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ORIGINAL ARTICLE

Medicine preparation errors in ten Spanish neonatal intensive care units

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Abstract This study assessed the rate of errors in intravenous medicine preparation at the bedside in neonatal intensive care units vs the preparation error rate in a hospital pharmacy service. We conducted a prospective observational study between June and September 2013. Ten Spanish neonatal intensive care units and one hospital pharmacy service participated in the study. Two types of preparation errors were considered: calculation errors and accuracy errors. A total of 522 samples were collected: 238 of vancomycin, 139 of gentamicin, 39 of phenobarbital and 88 of caffeine citrate preparations. Of these, 444 samples were collected by nurses in neonatal intensive care units, and 60 were provided by the hospital pharmacy service. Overall, 18 samples were excluded from the analysis. We detected calculation errors in 6/444 (1.35 %) and accuracy errors in 243/444 (54.7 %) samples from the neonatal intensive care units. In contrast, in samples from the hospital pharmacy service, no calculation errors were detected, but there were accuracy errors in 23/60 (38.3 %) samples.

Conclusion: While calculation errors can be eliminated using protocols based on standard drug concentrations, accuracy error rates depend on several variables that affect both neonatal intensive care units and hospital pharmacy services.

What is Known:
- *Medication use is associated with a risk of errors and adverse events. Medication errors are more frequent and have more severe consequences in paediatric patients.*
- *Lack of knowledge of drug pharmacokinetics and pharmacodynamics in relation to physiological immaturity makes neonates more vulnerable to medication errors.*

What is New:
- *Calculation errors are avoided using concentration standard preparation protocols.*
- *Accuracy in the preparation process depends mainly on the degree to which commercial drug preparations meet current legal requirements and the syringes and preparation techniques used.*

Keywords Accuracy · Newborn infant · Intravenous medicine · Medication errors · Neonatal intensive care unit · Preparation errors

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Abbreviations
HPS Hospital pharmacy service
NICU Neonatal intensive care unit

Introduction

Neonates are more prone than adults to medication errors. This higher risk is related to a lack of knowledge of drug pharmacokinetics and pharmacodynamics in relation to physiological immaturity, off-label use of drugs or unlicensed drugs and the unavailability of drug formulations and equipment for dilution expressly adapted for neonates [4, 8, 9, 11, 12, 14–16, 30, 31]. This lack of commercial drug formulations is well-known to be a source of preparation errors. Specifically, it results in nurses having to perform multiple steps before medicines are ready to be administered. Further, because small doses have to be prepared using commercial drug formulations for adults, medicine preparation for neonates requires nurses to have chemical knowledge and be trained in basic mathematical calculations, as well as the use of accurate working methods. Hence, in neonatal intensive care units (NICUs), variations between intended and measured concentrations of drugs can occur and these may have clinical effects.

To our knowledge, there is no consensus document on intravenous drug preparation in NICUs that contains information about preparation methodology. Several guides provide information about recommended concentrations, and others explain how to achieve those concentrations, but we have not found any publications describing the materials required and preparation process in detail [22, 28]. In this context, it is important to consider the risks associated with errors as we are conducting a complex process targeting high-risk patients.

Medicine preparation in a hospital pharmacy service (HPS) reduces medication errors and risk of microbiological contamination, as it ensures that processes are carried out with high safety standards (dedicated clean working areas, adequate equipment, specific training and minimal distractions, among other factors). Not all HPS, however, can take on responsibility for the preparation of all intravenous medicines administered in a hospital. Recently published recommendations set out preparation requirements, helping professionals with the decision of where to prepare medications: clinical areas vs. hospital pharmacy clean rooms [17]. If drug preparation were to be performed in a clinical area, the guideline states that a place that avoids airflows, poor lighting and the circulation of staff should be designated for the purpose.

The objectives of this study were to (1) measure intravenous medicine preparation error rates in several NICUs and (2) identify differences between preparations made in NICUs and those made by specialised nurses in an HPS, with the expectation that the preparation error rate would be lower in the HPS than in clinical areas.

Methods

Participants

Ten NICUs and the HPS of Cruces University Hospital, all in Spain, participated in the study. According to the care level classification published by the Spanish Neonatal Society, NICUs included in the study were level III (that is, part of a referral hospital with paediatric and maternity services, handling at least 1,000 deliveries a year and caring for complex critically ill neonates including those requiring mechanical ventilation). Characteristics of participating NICUs were as follows:

Number of births	Mean, 2,913	(Range, 1,577–4,609)
Number of infants admitted to neonatal unit/year	Mean, 492	(Range, 97–869)
Number of beds in intensive care unit	Mean, 8	(Range, 3–19)
Number of beds in intermediate care unit	Mean, 15	(Range, 5–26)

Drug selection

We focused on intravenously administered medications because of the difficulty of preparing them and the great potential for harm in the event of preparation errors. Among all the intravenous drugs used, we focused our study on vancomycin, gentamicin, phenobarbital and caffeine citrate, as they were used frequently, were classified as high- or moderate-risk products by the British National Patient Safety Agency [20] and are stable under frozen conditions. Further, for this decision, we took into account the results of a survey completed by the participating NICUs, indicating the intravenous drugs most frequently used in the unit and the way they were prepared before administration.

Commercial drug formulations had the following concentrations: vancomycin, 50 mg/mL after reconstitution following manufacturer instructions; gentamicin 10, 20 or 40 mg/mL; phenobarbital 200 mg/mL; and caffeine citrate, 10 or 20 mg/mL. The normal dosages of these drugs were as follows: vancomycin, 10 mg/kg/dose; gentamicin, 4–5 mg/kg/dose; phenobarbital, 2.5–10 mg/kg/dose; and caffeine citrate, 5–10 mg/kg/dose (loading dose 20 mg/kg). Therefore, nurses had to carry out multiple manipulations to obtain suitable volumes and concentrations [27].

Data collection

A prospective observational study was performed between June and September 2013. The study was approved by the Spanish Agency of Medicines and Medical Devices and by ethical committees of all participating hospitals. During the study period, dilutions prepared for administration were collected during all three nursing shifts in NICUs following a randomised list, while for samples to be collected in the HPS, we established a randomised list to define which drug had to be prepared each day.

In NICUs, medicine dilution was performed by a nurse on duty according to usual clinical practice, in an open non-aseptic environment. Once the dilution process was completed, nurses recorded details of the preparation process, then took one aliquot of the dilution to be administered and stored it frozen until it was sent to the hospital biochemistry laboratory for analysis. Patient data recorded were dosage prescribed, method used for reconstitution and/or dilution of the medication, diluent used, size of syringes used, volume that contained the dosage to be administered and the dilution volume that was used to programme the infusion pump.

Medicine dilutions prepared by specialised nurses in the HPS were used as controls. These drug preparations were made up following what we considered a safe preparation protocol within usual working hours (8:00–15:00, Monday to Friday). As for the samples prepared in NICUs, aliquots were frozen until analysis in the biochemistry laboratory.

Drug preparation protocols for the studied medications were collected from the participating NICUs and HPS, and videos were recorded of participants demonstrating their routine preparation process.

Measurement of drug concentrations

Samples were analysed at Cruces University Hospital biochemistry laboratory. The concentrations of vancomycin and gentamicin were measured with latex particle-enhanced turbidimetric inhibition immunoassays, using a Dimension Xpand® Plus system (Siemens, Munich, Germany). The sensitivity was 0.8 μg/mL for the vancomycin assay and 0.2 μg/mL for gentamicin, and imprecision (percent coefficient of variation, % CV) was 5.0 and 2.7 % for the two drugs, respectively. Caffeine concentrations were measured with homogeneous enzyme immunoassays, also using a Dimension Xpand® Plus system (Siemens). In this case, the sensitivity was 1 μg/mL and imprecision (% CV) 4.9 %. Lastly, phenobarbital concentrations were determined with competitive direct chemiluminescence immunoassays using an ADVIA Centaur XP system (Siemens), analytical sensitivity being 0.4 μg/mL and imprecision (% CV) 11.6 %.

Definitions of errors

Two types of errors were defined:

1. *Calculation errors*, when the magnitude of the deviation of the theoretical dose given, that is, the dose calculated by the person administering the drug, from the dose prescribed by the physician was more than 10 % of the intended concentration

$$\left|\frac{\text{Dose calculated by the nurse}-\text{Dose prescribed by the doctor}}{\text{Dose prescribed by the doctor}}\times 100\right| > 10\ \%$$

2. *Accuracy errors*, when the magnitude of the deviation between theoretical concentration and the concentration measured in the laboratory was over 10 % of the intended concentration

$$\left|\frac{\text{Measured drug concentration}-\text{Theoretical drug concentration}}{\text{Theoretical drug concentration}}\times 100\right| > 10\ \%$$

Two subcategories of accuracy errors were also established, namely, under- and overdosing errors corresponding to the cases when the deviation was greater than −10 and +10 %, respectively.

Data analysis

We performed a descriptive analysis of the errors that occurred during the study. Discrete variables were expressed

Table 1 Distribution of drug samples from neonatal intensive care units (NICUs) (hospitals 1–10) and the hospital pharmacy service (HPS)

Drug	1	2	3	4	5	6	7	8	9	10	HPS
Caffeine citrate	11	0	5	2	0	19	0	17	24	0	10
Phenobarbital	0	0	4	0	0	2	8	0	2	3	20
Gentamicin	1	22	3	30	26	9	24	14	0	0	10
Vancomycin	31	26	69	1	24	16	22	18	3	8	20
Total	43	48	81	33	50	46	54	49	29	11	60

as numbers of cases and percentages, and chi-squared tests were used for comparisons. Continuous variables were described with means and standard deviations, and means were compared using Student's *t* test, if the data were normally distributed; otherwise, they were described with medians and percentiles, and comparisons were made using the Wilcoxon test.

Results

A total of 522 samples were collected during the study. Eighteen samples (3.4 %) were excluded from the analysis for various reasons: not meeting inclusion criteria, missing data on the preparation process due to incorrectly completed records and no drug being detected in the laboratory analysis. The distribution of drug samples was (*N*): 238 vancomycin, 139 gentamicin, 39 phenobarbital and 88 caffeine citrate. Overall, 444 samples were collected by nurses in the NICUs, and 60 samples were collected from the HPS (control group) (Table 1).

Calculation errors

In 6/444 (1.35 %) of the samples collected in the NICUs, there were calculation errors: in two of the vancomycin, two of the caffeine citrate, one of the phenobarbital and one of the gentamicin samples. No calculation errors were detected in the control samples.

Table 2 Accuracy errors by drug

Accuracy error rate: % (frequency)		
Drug	NICUs	HPS
Caffeine citrate	64.1 (50/70)	20 (2/10)
Phenobarbital	89.5 (17/19)	40 (8/20)
Gentamicin	39.5 (51/129)	20 (2/10)
Vancomycin	57.3 (125/218)	55 (11/20)

Accuracy errors

Study group (NICUs) A lack of accuracy was detected in 243/444 samples (54.7 %). This rate corresponded to errors in 50/78 (64.1 %) of the caffeine citrate samples, 17/19 (89.5 %) of the phenobarbital samples, 51/129 (39.5 %) of the gentamicin samples and 125/218 (57.3 %) of the vancomycin samples (Table 2). In all these samples, Wilcoxon tests showed significant differences between theoretical concentrations and the concentrations measured in the laboratory ($p<0.001$). Overall, the errors were more commonly due to under- than overdosing (39.4 vs 15.3 %). By drug, there was a higher underdosing rate in caffeine citrate (50 vs 14.1 % due to overdosing), gentamicin (24 vs 15.5 %) and vancomycin (46.8 vs 10.6 %) samples, while the overdosing rate was higher in the case of phenobarbital samples (10.5 % due to underdosing vs 78.9 %). Further, deviations larger than the concentration variation considered acceptable (±10 %) were widespread, with accuracy errors in the ranges of −25.1 to −50 % and 25 to 50 % (Fig. 1).

Control group (HPS) A lack of accuracy was detected in 23/60 samples (38.3 %). This rate corresponded to errors in 2/10 (20 %) of caffeine citrate samples, 8/20 (40 %) of phenobarbital samples, 2/10 (20 %) of gentamicin samples and 11/20 (55 %) of vancomycin samples (Table 2). Overall, underdosing was more common than overdosing (21.6 vs 16.6 %). By drug, the two caffeine citrate errors were related to underdosing and the eight phenobarbital errors to overdosing, while the underdosing error rate was higher for vancomycin samples (20 vs. 5 %) and, in the case of gentamicin, underdosing and overdosing rates were the same (10 %). As in the study samples, deviations larger than the acceptable concentration variation (±10 %) were widespread, with accuracy errors ranging from −25.1 to −50 % and 25 to 50 % (Fig. 1).

Rates of accuracy errors varied considerably between NICUs (Table 3). Specifically, values ranged from 25.6 % (hospital 1) to 90.1 % (hospital 10), and the error rate was lower in two NICUs (25.6 %; 36 %) than in the control group (38.3 %). The difference between the overall accuracy error rate in NICUs and the HPS was statistically significant ($p=0.017$).

Protocol analysis

A multidisciplinary group reviewed all medicine preparation protocols submitted by each NICU. There were multiple differences between them in relation to concentrations, volumes and drug manipulation. In seven NICUs, protocols were based on standard concentrations, but we observed differences between them in relation to concentrations used and the manipulation process. In the other three NICUs, standard volumes to be administered were used, instead of standard concentrations.

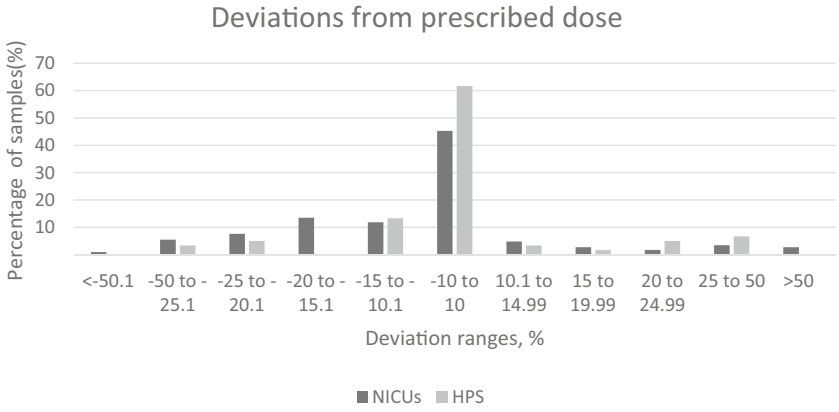

Fig. 1 Accuracy errors in terms of deviations from prescribed dose in samples from neonatal intensive care units (*NICUs*) and the hospital pharmacy service (*HPS*)

Neither the volume of syringe needed nor steps for making dilution were indicated in any of the preparation protocols.

Control group (HPS) protocols were also analysed by the multidisciplinary group. Protocols were all based on standard concentrations: two different concentrations for vancomycin (2.5 and 5 mg/mL) and phenobarbital (10 and 20 mg/mL) and a single standard concentration for caffeine (1 mg/mL) and for gentamicin (1 mg/mL). Standard concentrations were defined to enable doses to be prepared to an easily measured volume, avoiding decimal points and specifying volumes according to patient characteristics.

Video analysis

Weak points detected in the video analysis were the use of oversized syringes for the volume to be loaded, failure to achieve good mixing and lack of volume control when vials or ampoules were fully loaded in NICUs and an insufficient mixing time in the HPS.

Table 3 Accuracy errors by source of the sample: neonatal intensive care units (NICUs) (hospitals 1–10) and the hospital pharmacy service (HPS)

Accuracy errors			
Source of the sample		Frequency	Percentage
NICU	**1**	11/43	**25.6**
	2	36/48	**75**
	3	49/81	**60.5**
	4	19/33	**57.6**
	5	18/50	**36**
	6	23/46	**50**
	7	27/54	**50**
	8	25/49	**51**
	9	25/29	**86.2**
	10	10/11	**90.9**
HPS		23/60	**38.3**

Discussion

Many studies have been published analysing prescription, transcription, dispensing and medicine administration errors [5, 6, 18, 19, 25–27]. However, few studies related to preparation errors have been reported for patients of any age group. We identified four studies analysing the accuracy of the dilution process, when medications designed for adults were administered to neonates. Parshuram et al. [21] analysed morphine infusions prepared for children weighing 0.7–60 kg and identified an error rate of 65 %. Allegaert et al. [3] reported that in the case of amikacin, the use of paediatric vials improved dosing precision, as assessed by measurements of pharmacokinetic parameters. Popescu et al. [23] investigated the difference between the vancomycin concentration prescribed and that prepared by nurses at the bedside in a paediatric unit and found measured drug concentrations before administration to be a mean of 7 % lower than concentrations that had been prescribed by the doctor. Lastly, Aguado-Lorenzo et al. [2] studying the accuracy of the concentration of morphine infusions reported a mean deviation from intended concentrations of more than 20 %.

In our previous study on preparation errors in NICUs, we collected 91 samples over 24 non-consecutive working days in one NICU. After excluding four samples from analysis, we determined accuracy and calculation error rates in 50 vancomycin and 37 tobramycin samples. The accuracy error rate was 32 % for vancomycin and 46 % for tobramycin, while the overall calculation error rate was 4.6 % [7]. Hypothesising that error rates were similar in other NICUs and that HPS preparations were more accurate, we decided to replicate that study in ten NICUs using an HPS as a control group.

We established 10 % range to define a preparation error, taking into account our previous experience in recording medication errors and several studies that reported discrepancies between theoretical and measured drug concentrations [2, 6, 7, 21]. We also reviewed the United States Pharmacopeia, the Spanish Pharmacopeia and legislation for drug manufacturers before we defined a common range for the four drugs [24, 29].

Several studies have detected difficulties among healthcare professionals in performing simple mathematical calculations [13, 33]. We identified six samples with calculation errors in this study. Three of these came from NICUs that did not use standard concentration protocols; rather in these NICUs, standard volumes were used in the administration process. This method has an a priori high risk of calculation errors because each preparation is unique and requires new mathematical calculations. In the other three cases of calculation errors, the errors can be attributed to a failure to apply the standard concentrations protocols (skipping the protocol). We can assert that error calculations are avoided when standard concentrations are used, the method of preparation is always the same and protocols are followed. Nevertheless, standard concentration protocols do not ensure that accuracy errors are eliminated.

Our results showed a statistically significant difference between mean errors in NICUs and in the HPS. However, although the medicine preparation process in the HPS is safer than in medical wards, it may not always be more accurate. After analysing protocols and drug manipulation videos from the NICUs and the HPS, we observed several weak points in medicine preparation that influenced accuracy and that could explain different trends in three of the four drugs: namely, steps in drug preparation that made the process less accurate were the use of oversized syringes for the volume to load, a lack of good mixing and a lack of volume control when vials or ampoules were fully loaded. In line with these observations, we want to discuss three main factors that affect accuracy of both NICU and HPS nurses: (1) syringe specifications, (2) the homogenisation process and (3) drug manufacturer legislation.

1. Syringe specifications

   We observed that in many cases, the same syringe was used to load the drug and the diluent. We believe that this approach is not safe because large volume syringes tend to be less accurate than small volume syringes for loading a small volume, for instance, accuracy loading 1 mL would be greater with a 1-mL than with a 20-mL volume syringe. In addition, syringe providers have to comply with current legislation (UNE-EN-ISO 7886-1:1998). Among all their technical features, the tolerance on graduated capacity and dead space of syringes must be highlighted because these parameters affect accuracy. Tolerance on graduated capacity is ±5 % of the expelled volume for syringes with volumes up to 5 mL and ±4 % of the expelled volume for larger volume syringes. Allowed dead space varies from 0.07 to 0.20 mL depending on the syringe volume. Therefore, we believe both syringe volume and provider have an influence on accuracy error rates [1, 32].
2. Homogenisation process

   Lack of a correct solution-mixing process or insufficient reconstitution time, as observed in the videos, could explain underdosing in the case of vancomycin, for example. Nurses were unaware of the importance of mixing time and, due to their workload, they completed the process without allowing sufficient time to do the preparation well.
3. Drug manufacturer legislation

   Loading full ampoules and vials without checking volumes could be associated with overdosing in the case of phenobarbital and underdosing in the case of caffeine citrate. In all phenobarbital protocols, the volume to load from the ampoule was 1 mL, and this was the supposed volume of the commercial product. However, our experience indicated that not all ampoules contained exactly 1 mL, and hence, we reviewed the Spanish Pharmacopeia and contacted the drug manufacturer. The Spanish Pharmacopeia states that the volume contained in vials or ampoules has to ensure that the volume expelled by a syringe is at least the volume stated on the label and that any excess volume in single-dose preparations does not present a risk for the patient [24]. This excess would not be dangerous for an adult but when using this presentation in neonates, overdosing carries a very high potential for harm. The Spanish company that manufactures the phenobarbital formulation used confirmed that the maximum volume allowed was 1.15 mL/ampoule. The trend to underdosing of caffeine citrate could be explained by the fact that not all ampoules and vials permitted nurses to obtain as much as the volume indicated on the label.

Our results show that use of standard concentration protocols avoids calculation but not accuracy errors. In addition to standard concentration protocols, a good manipulation technique is necessary, with the practitioners being aware of the relevance of each step and consequences of using incorrect materials, or insufficient mixing time, as well as the lower accuracy associated with working faster than recommended.

We recommend thorough implementation of standard concentration protocols and educational interventions stressing the importance of the material used and the time necessary for correct preparation. In addition, health authorities, drug regulatory agencies and pharmaceutical companies should be involved in the development of safe and appropriate drug formulations for this small, vulnerable population. Both pharmaceutical formulations adapted for use in neonates and robotic systems [10] for dosing pharmaceutical preparations now on the market should be effective strategies to improve patient safety. To promote the development of specific paediatric drug preparations, the European Medicines Agency published a yearly revised priority list for off-patent medicines to be developed [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000092.jsp&mid=WC0b01ac05800260a4], and

the European Union (EU) funds the development of drugs on this list. Moreover, under the 2009 Medicines for Children call, the EU has funded the Global Research in Paediatrics (GRIP) project, which aims to analyse all the building blocks for the development of safer paediatric medicines and to develop a training programme in paediatric clinical pharmacology.

Limitations

Our study was limited to the assessment of four commonly used drugs. It would be interesting to extend this study to less frequently used drugs, especially high-risk drugs and those with narrow therapeutic indices. Each hospital used the commercial formulations routinely available in its organisation and these differed; therefore, variation in results between hospitals could be influenced by this variable. Further, we did not assess how preparation errors could have affected the clinical course of the disease because laboratory results were not available until weeks after sample collection. However, we believe errors in drug preparation can have clinical significance, because they would explain situations reported by clinicians working in NICUs, for example, excessive sedation after a correctly prescribed dose of phenobarbital.

Conclusions

Drug preparation for intravenous administration is a critical point in neonatal patient healthcare. While calculation errors can be avoided by adherence to protocols based on standard drug concentrations, accuracy errors depend on good practices in the preparation process and knowledge of syringe specifications as well as the characteristics of commercial drug formulations.

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References

1. AENOR. Sterile hypodermic syringes for single use. Part 1: syringes for manual use (ISO 7886-1:1993, including technical corrigendum 1:1995). http://www.aenor.es/aenor/normas/normas/fichanorma.asp?tipo=N&codigo=N0013672&pdf=. Accessed 11 August 2014
2. Aguado-Lorenzo V, Weeks K, Tunstell P, Karen T, Watts T, Arenas-Lopez S (2013) Accuracy of the concentration of morphine infusions prepared for patients in a neonatal intensive care unit. Arch Dis Child 98:975–979
3. Allegaert K, Anderson BJ, Vrancken M, Debeer A, Desmet K, Cosaert K et al (2006) Impact of a paediatric vial on the magnitude of systematic medication errors in neonates. Paediatr Perinat Drug Ther 7(2):59–63
4. Allegaert K, Langhendries JP, Van den Anker JN (2013) Do we need clinical pharmacologists? Eur J Pediatr 172:429–435
5. Avenel S, Bomkratz A, Dassieu G, Janaud JC, Danan C (2000) The incidence of prescriptions without marketing product license in a neonatal intensive care unit. Arch Pediatr 7(2):143–147
6. Campino A, Lopez Herrera MC, Garcia M, Lopez de Heredia Goya I, Valls i Soler A (2006) Medication prescription and transcription errors in a neonatal unit. An Pediatr (Barc) 64(4):330–335
7. Campino A, Santesteban E, Garcia M, Rueda M, Valls i Soler A (2013) Intravenous drug preparation errors in a neonatal intensive care unit. A potential source of adverse events. An Pediatr (Barc) 79(1):21–24
8. Chedoe I, Molendijk HA, Dittrich ST, Jansman FG, Harting JW, Brouwers JR et al (2007) Incidence and nature of medication errors in neonatal intensive care with strategies to improve safety—a review of the current literature. Drug Saf 30(6):503–513
9. Conroy S (2011) Association between licence status and medication errors. Arch Dis Child 96(3):305–306
10. Cote DD, Torchia MG (1989) Robotic system for i.v. antineoplastic drug preparations: description and preliminary evaluation under simulated conditions. Am J Hosp Pharm 46:2286–2293
11. Fahimi F, Ariapanah P, Faizi M, Shafaghi B, Namdar R, Ardakani MT (2008) Errors in preparation and administration of intravenous medications in the intensive care unit of a teaching hospital: an observational study. Aust Crit Care 21:110–116

12. Ghaleb MA, Barber N, Franklin BD, Yeung VW, Khaki ZF, Wong IC (2006) Systematic review of medication errors in pediatric patients. Ann Pharmacother 40:1766–1776
13. Glover ML, Sussmane JB (2002) Assessing pediatrics residents' mathematical skills for prescribing medication: a need for improved training. Acad Med 77(10):1007–1010
14. Hughes RG, Edgerton EA (2005) Reducing pediatric medication errors. Children are especially at risk for medication errors. Am J Nurs 105:79–84
15. Kaushal R, Bates D, Landrigan C, McKenna KJ, Clapp MD, Federico F et al (2001) Medication errors and adverse drug events in pediatric inpatients. JAMA 285:2114–2120
16. Lerner RBDM, De Carvalho M, Vieira AA, Lopes JM, Moreira ME (2008) Medication errors in a neonatal intensive care unit. J Pediatr 84(2):166–170
17. Martin de Rosales AN, Lopez C, Pernia MS, Devila Pousa C, Vila Clerigues MN, Alonso Herrero JM et al (2014) Recommendations for the safety preparation of sterile medicines in medical wards. Farm Hosp 38(1):57–64
18. Miller MR, Robinson KA, Lubomski LH, Rinke ML, Pronovost PJ (2007) Medication errors in pediatric care: a systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations. Qual Saf Health Care 16:116–126
19. Muñoz Labian MC, Pallas Alonso CR, De la Cruz Bertolo J, Lopez Maestro M, Moral Pumarega A, Balaustegui Cueto A (2001) Medication error in a neonatal unit. An Esp Pediatr (Barc) 55: 535–540
20. National Patient Safety Agency. Patient safety alert 20: promoting safer use of injectable medicines. London 2007 http://www.nrls.npsa.nhs.uk/resources/?entryid45=59812. Accessed 11 August 2014
21. Parshuram CS, Ng GY, Ho TK, Klein J, Moore AM, Bohn D et al (2003) Discrepancies between ordered and delivered concentrations of opiate infusions in critical care. Crit Care Med 31:2483–2487
22. Phelps SJ (2013) Pediatric injectable drugs. The Teddy Bear book, 10th edn
23. Popescu M, Vialet R, Loundou A, Peyron F, Buès-Charbit M (2011) Imprecision of vancomycin prepared for intravenous administration at the bedside in a neonatal intensive care unit. Ann Fr Anesth Reanim 30(10):726–729
24. Real Farmacopea Española, 5th edn. AEMPS 2015
25. Ross LM, Wallace J, Paton JY (2000) Medication errors in a paediatric teaching hospital in the UK: five years operational experience. Arch Dis Child 83:492–497
26. Snijders C, Van Lingen RA, Molendijk A, Fetter WP (2007) Incidents and errors in neonatal intensive care: a review of the literature. Arch Dis Child Fetal Neonatal 92:391–398
27. Stavroudis TA, Shore AD, Morlock L, Hicks RW, Bundy D, Miller MR (2010) NICU medication errors: identifying a risk profile for medication errors in the neonatal intensive care unit. J Perinatol 30(7):459–468
28. Takemoto CK (2014–2015) Pediatric and neonatal dosage handbook. 21th edn. Lexicomp
29. The United States Pharmacopeial Convention. United States Pharmacopeia, Rockville, MD. 1999
30. Tuleu C, Breitkreutz J (2013) Formulation-related issues in pediatric clinical pharmacology. Eur J Pediatr 172:717–720
31. Uppal N, Yasseen B, Seto W, Parshuram CS (2011) Drug formulations that require less than 0.1 mL of stock solution to prepare doses for infants and children. CMAJ 183:E246–E248
32. Watanachai A, Suprasongsin C (2003) Deadspace: a potential error in concentration of medication during dilutional process in neonates. J Med Assoc Thail 86(12):1128–1132
33. Wheeler W, Remoundos DD, Whittlestone K (2004) Calculation of doses of drugs in solution. Are medical students confused by the different means of expressing drug concentrations? Drug Saf 27(10):729–734