
⇒ The causality of suspected ADRs was not determined by algorithms (Naranjo, Du, Liverpool, etc), they were evaluated only according to criteria of temporal relationship and pharmacological plausibility.

BACKGROUND

Advances related to neonatal intensive care have enabled the survival of increasingly premature neonates, requiring, however, more complex drug treatment. These treatments must consider various factors such as organ immaturity and rapid changes in weight and body composition.[1–3] In addition, the ethical and technical difficulties associated with neonatal research justify the widespread use of off-label drugs, as well as the use of dose regimens extrapolated from those of adults and older children.[4 5] All these factors can lead to toxic plasma concentrations of the drugs, contributing to the appearance of adverse drug reactions (ADRs) in this population.[6]

About 15%–30% of neonates in intensive care suffer at least one ADRs, where 10% of these reactions are serious.[7–10] Although mostly preventable, ADRs in paediatrics increase hospitalisation time and costs.[11] An American study involving 700 admissions to a paediatric intensive care unit showed that hospital length of stay and hospitalisation costs were four times higher in patients with ADRs.[12]

Despite the significant occurrence of ADRs, pharmacovigilance activities in neonatal intensive care units (NICU) are still in the early stages. There are few studies that characterise ADRs in hospitalised neonates and

infants. Additionally, a feature that has not yet been described about ADRs is its temporal profile, most studies describe those with the highest occurrence, but do not relate them to specific periods of hospitalisation. Therefore, it is not known whether there is a difference between the incidence and types of ADRs in the first days compared with neonates who remain for longer periods. The understanding of this problem enables us to prevent and minimise the harmful effects of drugs, establishing safer and more effective therapies.[6] The aim of this study was to characterise ADRs in neonates in intensive care, identifying causative drugs, temporal profile and associated factors.

METHODS

Study design and participants

This is an observational, prospective study performed between January 2019 and April 2021 in the NICU of a reference public maternity unit for high-risk pregnancy in Natal/Brazil. The NICU has 23 beds and an average of 500 admissions per year. All neonates admitted to the NICU for a period of more than 24 hours and using at least one medication were included in the study.

Data collection

From electronic medical records, the following maternal data were collected: age, parity (primipara and miscarriage), pregnancy diseases, type of delivery and premature rupture of membranes. The neonates were characterised according to sex, gestational age at birth, birth weight, diagnosis of hospitalisation and length of stay in the NICU. Admission diagnoses and medications were grouped according to the International Classification of Diseases version 10 and Anatomical Therapeutic Chemical Code, respectively (R1, R2).

Events defined as unexpected changes in the clinical status of the patient such as signs, symptoms or other laboratory and clinical changes that occur after the use of drugs, which may have a causal relationship with the treatment were considered suspicious ADRs.[13] The process of detecting ADRs was carried out by the principal investigator and three pharmacy students who were appropriately trained during the patient's stay in the NICU. For this process, two strategies were used: active search for ADRs in electronic medical records and analysis of spontaneous notifications registered in the hospital's surveillance system.

The active search was carried out through a daily analysis of the medical records using a checklist specifically crafted for ADR detection (refer to the online supplemental file). This checklist was constructed based on monitoring parameters of medications frequently employed in NICU[14 15] and on ADR triggers extracted from the medication module of the IHI Global Triggers Tool.[16] The NICU staff was always contacted when there was doubt in the medical record regarding the altered parameters. Signs suggestive of ADRs identified in the checklist and spontaneous reports were evaluated by the principal investigator for temporality and pharmacological plausibility between the event and the suspected drug. Pharmacological plausibility was investigated through consulting the UpToDate database and conducting a search of scientific articles published in indexed journals. Events with no temporal relationship to the suspected drug or inconsistent with their pharmacological properties were excluded from the analysis to minimise potential bias in ADRs frequency estimation. ADRs were also evaluated for the onset and duration of symptoms, reviewed to avoid duplication of registration and grouped according to the potential causative drug.

Statistical analysis

The sample size of 600 neonates was calculated considering a 50% prevalence of ADRs for an absolute precision of 4% and a 95% CI in the estimates. The statistical analysis was performed in Stata software V.15 (Stata). In descriptive analysis, clinical and therapeutic population variables are presented by absolute and relative frequencies or median and percentiles (25% and 75%), as appropriate. The incidence was presented as ADRs per 1000 neonates-days. The causative drugs and clinical manifestations of ADRs are presented in absolute and relative frequency, and the main ADRs were related to the day of hospitalisation. To determine which clinical characteristics were associated with the occurrence of ADRs, a univariate logistic regression analysis was performed, calculating the respective OR and 95% CI. Variables that had a $p<0.10$ in the univariate analysis were included in a multivariate logistic regression model. Associations with $p<0.05$ were considered significant.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

During the study period (January 2019 to April 2021), 1013 neonates were admitted to the NICU. However, data collection was suspended from March 2020 to January 2021 due to the SARS-CoV-2 pandemic, impacting the loss of 361 patients. Of the remaining 652 patients, 600 were included in the study. Mothers had a median age of 28 years (22–33 years), with 36.3% (202) experiencing their first pregnancy, 24.5% (143) with a history of miscarriage and 31.7% (190) with hypertension as the most frequent disease during pregnancy. Most children were born by caesarean section (70.0%; 390), with a slight predominance of females (50.2%; 300), a median gestational age of 32.4 weeks (29.0–35.3 weeks) and a birth weight of 1635 g (1100.0–2487.5 g). The neonates were admitted to the NICU for a median of 15 days (7–35 days), in which unspecified respiratory distress was the main reason for admission (66.2%; 397). The in-NICU mortality rate was

Table 1 Characteristics of the study population

Characteristics	Value	
Mother's age in years (md, 25th–75th)	28	(22–33)
Primipara (n, %)	212	36.3
History of previous miscarriage (n, %)	143	24.5
Diseases in pregnancy (n, %)		
Gestational hypertension	190	31.7
Urinary tract Infection	175	29.3
Pre-eclampsia/eclampsia	117	19.5
Gestational diabetes	113	18.9
Placental abnormalities	27	30.3
Caesarean section (n, %)	390	70.0
Premature rupture of membranes (n, %)	184	34.1
Sex (n, %)		
Male	298	49.8
Female	300	50.2
Gestational age at birth in weeks (md, 25th–75th)	32.4	(29.0–35.3)
Postnatal age in days (md, 25th–75th)	4	(1.0–7.0)
Birth weight in grams (md, 25th–75th)	1635.0	(1100.0–2487.5)
Days of hospitalisation (md, 25th–75th)	15	(7–35)
Admission diagnoses (n, %)		
Respiratory distress of newborn, unspecified (P22.9)	397	66.2
Respiratory distress syndrome of newborn (P22.0)	54	9.0
Other respiratory distress of newborn (P22.8)	24	4.0
Preterm premature newborn other (P07.3)	13	2.2
Extreme immaturity of newborn (P07.2)	12	2.0
Transient tachypnea of newborn (P22.1)	8	1.3
Death (n, %)	78	13.0

md, 25th–75th: median and 25th and 75th percentile; n, %: absolute and relative frequency.

13% (78 deaths). The demographic and clinical characteristics of the patients are shown in table 1.

A total of 186 ADRs were detected in 118 patients, with 19.7% (95% CI 16.7% to 23.0%) having one or more ADRs. The median postnatal age when the ADR was detected was 10 days (4–20). Table 2 shows the incidence of ADRs grouped by causative drugs. The overall incidence of ADRs was 310.0 cases per 1000 neonates. Caffeine was responsible for 30.6% (95% CI 24.5% to 37.6%) of ADRs and an incidence of 95.0 ADRs per 1000 neonates (95% CI 72.6% to 122.2%), followed by fentanyl (10.2% of ADRs and 30.0 ADRs per 1000 neonates), dobutamine (9.2% and 26.7 ADRs/1000 neonates) and furosemide (8.7% and 25.0 ADRs/1000 neonates). Tachycardia was the most frequent ADRs (30.6% of the total), mainly associated with caffeine (21.5%) and dobutamine (6.5%). Other common ADRs were polyuria (9.1%), hypokalaemia (8.6%), hyperthermia (6.4%), lethargy (4.8%) and hypertension (4.3%).

Figure 1 shows the total and most frequent incidence rate of ADRs during the first 30 days of hospitalisation. The incidence rate in the first 5 days was 104.8 cases per 1000 neonates-days (95% CI 77.1 to 139.4), maintaining similar values until around day 20 (92.3 cases/1000 neonates-days; 95% CI 50.0 to 156.9). After this period, the incidence rate tends to increase until reaching values of 400.0 cases per 1000 neonates-days (95% CI 203.2 to 713.0) between the 25th and 30th day of hospitalisation. Among the most frequent ADRs, the incidence of tachycardia was highest in the first 5 days (57.1 ADR/1000 neonates-days; 95% CI 37.5 to 83.7), decreasing dramatically after day 20 (14.9 ADR/1000 neonates-days; 95% CI 7.5 to 73.6), similar to that observed with hyperthermia in a shorter period where the peak incidence occurred in the first 5 days (19.1 ADR/1000 neonates-days; 95% CI 8.8 to 36.2) and the lowest incidence between the 6th and 10th (5.5 ADR/1000 neonates-days; 95% CI 0.9 to 18.2). Following a distinct pattern, polyuria had an incidence of 7.1 ADR/1000 neonates-days (95% CI 1.8 to 19.4) in the first 5 days and remained at these levels in the first 3 weeks, however, it increased abruptly between the 25th and 30th day (120.0 ADR/1000 neonates-days; 95% CI 30.5 to 326.6). Hypokalaemia showed a similar pattern where its lowest incidence rate was detected between days 11 and 15 (4.7 ADR/1000 neonates-days; 95% CI 0.2 to 22.9), but it increased significantly until the end of the evaluated period (120.0 ADR/1000 neonates; 95% CI 30.5 to 326.6). The incidence of lethargy and hypertension was characterised by a homogeneous distribution throughout the period, ranging from 5.5 to 9.5 ADR per 1000 neonates-days.

The univariate analysis (figure 2) identified the following factors to be associated with the occurrence of ADRs: mothers with diabetes during pregnancy (OR 0.556, 95% CI 0.285 to 1.085; p=0.09), lower gestational age (OR 0.886, 95% CI 0.844 to 0932; p>0,01), lower birth weight (OR 0.9994, 95% CI 0.9991 to 0.9997; p>0.01), longer hospitalisation (OR 1.041, 95% CI 1.033 to 1.050; p>0.01) and number of prescribed drugs (OR 1.205, 95% CI 1.164 to 1.250; p<0.00). However, the multivariate analysis identified only longer hospitalisation time (OR 0.018, 95% CI 0.007 to 0.029; p<0.01) and number of prescribed drugs (OR 1.135, 95% CI 1.078 to 1.195; p<0.01) as being related to the occurrence of ADRs in neonates.

DISCUSSION

From a prospective cohort of 600 neonates in intensive care, we found that about one-fifth had at least one ADRs, mainly related to caffeine, fentanyl, dobutamine and furosemide. When considering all ADRs, their occurrence tends to increase after the fourth week of NICU, however, among the most frequent ADRs, there are

Table 2 Incidence of the main causative drugs and adverse drug reaction (ADRs) profile

Drugs	N	% (95% CI)	Incidence rate per 1000 (95%CI)	ADRs*
Caffeine	57	30.6 (24.5 to 37.6)	95.0 (72.6 to 122.2)	Tachycardia (40), reflux (10), hyperglycaemia (4), polyuria (1), tremors (1) and thromboembolism (1)
Fentanyl	19	10.2 (6.2 to 17.3)	30.0 (18.3 to 47.0)	Withdrawal syndrome (6), lethargy (4), spasms (3), constipation (2), hypertonia (2), agitation (1) and bradycardia (1).
Dobutamine	16	8.6 (5.4 to 13.5	26.7 (15.8 to 42.4)	Tachycardia (12) and hypertension (4)
Furosemide	15	8.1 (5.0 to 12.9)	25.0 (14.5 to 40.3)	Polyuria (9), hypokalaemia (5) and hyponatraemia (1)
Prostaglandin E1	14	7.5 (4.5 to 12.2)	23.3 (13.3 to 38.2)	Hyperthermia (11), bradycardia (1), periostitis (1) and hypoglycaemia (1)
Hydrochlorothiazide	13	7.0 (4.1 to 11.6)	21.7 (12.1 to 36.1)	Polyuria (5), hypokalaemia (5) and hyponatraemia (3)
Dopamine	6	3.2 (1.5 to 6.9)	10.0 (4.1 to 20.8)	Hypertension (3), tachycardia (2) and polyuria (1)
Amphotericin B	6	3.2 (1.5 to 6.9)	10.0 (4.1 to 20.8)	Hypokalaemia (5) and thrombocytopaenia (1)
Phenobarbital	5	1.7 (1.1 to 6.1)	8.3 (3.1 to 18.5)	Lethargy (4) and bradycardia (1)
Others	36	19.4 (14.3 to 25.6)	60.0 (42.7 to 82.2)	Hypotension (6), dyspnoea (4), rash (4), oliguria (4), tachycardia (3), eosinophilia (2), hyperchromia (2), lethargy (1), arrhythmia (1), diarrhoea (1), erythema (1), haematemesis (1), haematochezia (1), hypertension (1), hyperthermia (1), hypokalaemia (1), polyuria (1), osteodysplasia (1).
Total	186	100.0	310.0 (267.8 to 357.0)	–

*Value expressed in absolute frequency.

distinct temporal profiles. Tachycardia and hyperthermia manifest primarily in the first days and then gradually decrease; while polyuria and hypokalaemia predominate in neonates with longer hospital stays. A third profile involves a homogeneous incidence throughout the period (hypertension and lethargy). Additionally, we observed that the number of prescribed drugs and the length of hospital stay were associated with a higher occurrence of ADRs.

In this study, we detected ADRs through daily assessment of medical records guided by trigger signs. The prevalence of ADRs in our NICU was similar to that found by Belén Rivas *et al*[8] in which 17% of neonates in intensive care in a Spanish hospital had at least one ADRs. These authors used the same ADRs definition and detection method. On the other hand, De las Salas *et al*[10] following 285 patients from the neonatology service of two hospitals in Colombia, and Aranda *et al*[7] with 200 patients from a hospital in Canada, found higher prevalences, 28% and 30%, respectively. However, the former detected adverse reactions retrospectively in a cross-sectional study and the latter, published in 1981, shows a profile of prescribed drugs that is quite different from today.

Regarding our methodology, we highlight the daily monitoring of objective parameters such as heart rate, respiratory rate and body temperature, as well as the

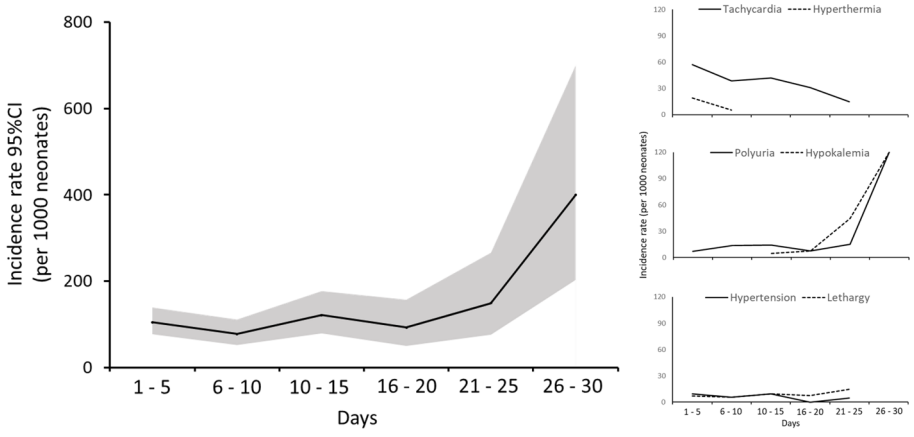

Figure 1 Incidence rate of total and principal adverse drug reactions detected during the first 30 days of hospitalisation in the neonatal intensive care unit.

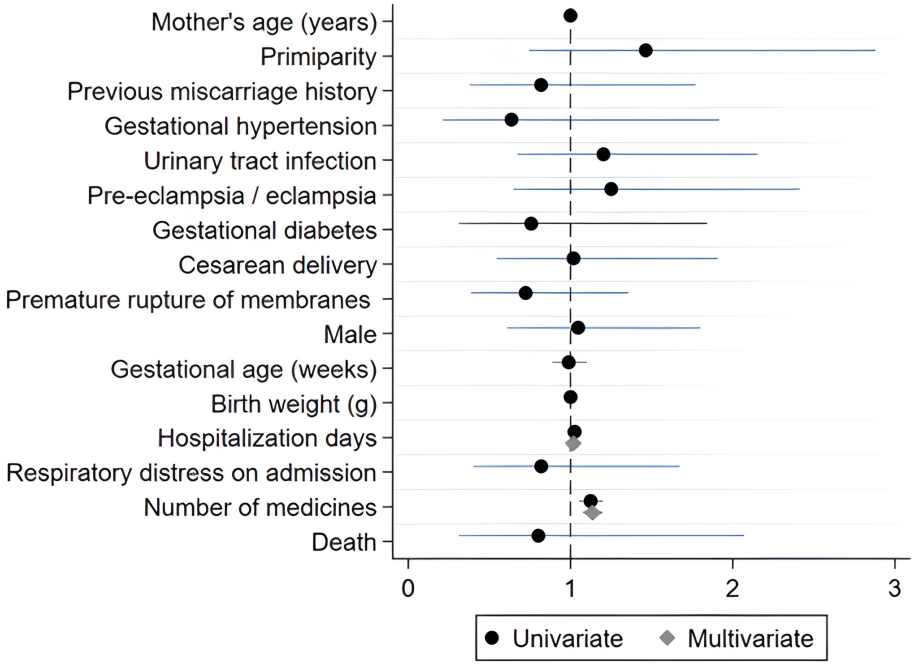

Figure 2 Univariate and multivariate logistic regression of predictors for adverse drug reactions occurrence.

search for potential adverse events with the NICU team. Unlike other authors,[8–10] antibiotic-induced cytotoxic reactions such as nephrotoxicity and thrombocytopaenia were not predominant in our study. These reactions are uncommon,[17] so such divergences may be due to methodological differences.

Most of the ADRs identified in our study were dose dependent, such as tachycardia associated with administration of dobutamine and caffeine. Neonates are more predisposed to drug accumulation in the body due to their physiological immaturity, with emphasis on lower liver and kidney activity, which progressively increases in the first 6 months of life.[2 3] Another feature of neonatal pharmacotherapy is the need for frequent dose adjustments because of changes in body weight; neonates may lose up to 15% of their total body water during the first 2 weeks of life.[2 4 18 19] Specifically, in the first weeks of life, variations in body weight and lower elimination capacity may contribute to drug accumulation and increased occurrence of ADRs.

To our knowledge, this is the first study to characterise ADRs during the length of stay of neonates in the NICU. We observed an increase in ADRs incidence with the length of hospitalisation, identifying three distinct profiles for the main ADRs. Tachycardia and hyperthermia associated with medication use predominated during the first 5 days of the patients' hospitalisation, with a significant reduction in the following days. Caffeine clearance in neonates depends on the renal maturation process, mainly on the glomerular filtration rate, which increases sharply in the first weeks of life, so tachycardia is common in this period.[20 21] Another potential explanation is the development of pharmacological tolerance due to prolonged use of caffeine, which is frequently administered to extremely premature neonates.[20] Hyperthermia induced by continuous infusion of prostaglandin E1 was a common occurrence in our sample. Prostaglandin E1 is a drug indicated to maintain the functioning of ductus arteriosus in neonates with channel-dependent heart disease.[22] Higher doses of the drug are usually employed at the beginning of treatment, but careful titrations are done later to mitigate its adverse effects.[23]

In contrast, polyuria and hypokalaemia have a low incidence in the initial days of hospitalisation but show a sharp increase from the 20th day onwards. The response of furosemide, the main causative drug, on the kidneys of neonates is directly related to the increased glomerular filtration rate, which occurs rapidly in the first month of life.[2 24–26] However, the increase in polyuria cases is possibly a consequence of the high prescription of diuretics for the treatment of patients with bronchopulmonary dysplasia, a disease that appears after a long period of mechanical ventilation.[25 27] The persistence of polyuria eventually leads to electrolyte disturbances such as hypokalaemia.[28]

Unlike the other ADRs described, hypertension and lethargy were events evenly distributed during hospitalisation. These events were mainly associated with the use of dobutamine in the case of hypertension, and continuous infusion of fentanyl and the use of phenobarbital in the case of lethargy. Reactions involving these drugs are quite common in NICU, especially in clinically unstable patients, because their dose adjustments depend exclusively on the patient's clinical response, such as stabilisation of blood perfusion, for dobutamine, seizure control, for phenobarbital, and pain relief, for fentanyl.[29–31]

Additionally, the sudden realisation of toxic concentrations for these drugs due to variability in body weight and postnatal age, and in the specific case of fentanyl, the lack of an adequate tool for monitoring analgesia contribute to the occurrence of these events.[29 32 33]

There are almost no studies addressing risk factors for ADRs in neonatology. Our study showed that polypharmacy and prolonged hospitalisation were associated with higher occurrence of ADRs in neonates in intensive care. Belén Rivas *et al*[8] and De las Salas *et al*[10] also identified an association between polypharmacy and adverse reactions, but they did not use a multivariate approach to analyse the data. Additionally, it is worth noting that polypharmacy is a risk factor for ADRs previously described in the literature in paediatrics.[11 34] The association between length of hospitalisation and ADRs was also observed by Rashed *et al*[11] and Du *et al*[12] in hospitalised children.

This study prospectively analysed ADRs in a large group of neonates undergoing daily intensive care during the hospitalisation period, employing clear and robust detection methods. However, a limitation of the study was that its performance was in a single centre, which may have compromised the generalisability of the findings. Another limitation was that we did not apply algorithms (Naranjo, Du, Liverpool, etc) for ADRs causality determination, but evaluated events according to temporal relationship criteria and pharmacological plausibility. We also did not include in our analysis the use of off-label and unlicensed drugs as a potential risk factor for ADRs, nor the outcomes of these events in the medium and long term. Studies to clarify these questions are needed.

It should be emphasised that to optimise the follow-up of neonates in NICUs, health professionals must perform a strict daily monitoring, making, when necessary, dose adjustments due to the constant changes in body composition. In addition, possible triggers for adverse reactions during the hospitalisation period should be monitored. This follow-up should focus mainly on monitoring heart rate and body temperature in the first days of hospitalisation and serum electrolytes later, at the end of the third week.

CONCLUSION

In summary, ADRs are common events in the NICU and their incidence increases with lengthening of hospitalisation time. Dose-dependent manifestations such as tachycardia (mainly induced by caffeine and dobutamine) and hyperthermia (prostaglandin E2) are more frequent in the first days of NICU. In contrast, polyuria and hypokalaemia related to diuretic administration occur after longer periods (> 3 weeks). Comparatively less frequent, hypertension and lethargy are evenly distributed throughout the NICU period. The number of prescribed drugs and the length of hospitalisation were independent factors associated with ADRs. These findings show that healthcare professionals should closely monitor neonates in their first week and from the fourth week of NICU. Also, these professionals should carefully evaluate patients with more than five prescribed drugs.

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Contributors Contributors RWDL, AGO and RRM designed the study. RWDL, DPM, LCR and FEMF collected the data. AGO and RRM analysed the data. DPM, LCR and FEMF prepared the draft of the manuscript. RWDL, AGO and RRM critically reviewed, rewrote, edited and finalised the manuscript. All authors reviewed the manuscript. RRM is the guarantor of the study.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study was approved by the Institutional Review Board of the University Hospital Onofre Lopes (No. 2.591.495/2018) and written consent was obtained from the guardians of each neonate. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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