Dose-Related Adverse Drug Events in Neonates: Recognition and Assessment

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Abstract

The efficacy and safety of a drug is dose or exposure related, and both are used to assess the benefit-risk balance of a given drug and ultimately to decide on the specific drug license, including its dose and indication(s). Unfortunately, both efficacy and safety are much more difficult to establish in neonates, resulting in very few drugs licensed for use in this vulnerable population. This review will focus on dose-related adverse events in neonates. Besides the regulatory classification on seriousness, adverse event assessment includes aspects related to signal detection, causality, and severity. Disentangling confounders from truly dose-related adverse drug events remains a major challenge, as illustrated for drug-induced renal impairment, drug-induced liver injury, and neurodevelopmental outcome. Causality assessment, using either routine tools (Naranjo algorithm, World Health Organization's Uppsala Monitoring Center causality tool) or a Naranjo algorithm tailored to neonates, still does not sufficiently and reliably document causality in neonates. Finally, very recently, a first neonatal severity-grading tool for neonates has been developed. Following the development of advanced pharmacokinetic approaches and techniques to predict and assess drug exposure, additional efforts are needed to truly and fully assess dose adverse drug events. To further operationalize the recently developed tools on causality and severity, reference databases on a palette of biomarkers and outcome variables and their covariates are an obvious next step. These databases should subsequently be integrated in modeling efforts to truly explore safety outcome, including aspects associated with or caused by drug dose or exposure.

Keywords

There are several reasons why drug development in neonates and its subsequent licensing remain very limited in neonates. The most relevant burden to consider is the cumbersome reliable documentation of efficacy and safety in this population, which is even more pronounced than in the pediatric setting.[1,2] This is because both efficacy and safety are dose or exposure related but are more difficult to establish in neonates.[3–5] Related to adverse events (AEs), this includes assessment of their presence (signal detection), causality, and severity, besides seriousness within the framework of regulatory requirements and guidelines (Figure 1).[3]

For signal detection, as well as for causality and severity assessment, disentangling confounders from adverse drug events remains a major challenge.[3,4] We first illustrate the relevance of dose-related adverse drug events, based on examples in which dose-related events are either not specific (aminoglycosides) or specific (caffeine, dexamethasone) to this population. A narrative review on the population-specific aspects related to either signal recognition (renal, hepatic, neurodevelopmental) or causality and severity assessment to further stress the burdens on safety assessment in neonates follows these illustrations. For issues related to dose selection in (pre)term neonates, we refer to another review on this specific topic in this supplement.[6]

Relevance of Dose-Related Adverse Drug Events in Neonates

Using an illustrative approach, we aim to highlight the relevance of the dose- or exposure-related toxicity of a drug with a similar (oto- and nephrotoxicity)—but not equal—toxicity profile (aminoglycosides), and

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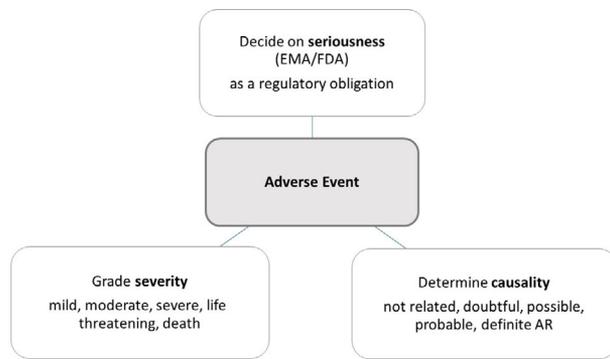Email: karel.allegaert@uzleuven.be

Decide on **seriousness**
(EMA/FDA)
as a regulatory obligation

Adverse Event

Grade **severity**
mild, moderate, severe, life
threatening, death

Determine **causality**
not related, doubtful, possible,
probable, definite AR

Figure 1. Adverse event assessment covers the assessment on seriousness, severity, and causality. AR, adverse reaction; EMA, European Medicines Agency; FDA, US Food and Drug Administration.

2 other examples with specific neonatal indications and adverse drug events (caffeine or dexamethasone, apnea and bronchopulmonary dysplasia as indications, dose-related AEs like bronchopulmonary dysplasia or neurodevelopmental outcome). With this approach, we aim to stress the different aspects of developmental toxicity in neonates: either differences in incidence and severity with similar exposure or differences in type of events because of population-specific events). This is relevant to neonatal drug development and pharmacotherapy, as exposure, intended effects, and AEs relate to dose, and all these issues (dose, effects, AEs) may be specific to neonates.

Toxicity has limited the use of aminoglycosides, but there is a consistently lower rate of oto- and nephrotoxicity in neonates as compared to adults. This suggests maturational toxicodynamics favoring neonates. The most recent Cochrane review on 1-dose-per-day ("extended time interval") gentamicin compared to multiple doses per day in neonates suggests (pooled, all dosing regimens) that the incidence of ototoxicity was 1.4% (n = 3/214), whereas no cases of nephrotoxicity (increased creatinine or decreased creatinine clearance, n = 348) were detected.[7] The extended time interval more commonly resulted in "target" drug exposure, but no differences in renal toxicity (creatinine, urine output) were observed. The same holds true for comparative studies (once- vs twice-daily dosing, same daily dose) of amikacin with a focus on renal tubular biomarkers (like retinol-binding protein, β2-microglobulin, or alkaline phosphatase).[8]

Although mechanisms related to aminoglycoside toxicity are largely unrelated to age (eg, bacterial resistance, nephro- and ototoxicity, impact on intestinal microbiome), maturation-related aspects may still result in differences in toxicity patterns in neonates, either protective or more vulnerable. Both nephro- and ototoxicity relate to cellular uptake and accumulation of aminoglycosides with subsequent mitochondrial stress

and apoptosis.[9] The uptake is facilitated at the surface of renal tubular or cochlear hair cells because of expression of specific ligands like megalin and the colocalized cubilin at their brush border. Maturation results in a lower expression of these ligands in neonates. Cellular aminoglycoside accumulation may also occur through a megalin-independent cation influx. This influx may be enhanced by noise (mechano-electronic transduction ion channels) or loop diuretics (cation channels). This explains that in epidemiologic studies, like a pooled analysis on 1629 neonates exposed to amikacin, associations between ototoxicity with amikacin exposure were documented, but prematurity, length of stay, and disease severity were much stronger predictors.[9]

Caffeine and dexamethasone are 2 examples of more newborn-specific safety outcome when considering dose-related adverse drug-related events. We have recently reported on the caffeine drug development program as conducted in the United States and assessed by the US Food and Drug Administration as an illustration of a disease (apnea of prematurity) for drugs not used for these specific diseases in adults or older pediatric populations.[5] In essence, the caffeine program was limited to a single double-blinded placebo-controlled clinical trial in preterm neonates (loading dose, 20 mg/kg; followed by 5 mg/kg caffeine citrate as maintenance daily dose) with apnea of prematurity with sparse pharmacokinetic (PK) sampling. As the disease is unique to neonates, a PK or PK/pharmacodynamic study would likely be conducted to inform dose selection for the pivotal efficacy study and evidence of effectiveness from >1 trial might have been useful.[5] In this case, the extensive clinical experience and academic research on caffeine in infants with apnea of prematurity was used as circumstantial supportive evidence, mainly driven by the Caffeine for Apnea of Prematurity trial.[10] In the mean time, the labeled dose has been further explored, as covariates (like postnatal age) were not yet fully considered.[11]

From a safety perspective, we highlight 2 specific illustrations (intracranial bleeding and seizures, bronchopulmonary dysplasia) showing the relevance of dose-related or adverse drug-related events for this drug. In a pilot study (n = 74), early high-dose caffeine (initial dose, 80 mg/kg vs 30 mg/kg in the first 36 hours), preterm infants randomly assigned to early high-dose caffeine had a higher incidence of cerebellar injury (36% vs 10%) with impact on early motor performance.[12] In a post hoc analysis, a trend to an increase in seizure incidence and burden was also observed.[13] Related to prevention of bronchopulmonary dysplasia (BPD) as an additional indication, the number needed to treat (6 to 22) strongly depends on the variable baseline risk.[14] However, the correlation between serum caffeine levels and cytokine

profiles (reflecting inflammation as the mechanism for BPD) displays a U-shaped pattern, both in animal experimental research and in the preterm newborn.[15,16] This is likely linked to Toll-like receptor-4 upregulation in umbilical cord leukocytes with high caffeine concentrations.[17]

Postnatal dexamethasone has also been assessed to either prevent or treat BPD in neonates, with at present a secondary prevention or curative concept to focus on short-term, low-dose (0.15 to 0.2 mg/kg/day) courses in the highest-risk cases.[18] This is because administering dexamethasone to prevent BPD in the first week of life has been associated with an increasing risk for cerebral palsy.[19] In contrast, BPD in itself is also associated with poorer neurodevelopmental outcome despite faster weaning from ventilator support, so that short-term, "early" curative treatment might be a balanced assessment on the risk related to exposure vs risk related to the disease.[18]

Signal Detection

Effective detection of a signal of an AE or (potential) adverse drug reaction (ADR) necessitates that clinicians, clinical researchers, sponsors, or authorities recognize an "abnormal" trend or event compared to "normal" events or reference values. Specific to neonatal pharmacovigilance, signal detection should occur in a setting with a lot of noise (extensive variability in commonly used biomarkers, relevant and diverse morbidity characteristics).[3]

Renal

Maturational physiological changes are most prominent in early infancy, and are further affected by additional covariates, like disease characteristics, therapeutic interventions, or pharmacotherapy. This results in extensive variability in glomerular filtration rate and subsequent biomarkers, like serum creatinine (most commonly used indicator of glomerular filtration rate). Furthermore, serum creatinine values are also assay dependent, as the Jaffe assay is affected by bilirubin or albumin, both of specific relevance in the neonatal population. In the mean time, enzymatic assays are more commonly used in neonates, while harmonization (isotope dilution mass spectrometry traceability) has further limited but not fully eliminated interassay variability.[20,21]

Jetton and Askenazi[22] constructed an acute kidney injury (AKI) definition (neonatal modified Kidney Disease: Improving Global Outcomes) specific for use in neonates. Besides urine output indicators, this definition is based on a creatinine increase ≥ 0.3 mg/dL or 1.5- to 1.9-fold increase from baseline within 48 hours or 7 days respectively (stage 1), a creatinine
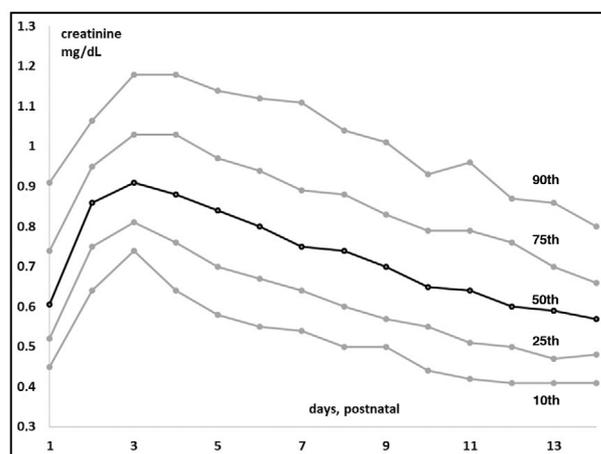

Figure 2. Creatinine values in a cohort of extremely low-birth-weight neonates as reference centile trends (table, gray lines) over time in the first 14 days of postnatal life.[23]

increase from baseline ≥ 2 to 2.9 (stage 2), or creatinine >2.5 mg/dL, renal ≥ 3-fold from baseline (stage 3). It is hereby suggested that a serum creatinine of 2.5 mg/dL reflects an estimated glomerular filtration rate <10 mL/min/1.73 m^2. However, when subsequently applied to clinical observations in extremely low-birth-weight infants, an AKI incidence of about 50% was observed.

This means that there is at least not sufficient granularity in this tool to fully discriminate between normal physiological trends and renal impairment, including drug- or dose-related AEs. The normal trends over postnatal age (days) for a cohort of extremely low-birth-weight cases are provided in Figure 2, illustrating an initial increase to peak on day 3, with a subsequent decrease in progress.[23] However, this increase is on average 0.3 mg/dL, equal to AKI stage 1. Another population of interest is term neonates following perinatal asphyxia. As AKI is rather common in this setting, it is again difficult to disentangle disease-related trends from, for example, therapeutic interventions like whole-body hypothermia (WBH) or to assess the (side) effects of add-on therapeutic interventions in neonates undergoing whole-body hypothermia.[21] This means that the baseline is to a certain extent a construct that does not fully serve physiological trends in creatinine in neonates.

Polypharmacy in neonatal intensive care patients is common. Consequently, besides the variability related to maturation and diseases, drugs and especially combinations of drugs are relevant when exploring signals of AKI. Although this may result in difficulties related to causality assessment, such studies are relevant because they are reflective of the level of tolerance of toxicity in a real-world setting. Aminoglycosides, glycopeptides (infectious diseases), and nonsteroidal anti-inflammatory drugs (to induce closure of a patent

ductus arteriosus) are commonly used drugs, and it has been reported that indomethacin results in a more pronounced decrease in renal clearance when compared to ibuprofen. When combined in a cohort of preterm neonates with an AKI incidence of 17%, and compared to gentamicin + indomethacin as reference, vancomycin + piperacillin-tazobactam, and furosemide + tobramycin were associated with a proportionally lower risk of developing AKI. However, the main driver to develop AKI was a longer duration (total dose, exposure) of a combination of nephrotoxic therapies.[24] In another study, the Baby NINJA (Nephrotoxic Injury Negated by Just-in-Time Action) study documented that a reduction of exposure of nephrotoxic drugs (duration of treatment) resulted in a decrease in AKI incidence and severity.[25] This illustrates that knowledge on drug-related nephrotoxic risks can result in improved clinical practice and outcome, and that–besides regulatory relevance–this also has an impact on routine clinical care.

Drug-Induced Liver Injury

Data suggest that the incidence and drugs involved in pediatric drug-induced liver injury (DILI) are not similar to those encountered in adult medicine, with, for example, valproic acid, dactinomycin, and ampicillin more frequently causing pediatric DILI.[26] This suggests that both drug use patterns and maturational pathophysiology (eg, lower; acetaminophen as illustration) should be considered when comparing DILI patterns in neonates compared to adults. Furthermore, signal detection is also an issue. This is because DILI assessment is generally detected or assessed based on "hepatic" biomarkers and their trends, like liver enzymes (alanine aminotransferase [ALT], aspartate transaminase [AST]), total bilirubin, or indicators of cholestasis (direct bilirubin, gamma-glutamyl transferase, alkaline phosphatase, bile acids).[26]

When applied to neonatal observations, these markers have their limitations as, for example, (indirect) hyperbilirubinemia is very common and part of normal developmental physiology in (pre)term neonates, with a natural trend over time to peak on days 3 to 4 with a subsequent decrease over the first 10 to 14 days of postnatal life. However, this natural pattern is further affected by phototherapy as therapeutic intervention, with thresholds to initiate treatment that varies based on the clinical characteristics (gestational age, postnatal age, disease severity or sepsis, perinatal asphyxia) of the individual newborn, with the intention to prevent kernicterus.[27] A specific risk relevant to neonatal clinical pharmacology is competitive drug-to-bilirubin albumin binding (ceftriaxone, ibuprofen, or indomethacin) as kernicterus relates to free unconjugated bilirubin levels.[28] A similar age-related aspect
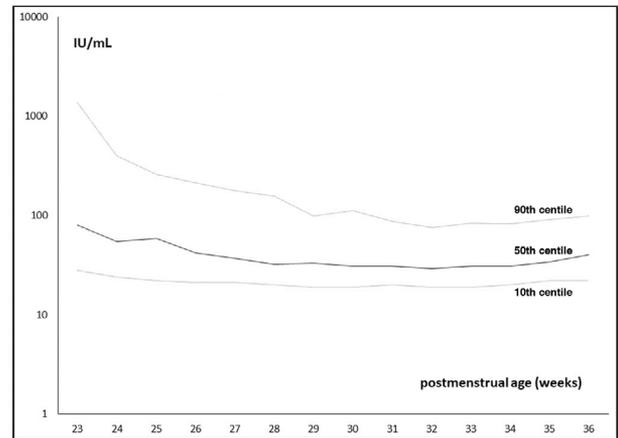

Figure 3. Postmenstrual age-driven trend in reference values (10th, 50th, 90th centiles) in aspartate transaminase (AST, log displayed) values.[30]

should be considered when assessing levels and trends in alkaline phosphatases in neonates or young infants, as this value commonly is a "pooled" value of hepatic, intestinal, and/or bone isoenzymes. Because metabolic bone disease is rather common in infants born preterm, elevated alkaline phosphatases are a poor DILI marker. However, alkaline phosphatase measurement as standalone to assess metabolic bone disease is not supported by currently available evidence.[29] Reference values of AST and ALT have been suggested, but such data sets do not yet fully explore aspects specific to either maturational or nonmaturational factors such as disease, interventions, and pharmacotherapy. At least, based on 7006 samples from 1860 neonates (gestational ages, 22 to 36 weeks), extremely premature infants have higher liver enzyme (ALT, AST) activities as compared to neonates at later corrected gestational ages. This can either relate to maturational differences or reflect more severe illness immediately after birth. To illustrate this, trends on AST plasma enzyme activity (10th, 50th, and 90th centiles) vs postmenstrual age are illustrated in Figure 3.[30]

A relevant clinical condition in neonates that has a nonmaturational impact on liver enzyme values is perinatal asphyxia, and the availability of reference values in such a specific population are relevant in the assessment of a potential DILI vs asphyxia-related events. Muniraman et al[31] reported on biomarkers of hepatic injury and function and described the impact of hypoxic ischemic encephalopathy severity and whole-body hypothermia on these patterns. To further illustrate the pattern over postnatal age, we have summarized the postnatal pattern in liver enzymes (AST, ALT) observed in a cohort of asphyxia cases undergoing whole-body hypothermia in Figure 4.

Such data sets can subsequently be used to compare results as collected in either randomized studies on the
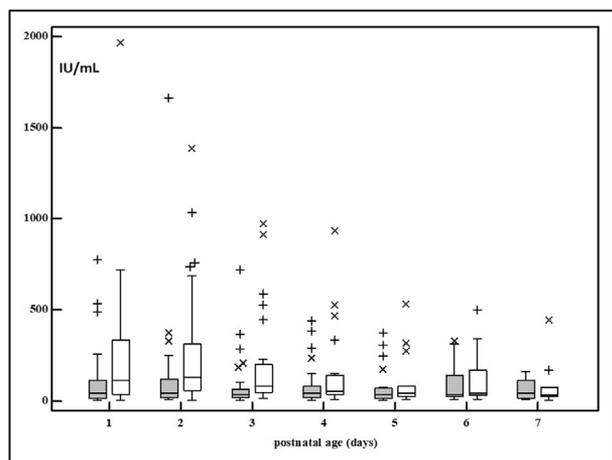
Figure 4. Postnatal (days) trends in aspartate transaminase (AST, white boxplots) and alanine aminotransferase (ALT, gray boxplots) in neonates undergoing whole-body hypothermia because of moderate to severe asphyxia.
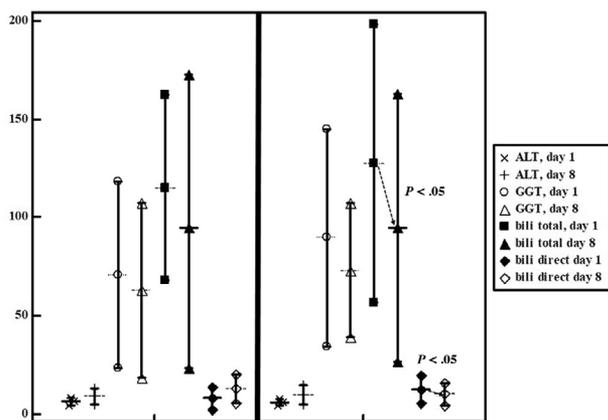

Figure 5. Hepatic biomarkers (ALT, GGT, total bilirubin, and direct bilirubin) as collected just before, and 1 week after initiation of intravenous lipids (either soybean, right panel [0] or soybean, medium-chain triglycerides, and olive and fish oils, left panel [1]).[33] ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase.

impact of specific compounds, like intravenous lipids or even excipients, or to assess the (side) effects of add-on therapeutic interventions in neonates undergoing whole-body hypothermia, like the ongoing study on allopurinol, as this drug might have hepato-protective effects.[32]

In neonates, prolonged total parenteral nutrition is associated with a relevant portion of neonatal DILI cases, with the type of lipid composition (soybean, medium-chain triglycerides, olive and fish oils vs soybean) as a modulating factor. In such studies, total and direct bilirubin were used as biomarkers for cholestasis, with a significantly more pronounced decrease for total bilirubin, and a less pronounced increase (both $P < .05$) in direct bilirubin in cases treated with soybean, medium-chain triglycerides, and olive and fish oils (Figure 5).[33] This is a clear illustration that very early

biomarkers of DILI in (pre)term neonates in a randomized controlled trial setting can result in useful observations as surrogate markers of differences in hepatic tolerance.[33]

Alternative approaches to search for signals are either intrapatient prospective trends of hepatic biomarkers before, during, and following exposure or to compare these trends in cases either exposed or not exposed to a given compound. Based on intrapatient trends and with ALT, AST, and gamma-glutamyl transferase as biomarkers, we generate evidence on the hepatic tolerance of intravenous paracetamol (acetaminophen) in (pre)term neonates.[34] Both approaches (intra trends + comparison) were combined to assess the hepatic tolerance of short-term, low propylene glycol exposure (34 mg/kg/24 h) in neonates, followed by a formulation-controlled evaluation (acetaminophen formulation, either containing or not containing propylene glycol) to further document hepatic tolerance.[35]

Long-Term Neurocognitive Outcome

Examining long-term outcome associated with neonatal drug exposure, either related or not related to a clinical study, remains an important effort that should be encouraged.[4] This is also reflected in the European Medicines Agency guideline on the investigation of medical products in the (pre)term neonate, where it is stated that "extrapolation of safety from other age groups to neonate is usually not possible. …" Additional end points related to long-term physical and psychosocial development should be studied. The difficulty to obtain data on short- and long-term effects of medicinal products on the developing brain, as effects may become apparent only later in life, increases the level of requirements for trials of medicinal products in neonates. Therefore, long-term monitoring for medicinal products affecting the central nervous system may be required."[36]

However, such long-term studies have major challenges related to logistics (patient retention, relocation), tools (quality control, diagnostic accuracy, interpretation of the measures) and–very relevant– environmental factors after discharge that have effects like parental education or socioeconomic status. These aspects overall result in a poor correlation between exposure and subsequent safety signals, either short term (until 24 months corrected age) or long term.[4] At least, it is important for researchers to consider if long-term neurodevelopmental outcome is a therapeutic outcome target or a safety outcome variable. This should be based on the potential of the investigational drug to cause such effects, with the earlier mentioned examples on aminoglycosides, caffeine, and dexamethasone to illustrate the relevance of such studies, including the fact that findings also depend on dosing or

exposure (dose-effect relationship) and indication (eg, dexamethasone prevention vs curative). A framework on how to approach the assessment of long-term neurodevelopmental outcome following a trial of medical products in the newborn has recently been published by the International Neonatal Consortium.[37] It is necessary to evaluate trial participants up to an age at which this provided reasonable reliable indicators of long-term neurodevelopmental outcome. For safety-focused assessment, the primary neurological outcome likely is at 2 years (corrected age in preterm infants).

To a large extent, this is also based on the fact that such data are commonly collected as a quality outcome assessment in former preterm neonates or term neonates with specific risks. Related to this, it reduces the additional burden for parents and patients, and a consensus scheme on categorization of health status (moderate or severe [neurodevelopmental] impairment criteria) at 2 years has been published.[37] Despite their common use and consensus, there are limitations like misclassification of the outcome or missing more "advanced" aspects of child development (like neurocognition, attention, social, behavior) so that the predictive power of 2-year outcome is limited and do not always predict function later in life.[38]

Causality and Severity Assessment

For signal detection, as well as for causality and severity assessment, disentangling confounders from adverse drug events remains a major challenge.[3,4] The principal difference between an AE and an ADR is that a causal relationship is at least suspected for the latter but is not required for the former. While the regulatory environment on causality assessment and reporting in neonates is similar to other populations, causality assessment of events in neonates is more difficult.[3] This is in part due to inconsistent terminology and case description but is further complicated by the need to disentangle real ADRs from confounders, as illustrated higher for drug-related AKI, DILI, or neurodevelopmental outcome: Signal detection in a setting with a lot of noise (extensive variability in commonly used biomarkers, relevant, and diverse morbidity characteristics) is cumbersome.[3]

Severity grading (grades 1-5) is commonly subdivided into mild, moderate, severe, life threatening, and death. Based on consensus documents, AE severity scales provide guidance on severity grading for a given AE or ADR and help to assess importance of the event. Standardization of AE severity criteria holds promise to make safety information more reliable and comparable across trials or in the clinical setting (pharmacovigilance), but the availability and validity of scales applicable to neonates is an issue.

Causality

Because of this "noise," commonly used scoring systems like the Naranjo algorithm or the World Health Organization's Uppsala Monitoring Center causality tool do not sufficiently and reliably document causality in neonates.[39] More recently, a population specific tool (modification of the original Naranjo algorithm to neonates) to assess causality in neonates has been reported by Du et al.[40] Based on 13 items (yes/no/not applicable) that could be quantified ($\geq$14, 7-13, 3-6, $\leq$2), categorization of causality (definite, probable, possible, unlikely, not related) was facilitated.[40]

However, their reliability remains fair, as illustrated in a recently reported prospective observational study in a single unit. Suspected ADRs—a subgroup of AEs–were observed to affect 18% of the admitted (n = 193) neonates, with most neonatal organ systems affected, and a wide range of drugs (top 3 = gentamicin, morphine, dopamine). These ADRs were subsequently assessed by 6 assessors, and 3 different existing methods (the modified Naranjo score, the Liverpool ADR Causality Assessment Tools, and the Karch and Lasagna method).[40,41] Irrespective of the score, and despite the fact that the study was conducted on a data set of suspected ADRs, only "fair" interrater and intertool reliability was reached.[41]

Severity

Scales to grade severity commonly have a specific focus on a therapeutic or disease area and not so much a population, as has been illustrated for vaccine trials (Division of Microbiology and Infectious Diseases), acquired immune deficiency syndrome (Division of AIDS table), or–with a background in oncology–the common terminology criteria for adverse events (CTCAE). However, all these scales are compatible for assessment in adults and children, while none of these grading systems are tailored or fitted to neonatal AE assessment.[3,39] To further illustrate this, the CTCAE grading system includes "instrumental activities of daily life and self-care" as severity markers, they are not applicable to neonates. Furthermore, in the most recent revision to the CTCAE, terms, definitions, and grading are proposed within a generic framework using a descriptive terminology that incorporates system organ class. Neonatal event-specific scales to assess safety should include neurological, cardiovascular, respiratory, gastrointestinal, and infectious events, linked to terms in the Medical Dictionary for Regulatory Activities.[3,4] This coaligns with the pediatric terminology AE working group initiative, but with a focus on neonates.[42]

Very recently, the International Neonatal Consortium Adverse Event Severity Scale has been constructed, based on a stepwise, Delphi structured

approach as an attempt to address this gap in neonatal clinical research. Immediate functional consequences (on age-appropriate behavior and basal physiological functions), together with resulting care changes were established as the parameters of the generic AE severity scale. Age-appropriate behavior hereby refers to oral feeding behavior, voluntary movements and activity, crying pattern, social interactions, and perception of pain as the "instrumental activities of daily life and self-care" construct applied to the neonatal population. *Care changes* were either "minor" (brief, local, noninvasive, or symptomatic treatments) or "major" (surgery, addition of long-term treatment, upscaling care level). We hereby explicitly decided not to include long-term outcome as a marker of AE severity, as it might be difficult to establish a direct causal link. Furthermore, the overall goal of this scale is to create reliable and immediate safety signals prompting awareness, which is not compatible with assessing the severity of an event when the final outcome is only known years later.

This generic AE severity scale was subsequently tailored to 35 event-specific severity criteria in the field of neurological, cardiovascular, respiratory, gastrointestinal, infectious, or general neonatal care–related events (eg, neonatal rash or administration site complication).[4,43] All AE terms were linked to lowest-level terms in the Medical Dictionary for Regulatory Activities (from version 22.0 on), while definitions for AEs were based on the National Institute of Child Health and Human Development Pediatric AE Terminology (Pediatric Adverse Event Terminology Subset) to further facilitate development.[42] As the final aim of such scale is to reduce subjectivity and observer-related variability, this scale is currently undergoing validation efforts.

Discussion

AE assessment includes signal detection, causality, and severity. Disentangling confounders from truly dose-related adverse drug events remains a major challenge, as illustrated for AKI, DILI, and neurodevelopmental outcome. Causality assessment tools still do not sufficiently and reliably document causality in neonates, while a neonatal severity grading tool to neonates has only very recently been developed. Following the development of advanced PK approaches and techniques to predict and assess drug exposure, additional efforts are needed to truly and fully assess dose adverse drug events, similar to how maturational physiological data were converted to physiology-based PK models. To further operationalize the recently developed tools on causality and severity, there is a need for a reference databases on a pallet of biomarkers and outcome variables and their covariates to become further op-

erationalized. These databases should subsequently be integrated in modeling efforts to truly explore safety outcome, including aspects associated with or caused by drug dose or exposure. Real-world data approaches to generate real-world evidence are needed to describe actionable reference ranges of laboratory values, while natural history models for the most commonly observed morbidities (like BPD, retinopathy of prematurity, necrotizing enterocolitis, or infectious diseases) should facilitate the assessment of the impact (efficacy and safety) of a given intervention or a bundle of interventions.[44]

Data standardization and harmonized definitions are hereby crucial to generate "big data" data sets to accelerate drug development to improve neonatal care, and such initiatives are ongoing.[45] The UK Medicines for Neonates research program described the feasibility of developing routinely recorded operational clinical data from electronic patient records as a reliable resource to improve health care.[46] The earlier mentioned Salerno et al analysis on the association of drug combinations and their duration of administration with AKI incidence serves as an illustration on the potential of such an approach.[24] As another illustration, the association between caffeine exposure and sleep-wake behavior patterns in preterm neonates has been described. The authors hereby concluded that caffeine increased the fraction of wakefulness, alertness, and arousability, at the cost of active but not quiet sleep.[47]

In conclusion, following the development of assessment tools to better assess causality and severity of adverse drug-related events in neonates. To further operationalize the recently developed tools on causality and severity, reference databases on a pallet of biomarkers and outcome variables and their covariates are an obvious next step. These databases should subsequently be integrated in modeling efforts to truly explore safety outcome, including aspects associated with or caused by drug dose or exposure.

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