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Abstracts

Selected Abstracts of the 1st Congress of joint European Neonatal Societies (jENS 2015) · Session "Pharmacology"

BUDAPEST (HUNGARY) · SEPTEMBER 16TH-20TH 2015

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POSTER PRESENTATIONS

ABS 1

BABY SKIN CARE PRODUCTS

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INTRODUCTION

In consequence of the development of dermato-cosmetic industry, nowadays a great number of skin care products specially formulated for babies and children are available. The most frequently used skin care products are baby wash and bath products, shampoos, emollients and barrier preparations providing protection for the skin in the diaper-covered genital and gluteal areas. It is essential that these products should not only provide the desired effects, but at the same time, they should be absolutely safe to use, without causing any unwanted effect. Finding the best products can be challenging for both the health care professionals and for parents, as well.

PATIENTS AND METHODS

The aim of our present study was to investigate the types, ingredients and market prices of various baby skin care products that are available for the customers in supermarkets, drogeries and pharmacies. Skin care products contain several ingredients, including the active components ensuring the achievement of the desired effects, preservatives responsible for microbiological stability, surfactants, fragrances and various inactive agents. The information regarding the compositions of the products were collected from the products' labels.

RESULTS

In our survey we included a total of 51 different baby care products: 13 body washes, 13 emollients, 9 shampoos, 12 barrier creams for nappy area and 4 baby powders. These products contained 258 different ingredients, of which 52 were considered as active ingredients, 39 as emollients, 35 surfactant, 21 preservatives, 14 fragrances, and 97 other inactive ingredients. The average number of ingredients per product was 14.6 ± 6.5 (mean ± SD). Emollient products consisted of the higher number of ingredients (17.8 ± 7.6) while baby powders had the lowest number of ingredients (4.3 ± 1.5). Preservatives were present in 63.3% of the products, and 73.5% contained fragrances. The prices of the products showed large variety, the differences in the unit price (per gram or per milliliter) between the cheapest and most expensive product in several product categories were above 15 folds.

CONCLUSIONS

Skin care products made for babies have to meet strict quality requirements. Besides achieving the desired effects, it is vital that products contain no unnecessary, allergizing, irritative agents, fragrances and colouring ingredients, and be affordable for customers; moreover the corroboration of their efficacy by surveys conducted on large patient groups in accordance with the principles of evidence based medicine is also of great importance.

ABS 2

MATHEMATICAL MODELING TO PREDICT IN-HOSPITAL NATURAL WEIGHT CHANGES IN TERM NEONATES

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INTRODUCTION

Weight loss (WL) within the first days of life is normal in exclusively breastfed newborns. The magnitude of WL varies strongly among newborns

and can reach high levels resulting in serious complications. Once the food intake outweighs the fluid loss, the nadir of WL is achieved and weight gain (WG) follows. However, the impact and the interdependencies of the various maternal and neonatal factors on weight changes after birth are incomplete understood. The objectives of this study were (1) to develop a semi-mechanistic model that can be used, (2) to characterize natural weight changes during first days of life and (3) to identify and quantify effects of key covariates on weight changes.

PATIENTS AND METHODS

A retrospective, single-center study of prospectively recorded maternal and neonatal data from exclusively breastfed term newborns was performed at the University Hospital of Basel. Two complete birth years (2009 and 2010) of term born neonates were screened (n = 4,128). Exclusion criteria: any formula feeding (n = 2,430), only one observed weight (n = 24), transfer to a neonatal ward (n = 267), multiples (n = 72). Thus, longitudinal weight data were characterized of 1,335 neonates with a novel semi-mechanistic model considering inter-individual variability, the non-linear mixed effects modeling approach, implemented in NONMEM 7.3. Model selection was based on the likelihood, goodness-of-fit plots, and simulation-based diagnostics. Covariate testing was assessed using a forward-backward approach.

RESULTS

Key patient characteristics (median, range) were: GA 39.7 weeks (37.0-42.1), birth weight (BW) 3,270 g (2,235-4,610), arterial umbilical cord pH 7.28 (7.04-7.48), mother blood loss 400 mL (40-2,200), females n = 662, primary n = 121 and secondary n = 88 C-section, vaginal delivery n = 1,126. Weight changes by time were described as a balance between WG rate (KIN) and WL rate (KOUT), **Fig. 1**. KIN was modeled as a function of time. KOUT was modeled with a saturable (E_{max}) function to describe the initial fluid loss followed by a second time-dependent component. BW (WT0) and maximal WG was higher in males and neonates with higher GA. Positive associations were found between blood loss and BW and between CS and slower WG. According to goodness-of-fit plots, weight changes were properly fitted in neonates (**Fig. 1**). Visual predictive check demonstrated the good predictive performance of the model.

CONCLUSIONS

We provide the pattern of physiological weight changes in healthy breastfed neonates in the first days of life in our population. By including factors affecting postnatal weight loss and weight gain an accurate model for predicting postnatal weight development was established which provides clinicians a useful tool to detect neonates at risk for morbidities.

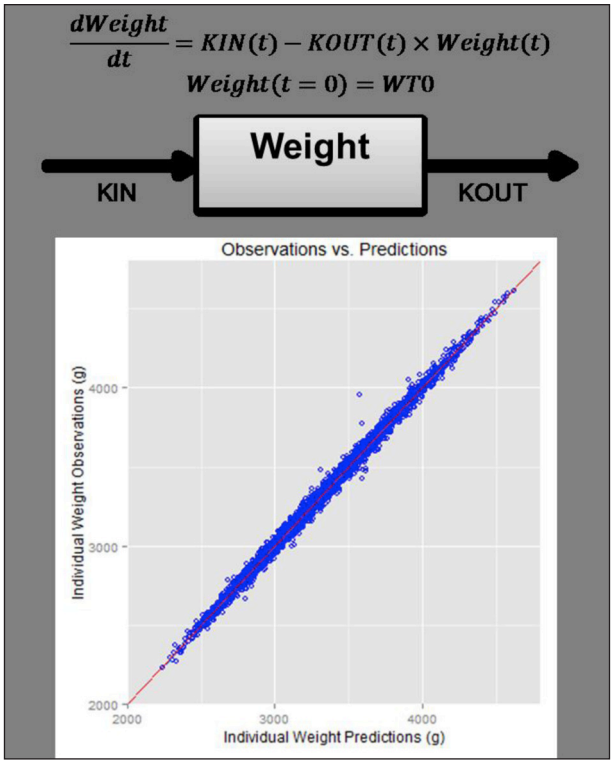

Figure 1 (ABS 2). Prediction of postnatal weight changes.

Good clinical practice – in practice

ABS 3

IMPROVING PARENTERAL NUTRITION IN THE NEONATE – A PRACTICAL GUIDELINE

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INTRODUCTION

Many newborns are dependent on parenteral nutrition for days or weeks for optimal growth. The calculation and preparing of solutions is time-consuming, and the risk of mistakes is high, with potentially serious consequences. In the first days the parenteral nutrition needs to be individualized

and standard bags from the industry will either give too little nutrition or volume overload if the recommended amounts of protein, glucose and fat emulsion shall be given. The first days the nutrition is therefore given in separate syringes and the amounts and the strength of glucose must be adapted to the total available volume to be able to give adequate nutrition.

METHODS

A combination of a pharmacy-developed guideline for additives in different solutions, a hospital-developed guideline for recommended amounts of glucose, amino acids, fat and additives, and an Excel® calculation sheet that takes into account the enteral feed and drug infusions given, minimize the risk of error in calculation of parenteral nutrition, improve the quality of parenteral nutrition and is time-effective.

RESULTS

The guidelines and examples of calculation will be presented.

CONCLUSIONS

Close cooperation between clinical pharmacists, neonatologists and specialist nurses, and the implementation of simple programs for calculation of nutrition and fluid therapy is essential to improve quality of parenteral and enteral nutrition and reduce the risk of errors.

ABS 4

INVOLUTION OF RETINOPATHY OF PREMATURITY AND NEURODEVELOPMENTAL OUTCOME AFTER BEVACIZUMAB TREATMENT

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INTRODUCTION

Retinopathy of prematurity (ROP) remains the leading cause of childhood blindness. The BEATROP study found that intravitreal bevacizumab (IVB) was effective in the treatment of ROP. Previous studies showed that bevacizumab is effective and well-tolerated in treating prethreshold ROP. However, information about serial retinal changes after bevacizumab therapy is limited. In addition, potential systemic side-effects of IVB remain unclear. In this study, we aim to evaluate the timing of full involution and/or development of retinal detachment after IVB, and its possible influence on postnatal growth and neurodevelopmental outcome.

PATIENTS AND METHODS

This is a single-centered, retrospective cohort study. We collected inborn premature infants who had received intravitreal bevacizumab (IVB) for the treatment of ROP from 2008 to 2014. Eye-ground examination was performed weekly after IVB treatment. Thirty-six gestational age (GA)-matched infants who had ROP but regressed without treatment were recruited as controls. Retrospective chart review was performed to collect data including maternal characteristics, neonatal morbidities, oxygen exposure and respiratory support during NICU stay, serial eye ground exam reports, postnatal growth and neurodevelopmental outcomes.

RESULTS

In total, 37 eyes from 20 patients were treated with bevacizumab as first-line treatment for prethreshold ROP; 1 eye was treated with bevacizumab as salvage treatment after ranibizumab treatment failed. The postmenstrual age of ROP onset did not differ between treatment and control groups. Twenty-six eyes (68.4%) exhibited ROP regression after single dose of IVB. The median timing for regression of plus sign, neovascularization, and fibrovascular proliferation after IVB was 1 week, 2 weeks and 2 weeks respectively. The median PMA of reaching complete retinal vascularization was longer in treatment group compared with control (57 wks vs. 49 wks, $p = 0.001$). Long-term follow-up showed no difference in body weight and BSID (III) scores at corrected age of 6-m, 1-yr and 2-yr between these two groups.

CONCLUSIONS

In our study, 68.4% of eyes exhibited ROP regression after single dose of IVB. The median PMA of reaching complete retinal vascularization was significantly longer in the treatment group. The majority of plus sign and neovascularization regressed within two weeks after IVB. Long-term follow-up of visual acuity is important for these patients.

ABS 5

RELATIONSHIP BETWEEN ADVERSE DRUG REACTIONS AND OFF-LABEL/UNLICENSED DRUG USE IN HOSPITALISED CHILDREN. EREMI STUDY

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INTRODUCTION

To date few studies have shown a significant association between the off-label drug use and adverse drug reactions (ADRs) (Santos, 2008, RR: 2.44 [2.12; 2.89]; Bellis, 2013, OR: 2.25 [2.82; 4.44]; Bellis 2014, OR: 1.71 [1.42; 2.05]). The main aims of this study are to evaluate the relationship between ADRs and unlicensed or off-label drugs prospectively in hospitalized children and to provide more information on prescribing practice, the amplitude, nature and consequences of unlicensed or off-label drug use in pediatric inpatients.

PATIENTS AND METHODS

In this ongoing multi-center prospective study an automatic data extraction has been set up to populate the database. A computer algorithm allows for determining pediatric drug labelling (i.e. off-label or unlicensed use) using as a primary reference source the French summaries of product characteristics in Theriaque® (a prescription products guide). Detection of ADRs is carried out by healthcare professionals and research groups using a trigger tool and patients' electronic health records (**Fig. 1**); their validation, MedDRA coding and suspected drugs causality is performed by Pharmacovigilance Centers. A cross validation is performed by an Independent Pharmacovigilance Board who in addition determine the avoidability of suspected medications and the existence of therapeutic alternatives.

RESULTS

In Lyon, after a 14 month period, 1,973 patients have been included, 224,932 drug administrations have been extracted. One third of these administrations have been performed in the pediatric resuscitation ward; diuretics represent 65% of the marketed administered drugs and spironolactone is the most frequent extemporaneous preparation. 242 ADRs

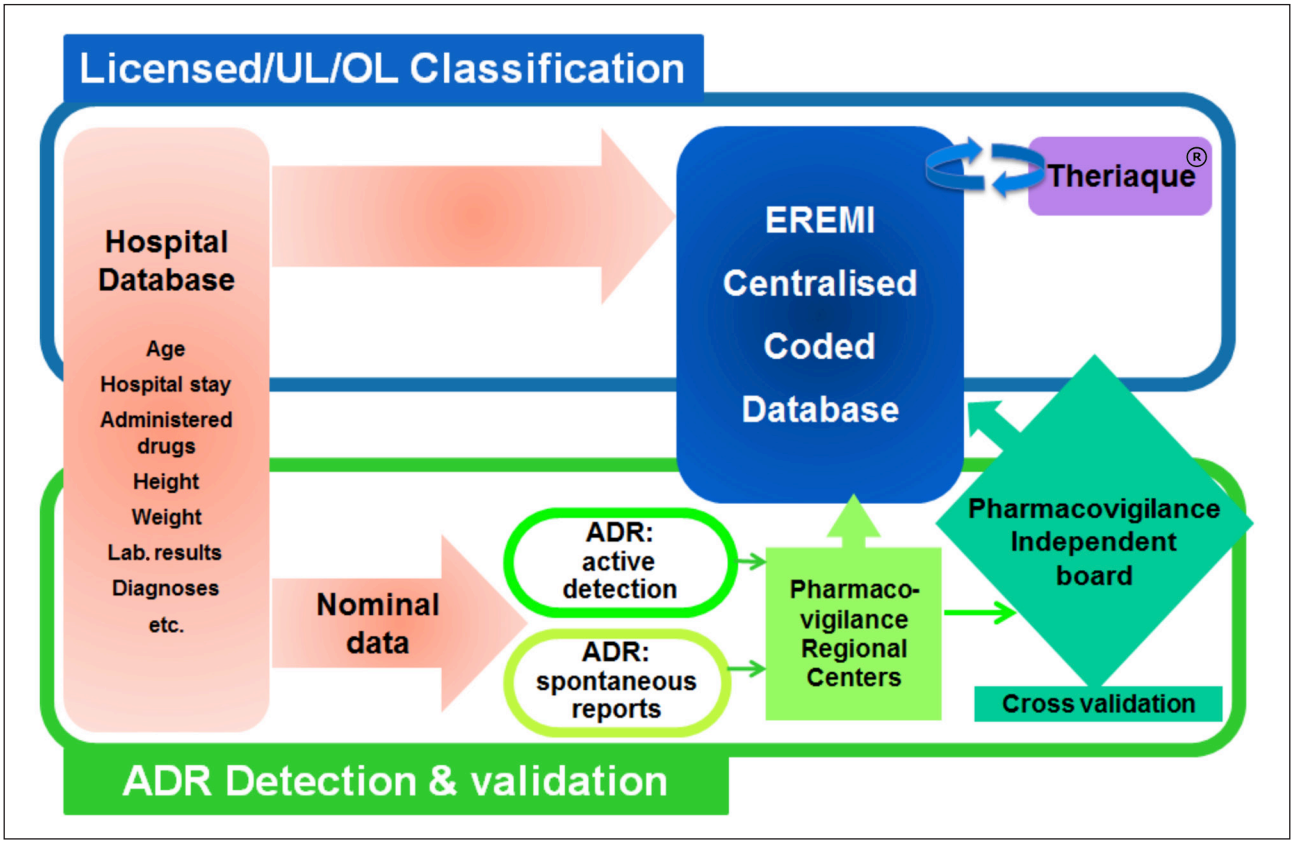

Figure 1 (ABS 5). Adverse drug reactions (ADRs) detection and validation using patients' electronic health records.

were detected during the same period; most of them belong to the category "nervous system disorders". From the 10 therapeutic alternatives proposed by the Pharmacovigilance Independent Board, 6 concern nervous system medications. In Paris, 693 patients have been included, most of them in the general pediatric ward, and 40 ADRs detected during a 6-month period.

CONCLUSIONS

This is the first large multi-center prospective study in France that evaluates the relationship between ADRs and unlicensed or off-label drugs in hospitalized children. This study will help to identify the risk factors that could be used to adjust preventive actions in children care, guide future research in the field and increase the awareness of physicians in detecting and declaring ADRs. This study is funded by ANSM, the French medicines agency.

ABS 6

A SYSTEMATIC REVIEW OF OFF-LABEL AND UNLICENSED DRUGS USE AND ADVERSE DRUG REACTIONS IN HOSPITALIZED CHILDREN

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OBJECTIVE

The aim was to provide a systematic review and meta-analysis of the relationship between adverse drug reactions (ADRs) and off-label or unlicensed drug use in paediatric in-patients.

PATIENTS AND METHODS

We conducted a systematic review of prospective and retrospective studies evaluating the relationship between ADRs and off-label or unlicensed (OLUL) drug use in hospitalised children. Medline, Embase and Cochrane Library were searched and updated until February 2015 with no language limitations. The reference lists of all identified articles were manually checked for additional potentially relevant articles.

RESULTS

Eighteen potentially relevant studies were identified. Five studies were selected in this systematic review and four studies were included in the meta-analysis. Compared to licensed medications, off-label and unlicensed drugs increased significantly the risk of ADR (OR 1.95, 95% CI 1.39 to 2.74). Heterogeneity was observed across studies I^2 = 72% and p = 0.01.

CONCLUSIONS

Four prospective studies published between 1999 and 2013 demonstrated an increased risk of ADRs with off-label and unlicensed medicine use and a higher risk of ADRs for patients exposed to at least one OLUL drug during their hospitalization. Further researches are needed with harmonized OLUL definitions, common comprehensive reference source, and efficient methods for the detection, assessment and the prevention of ADRs.

ABS 7

EFFICACY AND SAFETY OF PROPOFOL SEDATION FOR THE TREATMENT OF RETINOPATHY OF PREMATURITY IN SPONTANEOUS BREATHING

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INTRODUCTION

Despite the optimization of oxygen administration, ventilatory assistance and blood gas monitoring, severe retinopathy of prematurity (ROP, stage III-IV) remains a common condition among preterm infants, with an incidence of approximately 20% among neonates with BW between 500 and 1,000 g and 33% among neonates with BW < 600 g.

Severe ROP requires surgery, which in turn requires general anesthesia and intubation. Extubation at the end of the procedure can nevertheless be difficult is these delicate infants who often present chronic lung disease.

Propofol has a rapid clearance and, therefore, a very rapid offset of action. Although it is a potent sleep inducer, it allows spontaneous breathing.

PATIENTS AND METHODS

Our aim was to evaluate safety and effectiveness of propofol sedation associated with fentanyl analgesia for the treatment of neonates requiring laser therapy for ROP, to avoid intubation and to minimize side-effects of anesthesia and

ventilation. At study entry, a laryngeal mask was placed and ventilation was assisted when needed with a flow inflating resuscitation bag. Pulse oximetry (SpO_2), respiratory rate, heart rate and noninvasive blood pressure were continuously recorded. Propofol was administered at a dosage ranging from 2 to 4 mg/kg followed by a bolus of fentanyl 1 μg/kg, subsequently propofol was infused at a dosage ranging from 4 to 6 mg/kg/hour continuously, taking into account haemodynamic and spontaneous movements. At the end of surgery propofol infusion was discontinued.

RESULTS

Thirteen neonates on spontaneous breath requiring laser therapy for severe ROP from November 2013 to January 2014 were treated with propofol sedation combined with fentanyl analgesia, allowing to perform surgery in spontaneous breathing without side-effects related to propofol administration. Only 2 neonates had to be assisted with ventilation during the procedure. No episodes of bradycardia or hypotension were recorded. The laryngeal mask was always successfully removed at the end of the procedure. During the first hour after the procedure 4 neonates presented apnea and required caffeine administration, 2 neonates required nCPAP for 2 hours. None of the treated neonates required intubation or mechanical ventilation (**Tab. 1**). Laser therapy was successful in every treated neonate.

CONCLUSIONS

The rapid recovery, together with the absence of side-effects and the good level of anesthesia and analgesia achieved confirm the efficacy and safety of sedation with propofol in these babies. Furthermore it can be performed in the NICU, thus avoiding transportation of preterm infants to the operating room, minimizing the risk of hypothermia. Surgery was not affected negatively by this new anesthetic procedure.

Table 1 (ABS 7). Characteristics of the patients undergoing laser therapy for ROP.

	13 patients mean + SD (range)
Gender (male/female)	9/4
Gestational age at birth, weeks	26 ± 1.3 (24-28)
Birth weight, g	876 ± 205 (540-1,100)
Age at procedure, days	85 ± 23 (60-120)
Weight at procedure, g	2,235 ± 751 (1,250-4,150)
Chronic lung disease, n (%)	11 (84%)

ABS 8

ELEVATED TROUGH SERUM GENTAMICIN CONCENTRATIONS AND OTOTOXICITY

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INTRODUCTION

Gentamicin is the most frequently administered antibiotic in neonatal intensive care units. Aminoglycosides are known to cause permanent cochlear and vestibular damage. UK National Guidelines (Newborn Hearing Screening Programme) recommend babies with high levels of ototoxic medication (outside the therapeutic range, gentamicin serum trough concentration > 2.0 mmol/l) should be referred for audiological assessment around 8 months or sooner irrespective of newborn hearing screen outcome. Following the above protocol, referrals for the 8 month targeted screen increased significantly which has impacted on service capacity. Around 47% of neonatal hearing impairment has no aetiology.

PATIENTS AND METHODS

In our hospital, we routinely monitor gentamicin trough levels in all infants receiving gentamicin before the 3rd dose. We collect data on all high gentamicin levels and refer them for targeted audiological assessment at 8 months of age. Our objective was to ascertain if well near term and term babies (> 35 weeks gestation) with high gentamicin trough levels and no other risk factors developed sensorineural deafness. We collected the data between 1 Jan. to 31 Dec. 2013. We searched Badger neonatal database for all well infants born > 35 weeks gestation and received gentamicin for suspected sepsis and the national hearing screening database (eSP) for all sensorineural hearing loss for babies born locally in 2013 and confirmed these with the audiology department.

RESULTS

We had a total of 476 infants who were > 35 weeks and received gentamicin in 2013. 26 children who were born at near term and term in 2013 were found to have sensorineural deafness. 15 had bilateral and 11 had unilateral sensorineural deafness. 4 of those 26 children received gentamicin in the neonatal period but only 2 had high levels. Further detailed analysis found that those 2 children had congenital

malformations; 1 with malformation of ear and the other cleft lip and palate. Therefore none of those with sensorineural deafness could be attributed to high gentamicin level alone (OR < 0.01).

CONCLUSIONS

In this single centre data analysis over a year, in near term and term infants we did not find any evidence to suggest an increased risk of sensorineural deafness as a result of high trough level gentamicin. We are still left with the question of weather trough level gentamicin, as a sole risk factor in well near term and term babies need 8 month targeted audiology assessment.

ABS 9

RELATIONSHIP BETWEEN DOPAMINE INFUSION AND HEMODYNAMIC PARAMETERS IN PRETERM INFANTS

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INTRODUCTION

Inotropics are frequently used for treatment of hypotension. The most frequently used inotropic drug is dopamine which is administered by a multi-infusion system. Multi-infusion allows parallel administration of multiple drugs, but often leads to unpredictable drug administration, like a long start-up delay, resulting in a delay in patient response.

We investigated the relationship between start-up delay of dopamine infusion and the hemodynamic parameters mean arterial blood pressure (MABP) and cerebral oxygenation ($rScO_2$) of the preterm infant. Furthermore we compared start-up delay of two commercially available IV-sets.

PATIENTS AND METHODS

We performed retrospective data analysis on 38 hypotensive preterm infants receiving dopamine infusion by a stopcock IV set. MABP and $rScO_2$ (measured by near infrared spectroscopy) were continuously monitored (**Fig. 1**).

Secondly, start up delay of 2 different IV sets was assessed by means of *in vivo* simulation measurements. The lab set-up was able to measure fluid concentrations of multiple lines by using absorption spectral-photometry (**Fig. 2**).

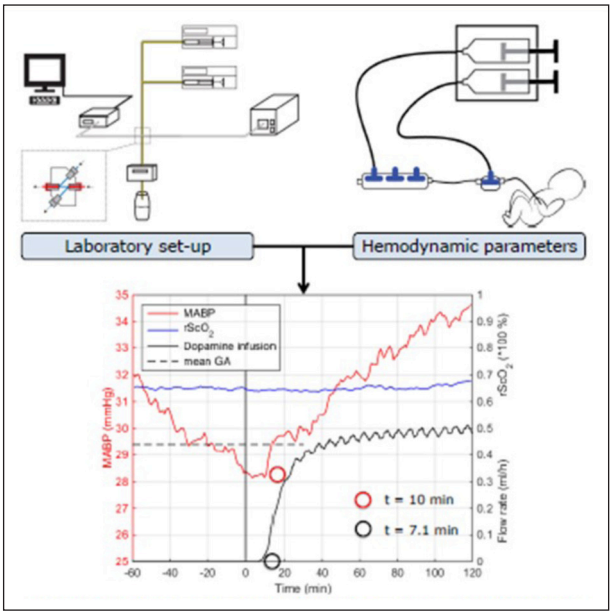

Figure 1 (ABS 9). Dopamine start-up delay (*in vitro* experiments, n = 3) and MABP and $rScO_2$ in preterm infants (retrospective *in vivo* analysis, n = 38).

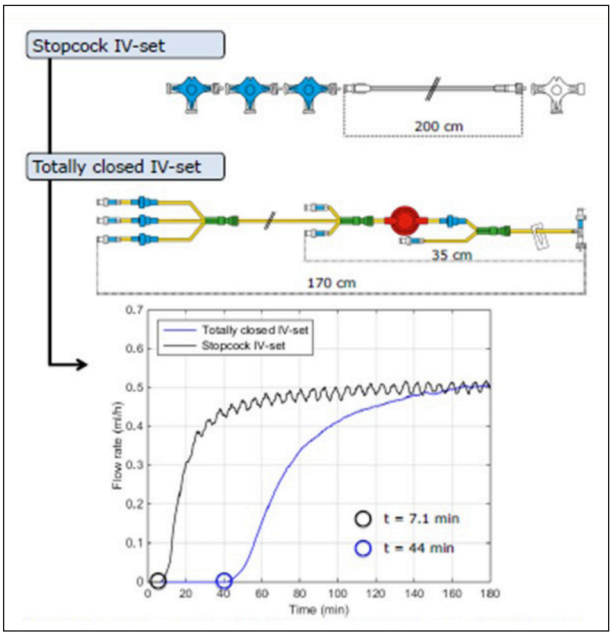

Figure 2 (ABS 9). Dopamine start-up delay (*in vitro* experiments, n = 3) of the two infusion sets.

RESULTS

An apparent relationship between the start-up delay of dopamine infusion and MABP was observed. After dopamine infusion (5 µg/kg/min, flow rate 0.5 ml/h) was started, MABP starts to increase at t = 10 min *in vivo*, in the lab setting

the start-up delay was 7.1 min. There was no significant change in cerebral oxygenation.
The currently used closed IV set had a start up delay of 44 minutes in the lab setting.

CONCLUSIONS

The delay in effect of dopamine on blood pressure *in vivo* with stopcock IV set was similar to start up delay *in vitro*. Cerebral oxygenation remained stable despite changes in blood pressure, suggesting intact autoregulatory ability. The current used IV set showed longer start up delay, which may have negative clinical implications. *In vitro* tests has to be done before introduction of IV systems and better designed IV systems have to be developed for safe and controlled drug administration.

Pharmacokinetics in the newborn period

ABS 10

DOPAMINE AND DOBUTAMINE: DOES TEMPERATURE OR INTRAVENOUS VEHICLE AFFECT STABILITY?

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INTRODUCTION

The most popular inotropes used for hypotension are dopamine and dobutamine. The EU and the Best Pharmaceuticals for Children Act in the USA has highlighted these medications as ones that require further investigation. Both medications are part of large EU funded FP7 Health trials – Neo-CIRC and The HIP trial. We have noticed locally that blood pressure appears to drop towards prior to a change in infusion syringes with these drugs. In our tertiary unit infusions of these drugs are changed every 24 hours. We have carried out an analysis to see whether the solution either drug is mixed with or the temperature the syringes that contained each solution are kept in affects their stability.

PATIENTS AND METHODS

A total of twenty four 50 ml syringes of either dopamine and dobutamine solutions where drawn up to a dose of 10 μg/kg/min for babies weighing 450 g, 2.5 kg and 4.5 kg. Dopamine and dobutamine were mixed with either 5% dextrose of 0.9% sodium chloride. These syringes were then kept in temperatures of either 21°C or 28°C. Cyclic voltammetry (CH Instruments 1206B Potentiostat) was used for detection; the current monitored was proportional to the concentration of both drug samples present. The current obtained from t = 0 was taken to be 100% and the concentration loss from this point recorded at pre-determined time points t = 2, 6, 10, 24, 28 hours. A 2-way ANOVA with Bonferroni post tests were used with results reported as means and ranges with a p-value of < 0.05 considered significant.

RESULTS

There was no observed colour change for dopamine or dobutamine in glucose or saline at either temperature. At 21°C there was a significant dose dependent increase in the rate of degradation with dopamine when prepared in 5% glucose (**Fig. 1** and **Fig. 2**). Within 6 hours, greater than 7% of the prepared drug concentration had degraded in syringes prepared for hypothetical babies weighing > 2.5 kg (**Tab. 1** and **Tab. 2**). No significant differences in the stability of dopamine in 0.9% saline and dobutamine in both 0.9% saline and 5% glucose were observed over the 28 hour period investigated. When the temperature was elevated to 28°C, there was a > 7% reduction in the prepared concentration of dopamine in both 0.9% saline and 5% glucose. Once again, no significant effects of temperature were observed on the stability of dobutamine syringes for 28 hours at 28°C.

CONCLUSIONS

Significant reductions in dopamine concentration are observed at 21°C when prepared in glucose. At 28°C dopamine stability is reduced in both vehicles. Based on the trends observed, we hypothesise that the loss in stability is due oxidation by light. Dobutamine remains stable for 24 hours in both saline and glucose at ambient temperature.
These results have implications for future pharmacokinetic and pharmacodynamics studies of these drugs.

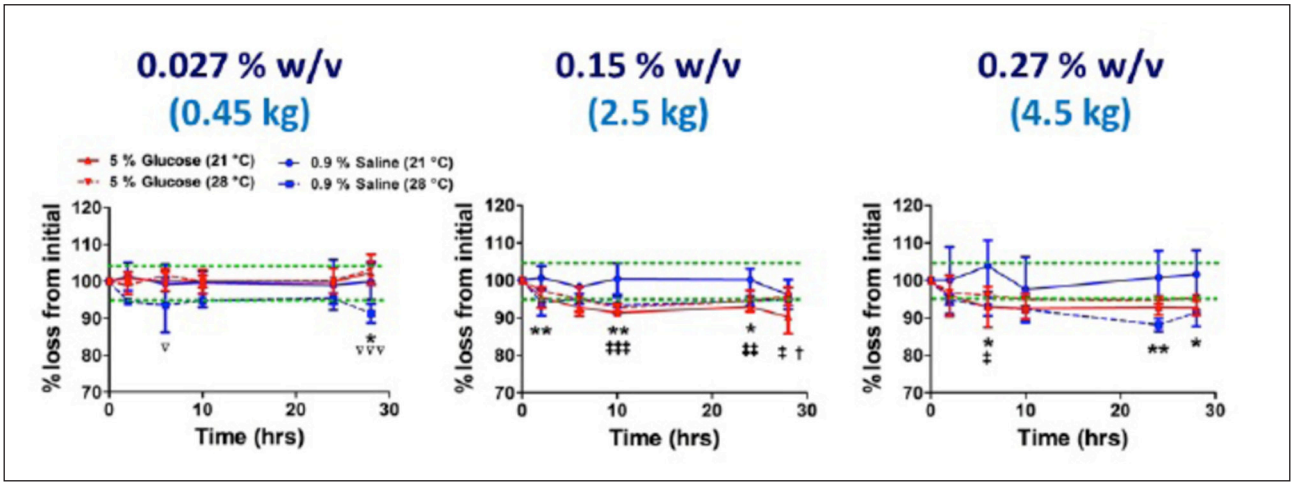

Figure 1 (ABS 10). Displaying the stability of dopamine in different condition and with different infusion fluid over 28 hours.

Effect of vehicle: ‡p < 0.05, ‡‡p < 0.01 and ‡‡‡p < 0.001 – *Saline vs. glucose at 21°C;* ▽p < 0.05, ▽▽▽p < 0.001 – *Saline vs. glucose at 28°C.*
Effect of temperature: *p < 0.05, **p < 0.01 and ***p < 0.001 – *Saline 21°C vs. 28°C;* †p < 0.05 – *Glucose 21°C vs. 28°C.*

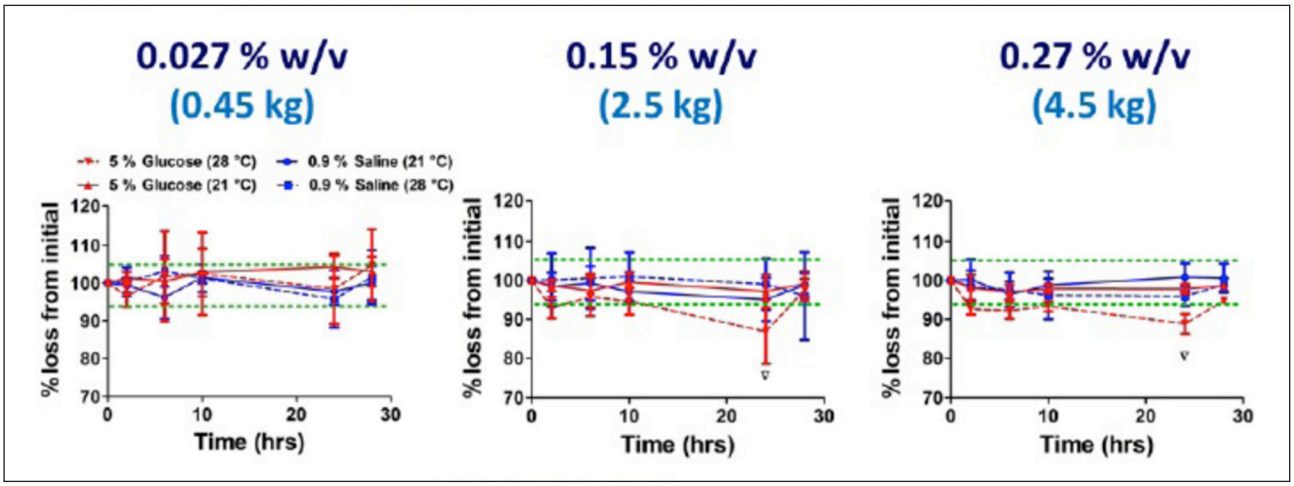

Figure 2 (ABS 10). Displaying the stability of dobutamine in different condition and with different infusion fluid over 28 hours.

Effect of vehicle: ‡p < 0.05, ‡‡p < 0.01 and ‡‡‡p < 0.001 – *Saline vs. glucose at 21°C;* ▽p < 0.05, ▽▽▽p < 0.001 – *Saline vs. glucose at 28°C.*
Effect of temperature: *p < 0.05, **p < 0.01 and ***p < 0.001 – *Saline 21°C vs. 28°C;* †p < 0.05 – *Glucose 21°C vs. 28°C.*

Table 1 (ABS 10). Showing cyclic voltammetry results for dopamine syringes gained at each time point.

Time (hours)	Dopamine concentration (% v/w) at room temperature (21°C)						Dopamine concentration (% v/w) at 28°C					
	0.9% Saline			5% Dextrose			0.9% Saline			5% Dextrose		
	0.45 kg	2.5 kg	4.5 kg	0.45 kg	2.5 kg	4.5 kg	4.5 kg	2.5 kg	4.5 kg	0.45 kg	2.5 kg	4.5 kg
0	0.270	0.270	0.150	0.027	0.270	0.150	0.270	0.150	0.027	0.270	0.150	0.027
2	0.270	0.270	0.151	0.027	0.259	0.143	0.256	0.141	0.026	0.261	0.146	0.027
6	0.280	0.280	0.099	0.027	0.251	0.139	0.251	0.143	0.025	0.259	0.142	0.027
10	0.264	0.264	0.151	0.027	0.250	0.137	0.249	0.140	0.026	0.256	0.139	0.027
24	0.272	0.272	0.150	0.027	0.251	0.139	0.238	0.142	0.026	0.256	0.142	0.027
28	0.274	0.274	0.144	0.027	0.250	0.135	0.247	0.142	0.025	0.257	0.144	0.028

Table 2 (ABS 10). Showing cyclic voltammetry results for dobutamine syringes gained at each time point.

Time (hours)	Dobutamine concentration (% v/w) at room temperature (21°C)						Dobutamine concentration (% v/w) at 28°C					
	0.9% Saline			5% Dextrose			0.9% Saline			5% Dextrose		
	0.45 kg	2.5 kg	4.5 kg	0.45 kg	2.5 kg	4.5 kg	0.45 kg	2.5 kg	4.5 kg	0.45 kg	2.5 kg	4.5 kg
0	0.270	0.150	0.027	0.270	0.150	0.027	0.270	0.150	0.027	0.270	0.150	0.027
2	0.270	0.148	0.027	0.265	0.148	0.027	0.266	0.150	0.027	0.250	0.140	0.026
6	0.280	0.149	0.027	0.262	0.146	0.027	0.263	0.151	0.028	0.249	0.144	0.027
10	0.264	0.146	0.027	0.264	0.149	0.028	0.260	0.151	0.027	0.252	0.142	0.028
24	0.272	0.143	0.027	0.264	0.146	0.028	0.259	0.149	0.026	0.240	0.130	0.027
28	0.270	0.148	0.027	0.266	0.149	0.028	0.267	0.144	0.027	0.256	0.146	0.028

Testing medicines in children

ABS 11

COMPARISON OF THE EARLY AND LATE CAFFEINE THERAPY ON CLINICAL OUTCOMES IN PRETERM NEONATES

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INTRODUCTION

In early 1970's methylxanthine products were introduced as therapy for apnea of prematurity. This study was designed to evaluate caffeine efficacy in low birth weight neonates admitted in neonatal care unit in Mashhad.

PATIENTS AND METHODS

In a control trial, after ethical approval 40 preterm neonates were selected regard to inclusion criteria. They were divided into two groups: the first group received 20 mg/kg caffeine for loading dose within the first three days of life which was continued by 5 mg/kg daily and the second group received the same dose after the third day of life. Neonates were followed up for 28 days. Data was analyzed by SPSS® version 11.5.

RESULTS

Neonates mean weight was 1,144 ± 229 grams, their mean age was 29.5 ± 2.0 week and mean mechanical ventilation duration was 16.4 ± 1.1 day. Weight changes were not significant in early and late caffeine administered groups ($p > 0.05$). Bronchopulmonary dysplasia and intracranial hemorrhage did not differ between two groups. Patients' outcome was the same in both groups. Apnea incidence was lower in early caffeine administered group ($p = 0.013$).

CONCLUSIONS

Caffeine administration in the first three days of life can reduce the risk of apnea prematurity in low birth weight neonates.

ABS 12

COMPARISON OF ORAL IBUPROFEN AND INTRAVENOUS IBUPROFEN IN NEONATES WITH PATENT DUCTUS ARTERIOSUS IN A TERTIARY MEDICAL CENTER OF TAIWAN

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INTRODUCTION

Hemodynamically significant patent ductus arteriosus (PDA), common in preterm infants, could lead to serious morbidities and mortalities. Either pharmacological or surgical closure is indicated when PDA existed pathologically. Intravenous indomethacin and intravenous ibuprofen had been used for decades. More and more studies emphasized the therapeutic potential of oral form ibuprofen. Our study aimed to compare intravenous and oral form ibuprofen to determine whether oral form ibuprofen could be introduced not only from the aspect of cost, and another goal of our study is to

investigate which group of infants will benefit more in using oral form ibuprofen for treating PDA.

PATIENTS AND METHODS

Our study is a retrospective study that reviewed medical charts of infants who received intravenous or oral form ibuprofen for significant PDA in a single neonatal intensive care unit of a medical center from May 2010 to December 2013. The dosage of these two formulations is 10 mg/kg for the first dose followed by 5 mg/kg at the interval of 24 hours for the rest two doses. We compared the basic characteristics of infants who received intravenous or oral form ibuprofen as well as primary and overall closure rate and the frequency of adverse effects.

RESULTS

A total number of 95 infants were enrolled in our study. 29 infants received oral form ibuprofen (referred as oral group) and 66 infants were treated with intravenous form ibuprofen (referred as IV group) (**Fig. 1** and **Fig. 2**). The basic characteristic information between two groups was generally similar except for the frequency of antenatal steroid usage (**Tab. 1**). The primary closure rate was 72.4% in the oral group and 68.2% in the IV group (p = 0.810). The overall closure rates were 65.5% and 62.1% in oral group and IV group (p = 0.820), respectively (**Tab. 2**). After subgroup analysis, infants with greater gestational age and larger birth weight still respond to oral form medication. Differences about acute complications (oliguria: p = 1, GI bleeding: p = 1, NEC: p = 1, SIP: p = 1, IVH: p = 0.305) or long term morbidities (BPD: p = 1, PVL: p = 0.242) were not noted among these two groups (**Tab. 3**).

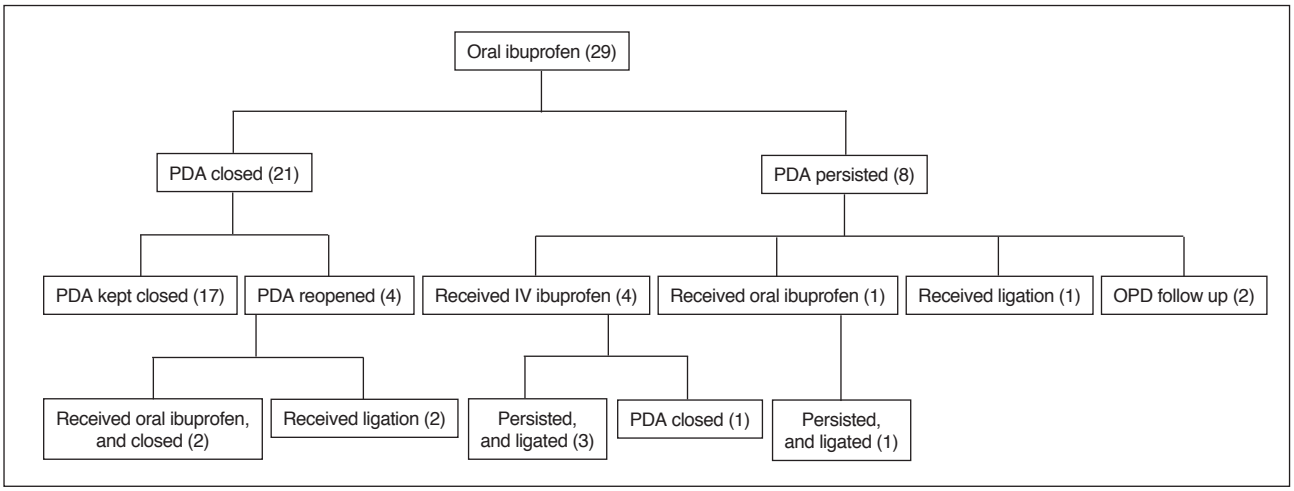

Figure 1 (ABS 12). Flow chart of therapy with initial oral ibuprofen.

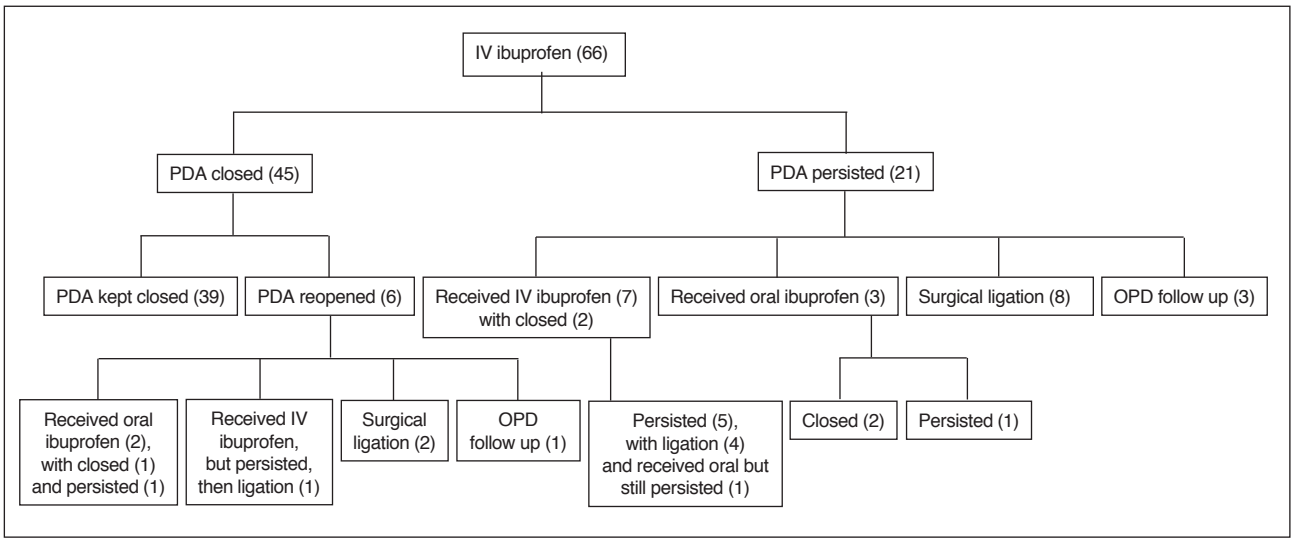

Figure 2 (ABS 12). Flow chart of therapy with initial IV ibuprofen.

Table 1 (ABS 12). Basic characteristics of the two groups.

	Oral group n = 29	IV group n = 66	p
GA	29 (25-38)	28 (23-36)	0.062
BBW	1,385 (528-3,440)	1,145 (500-2,634)	0.232
Gender (F:M , F %)	16:13 (55%)	33:33 (50%)	0.663
CS	24/29 (83%)	53/66 (80%)	1.000
AS (1)	5 (1-8)	4 (1-9)	0.970
AS (5)	8 (3-9)	8 (3-10)	0.442
Maternal PIH	4/19 (14%)	6/66 (9%)	0.488
Antenatal steroid	22/29 (76%)	61/66 (92%)	0.041
Surfactant	11/29 (38%)	36/66 (55%)	0.182
Ductal diameter (cm)	2.0 (1.5-3.4)	2.0 (0.9-3.6)	0.686
LA/Ao	1.7(1.1-4.3)	1.6 (0.9-3.0)	0.346
U/O before Tx (ml/kg/hr)	3.1 (2.0-5.3)	3.1 (1.3-5.8)	0.784
PLT before Tx (K/μL)	195 (79-452)	193 (66-786)	0.660
Cre before Tx (mg/dL)	0.8 (0.5-1.3)	0.9 (0.5-1.45)	0.663
Date of treatment	6 (3-19)	7 (3-21)	0.669

Data are presented as medians (ranges) and numbers (percentage).

Table 2 (ABS 12). Primary and overall closure rates of the two groups.

	Oral group n = 29	IV group n = 66	p
Primary closure rate	21/29 (72.4%)	45/66 (68.2%)	0.810
Subgroup analysis			
BW < 1,000 g (n = 36)	6/8 (75%)	20/28 (71%)	1.000
BW 1,000-1,500 g (n = 26)	5/9 (56%)	12/17 (70%)	0.667
BW ≥ 1,500 g (n = 33)	10/12(83%)	13/21 (62%)	0.259
BW < 1,000 g (n = 36)	6/8 (75%)	20/28 (71%)	1.000
BW 1,000-2,000 g (n = 51)	11/17 (65%)	22/34 (65%)	0.618
BW ≥ 2,000 g (n = 8)	4/4 (100%)	3/4 (75%)	1.000
BW < 1,500 g (n = 62)	11/17 (65%)	32/45 (71%)	0.759
BW ≥ 1,500 g (n = 33)	10/12 (83%)	13/21 (62%)	0.259
GA < 30 weeks (n = 56)	11/15 (73%)	28/41 (68%)	1.000
GA 30-34 weeks (n = 34)	7/11 (64%)	15/23 (65%)	1.000
GA ≥ 35 weeks (n = 5)	3/3 (100%)	2/2 (100%)	1.000
GA < 32 weeks (n = 75)	14/20 (70%)	36/55 (65%)	0.788
GA ≥ 32 weeks (n = 20)	7/9 (78%)	9/11 (82%)	1.000
Overall closure rate	19/29 (65.5%)	41/66 (62.1%)	0.820

Data are presented as numbers (percentage).

Table 3 (ABS 12). Treatment related side-effects and long-term complications of the two groups.

	Oral group n = 29	IV group n = 66	p
Treatment related side-effects			
Oliguria	0/29	0/66	1.000
GI bleeding	1/29	3/66	1.000
NEC	0/29	1/66	1.000
SIP	0/29	2/66	1.000
IVH	1/29	0/66	0.305
Long term morbidities			
BPD	9/29	22/66	1.000
PVL	4/29	4/66	0.242

Data are presented as numbers.

CONCLUSIONS

Our study might be the first study in Taiwan to compare these two formulation in managing PDA. Oral form ibuprofen for treating PDA in neonates is as effective and safe as intravenous form medication. Oral form ibuprofen also work effectively in infants with larger gestational age and larger birth weight.

ORAL COMMUNICATIONS

ABS 13

REDUCTION IN PRESCRIPTION ERRORS IN A NEONATAL INTENSIVE CARE UNIT: A COMPLETED AUDIT CYCLE

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INTRODUCTION

Neonates are particularly vulnerable to harm from medication-related errors. Prescription errors are one of the most important sources of potential harm accounting for approximately two-thirds of all medication-related incidents in this population.

Our aims were to evaluate the impact of a package of interventions designed to improve prescribing practice by doctors and advanced neonatal practitioners (ANNPs) working in a large UK NICU.

PATIENTS AND METHODS

We devised an audit tool to capture data relating to the quality of prescribing across a range of neonatal prescriptions. The accuracy and completeness of prescriptions were assessed against a list of agreed standards. Prescription charts were selected at random, weekly on the same day each week over a seven week period in both audits; a single individual undertook the baseline audit whereas two individuals performed the re-audit. Following the baseline audit a number of interventions were introduced and implemented including modification of prescription charts, specific improvements in education and training and anonymised publication of prescribers' error rates. Prescribing practice was re-assessed one year later after the package of interventions had been embedded into routine practice.

RESULTS

1,087 individual prescriptions were reviewed in total. During the initial audit, there were 16 errors in a total 292 prescriptions assessed giving an error rate of 5.5 per 100 prescriptions. In the re-audit, there were a total of 13 errors in 795 prescriptions examined giving an error rate of 1.64 errors per 100 prescriptions ($p = 0.003$ compared with the baseline audit) (**Tab. 1**). All 13 observed errors were deemed relatively minor prescribing errors and none led to any patient harm. Prescribers were not identifiable in 126 prescriptions (16%).

CONCLUSIONS

Prescribing errors in neonatal practice are relatively common but rarely result in patient harm. Using a completed audit cycle, we have shown a reduction in prescribing error rates following the implementation of a range of interventions that combined to improve prescribing practice of junior doctors and ANNPs.

Table 1 (ABS 13). Number of prescriptions reviewed in the first and in the second audit and number of errors observed.

	Prescription type					
	IV fluids	**Total parenteral nutrition**	**Gentamicin (first dose)**	**Gentamicin (second dose)**	**Drug Kardexes**	**Total**
Number of prescriptions reviewed in first audit	56	28	32	18	176	310
Number of errors observed in first audit	2	1	4	4	5	**16**
Number of prescriptions reviewed during second audit	157	51	65	45	477	795
Number of errors observed during second audit	2	2	4	2	3	**13**

Good clinical practice – in practice

ABS 14

POTENTIALLY HARMFUL EXCIPIENTS IN MEDICINES PRESCRIBED IN NEONATAL INTENSIVE CARE UNITS (NICUs) – PRODUCT SUBSTITUTION AS A WAY FORWARD

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INTRODUCTION

Regional variations in neonatal administration of potentially harmful excipients – excipients of interest (EOIs) – parabens, polysorbate 80, propylene glycol, benzoates, saccharin sodium and ethanol – were previously demonstrated in the European study of neonatal exposure to excipients. This suggests a possibility to reduce exposure through product substitution. We aimed to identify potential reduction of neonatal exposure to EOIs if all substitution possibilities – according to active pharmaceutical ingredient (API), route of administration and dosage form – among frequently used medicines were taken into account.

PATIENTS AND METHODS

A three-day Service Evaluation Survey (SES; registered all medicines) and one-day Point Prevalence Study (PPS; registered individual prescriptions) were performed in 20 and 21 European countries. Product substitution was investigated for APIs with products containing EOIs and used in more than 10% of participating units in SES, excluding multivitamins. The same APIs were used to evaluate the reduction of individual exposure through substitution in PPS. Substitution was defined as EOIs-containing product for which an EOIs-free formulation with identical APIs, route of administration and dosage form was available.

RESULTS

In SES, 137 products for 25 APIs contained EOIs; for 47% (n = 64) and 56% (n = 14) substitution with EOIs-free product(s) was available, respectively. Overall, 456 neonates were exposed to EOIs in PPS through 142 products and 638 prescriptions. Individual substitution analysis included 22 APIs represented by 195 products (**Tab. 1**). For 16 APIs, products with EOIs were found; a third of products and half of prescriptions contained EOIs; 315 (64%) neonates received at least one EOI through these products. After all potential product substitutions the number of neonates exposed to EOIs would decrease by 85% (**Tab. 1**). For 69% (11/16) of studied APIs EOIs-free products were available. Overall, substitution of only most frequently used products would reduce the number of exposed neonates by 44% (from 456 to 257).

CONCLUSIONS

EOIs-free products available on the European market could be used to significantly reduce neonatal exposure to EOIs through product substitution. Substitution of most often used products may spare almost a half of neonates from unnecessary exposure.

Table 1 (ABS 14). Number of active pharmaceutical ingredients (APIs), products and prescriptions containing specified excipients of interest (EOIs) and neonates exposed before and after substitution.

EOI	No. of APIs (n = 22) before/after	No. of products (n = 195) before/after	No. of prescriptions (n = 776) before/after	No. of neonates (n = 491) before/after
Polysorbate 80	3/0	4/0	63/0	63/0
Propylene glycol	6/1	11/1	76/1	75/1
Ethanol	8/3	13/6	34/20	34/20
Parabens	10/4	46/12	249/43	227/41
Benzoates	7/2	12/3	58/4	47/4
Saccharin sodium	7/4	14/10	44/29	40/25
Sorbitol	4/3	14/8	42/25	38/21
At least one EOI	**16/5**	**71/18**	**372/51**	**315/46**

EOI: excipient of interest; API: active pharmaceutical ingredient.

ABS 15

NEPHROTOXICITY RELATED TO VANCOMYCIN AND AMIKACYN ASSOCIATION IN NEONATAL PATIENTS

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INTRODUCTION

Neonates have a large susceptibility to infection which may lead to high rate of mortality.

Vancomycin is a glycopeptide antibiotic with activity against Gram-positive bacteria although nephrotoxicity and ototoxicity are described as drug-related adverse effects.

This study investigates vancomycin associated drugs in newborn infection control.

PATIENTS AND METHODS

Our retrospective study included 34 newborn patients with mean gestational age of 30.51 ± 0.74 weeks, mean birthweight of 1,384 ± 123 g admitted in a private hospital neonatal intensive care unit, with a mean hospitalization period of 62 ± 5.98 days.

RESULTS

Vancomycin 36.31 ± 4.97 mg/kg/day was administered to 100% of the patients in a period of 13.56 ± 2.21 days to treat pulmonary and urinary tract infection 50% (n = 17) and sepsis 50% (n = 17).

The association of amikacin to vancomycin was observed in 58.82% (n = 20) of patients.

These same patients 58.82% (n = 20) presented urine volume reduction and received either furosemide 1.07 ± 0.16 mg/kg/day (29.41%) or the association of furosemide and hydrochlorothiazide 1.12 ± 0.14 mg/kg/day (29.41% of patients) in a period of 30.10 ± 6.05 days of treatment.

CONCLUSIONS

Nephrotoxicity of vancomycin should be considered specially when associated to another nephrotoxic drug such as amikacin.

The association of furosemide may lead to increase renal impairment considering that furosemide is also nephrotoxic.

Slow (60 minutes) intravenous continuous infusion of those antibiotics may reduce the maximum peak concentration of vancomycin and amikacin thus reducing nephrotoxicity.

Markers of renal function such as urea and creatinine should be monitorized.

ABS 16

REVIEW OF SECOND LINE ANTIBIOTIC CHOICE ON A TERTIARY NEONATAL UNIT IN THE UNITED KINGDOM

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INTRODUCTION

Neonatal sepsis is a major cause of morbidity and mortality. Initial empirical antibiotic choice is based on likely causative organisms. A national guideline exists for early onset sepsis. Organisms causing late onset sepsis are more varied encompassing gram-negatives and line sepsis. Good practice recommendations dictate regular review of antibiotic choice on neonatal units. This study's aim was to review whether current second line antibiotic choice of flucloxacillin and gentamicin (without long line) and cefotaxime and vancomycin (with long line) is optimal, based on local micro-organism sensitivities. Alongside, we surveyed second line antibiotic choice in level 3 units across the UK.

PATIENTS AND METHODS

We undertook a retrospective review of all positive blood cultures from babies admitted to our level 3 neonatal unit between January 2012 and December 2013. This time period was of particular significance as it followed an extended-spectrum β-lactamase (ESBL) outbreak on the unit in late 2011 during which 2 babies died. Positive blood cultures were identified via the microbiology reporting system. Organisms and antibiotic sensitivities were analysed. Contaminants were excluded according to Vermount Oxford Network (VON) criteria. Results were collected and analysed using Microsoft® Excel®.

Alongside the study, a telephone survey of second line antibiotic choice on the 45 UK level 3 neonatal units was undertaken to compare practice nationally.

RESULTS

1,173 blood cultures were taken in the 2 year study period with 10.3% proving positive. 32% were identified as contaminants, leaving 82 blood cultures from 59 patients. After exclusions these were divided into 59 sepsis episodes.

27% of sepsis episodes showed resistance to flucloxacillin and gentamicin in combination. 3%

were resistant to cefotaxime and vancomycin and over half were not reported. 19% showed resistance to vancomycin and gentamicin with only 8% unreported. Of note no resistance was found to third line antibiotic choice meropenem.
37 of the 45 UK level 3 units responded to the telephone survey. Results showed expected regional diversity. The majority (48%) used flucloxacillin and gentamicin for those without a long line. Only 6% used cefotaxime and vancomycin for those with a long line, with the majority of 32% using vancomycin and gentamicin.
CONCLUSIONS
Flucloxacillin and gentamicin are appropriate second line antibiotics for local micro-organisms. Sensitivity to cefotaxime is a largely unknown quantity. We recommend changing to vancomycin and gentamicin for babies with central lines and aim to repeat the study in 2 years time. Of course, the emphasis must remain on recognising early signs of sepsis in our vulnerable patient population with prompt administration of IV antibiotics.

ABS 17

DOXAPRAM THERAPY IN NEWBORNS; SHOULD WE STILL USE IT?

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INTRODUCTION
Apnea of prematurity (AOP) are primarily treated with caffeine and maximal non-invasive ventilation. If apneic spells persist, treatment with doxapram might be indicated although sparse evidence and off-label for use in neonates. This study aimed to evaluate the success-rate of doxapram treatment and to find the determining covariates for success.
PATIENTS AND METHODS
A retrospective analysis of prospectively collected data was performed concerning all patients born between January 2006 and August 2014, who were admitted to the level III Neonatal Intensive Care Unit of the Erasmus MC-Sophia Children's hospital and received doxapram therapy. Doxapram was started in addition to caffeine treatment with a loading dose of 2.5 mg/kg followed by a maintenance dose of 2.0 mg/kg/hr. Subsequently the dosage was decreased if apneic spells were absent. Successfully treated patients, defined as those who did not need endotracheal intubation because of AOPs, were compared to unsuccessfully treated patients, and covariates were evaluated that determine success.
RESULTS
In total 194 patients with a median gestational age of 26^{+1} weeks (IQR 2^{+2} weeks) were included. One up to five episodes of doxapram treatment were given to 139 (71%); 38 (20%); 10 (5%); 6 (3%) and 1 (1%) patients respectively. The median postnatal age at start of the first episode of doxapram therapy was 20 days (IQR 17 days). 31% of the patients received doxapram only via intravenous infusion, 15% only orally via a gastric tube and 54% received doxapram via both routes of administration. 119 (61.3%) patients were successfully treated with doxapram. The success rate of doxapram therapy was 65%, 81% and 94% for patients in the first, second and third episode of treatment respectively. Successfully treated neonates had higher gestational ages and postnatal ages, higher weights at admission and were treated later after birth.
CONCLUSIONS
We showed that doxapram was frequently used for the treatment of AOP in preterm infants and was successful in avoiding intubation in 61.3% of the cases. Success of doxapram treatment increased with gestational age, bodyweight at admission and with postnatal age at start of doxapram therapy. In conclusion, our results show doxapram to be effective via oral and intravenous administration in an important part of patients treated for AOP.

Pharmacokinetics in the newborn period

ABS 18

VANCOMYCIN THERAPEUTIC DRUG MONITORING IN NEONATES: ARE THERE INTRA-ASSAY DIFFERENCES?

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INTRODUCTION
Vancomycin has been used in neonates for more than 50 years, but validated dosing regimens

are still lacking and cross validation of different published models on vancomycin pharmacokinetics (PK) in neonates failed, in part due to assay related differences to measure vancomycin. As part of a project on vancomycin diposition and quantification, we here focus on the impact of intra-assay differences for vancomycin in neonatal plasma matrix.

PATIENTS AND METHODS

Following study registration and parental consent, trough vancomycin therapeutic drug monitoring (TDM) samples were collected and analyzed twice using the same technique (COBAS® c702 immunoassay, Roche Diagnostics, Basel). A first analysis was done based on the clinical indication and laboratory facilities (ISO15189 certified) in the hours after sampling. A second analysis was performed in a second sample, simultaneously collected but analysed at the end of sample collection (2-3 months) in one batch with the same equipment. Until analysis, the second TDM samples were centrifuged and subsequently stored at -80°C. Wilcoxon, Passing-Bablok and Bland Altman were applied (MedCalc).

RESULTS

Samples collected on 25 occasions were available for TDM analysis. Mean (range) values for the first and second analysis were 12.8 (6.5-23.7) and 12.7 (5.8-21.3) mg/l ($p = 0.81$). Passing Bablok regression was $y = 0.19 + 0.96 x$ ($p = 0.48$).

CONCLUSIONS

Within the clinical setting of a certified laboratory, there is very limited at random variability in vancomycin TDM measurement with the COBAS® technique. In contrast, the impact of between assay variability in neonatal matrix (total concentration, free fraction) warrants further exploration.

ABS 19

GENTAMICIN EXPOSURE AND SENSORINEURAL HEARING LOSS IN PRETERM INFANTS

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INTRODUCTION

Sensorineural hearing loss (SNHL) occurs in the wide range of 0.4-5% in very low birth weight (VLBW) premature infants. While multiple risk factors have been identified, the contribution of gentamicin treatment to the development of SNHL remains a subject of debate. We aimed to determine the impact of gentamicin exposure on SNHL in VLBW infants.

PATIENTS AND METHODS

Exposure to gentamicin was measured in infants born between 1993 and 2010 at a gestational age < 32 weeks and/or with a birthweight < 1,500 g, who presented with SNHL during the first 5 years of life. For each case, we selected two controls matched for gender, gestational age, birthweight, and date of birth. The influence of other potential risk factors on SNHL was also investigated, and neurodevelopmental outcome was recorded.

RESULTS

We identified a study group of 25 infants affected by SNHL, leading to an incidence of SNHL of 1.58% in VLBW infants. The proportion of infants treated with gentamicin was 76% in the study group and 70% in controls ($p = 0.59$). The total cumulative dose of gentamicin was not different between the study group (median 12.0 mg/kg, IQR: 2.0-15.2) and the control group (median 9.7 mg/kg, IQR: 0-14.6; $p = 0.62$). The median duration of gentamicin treatment was 4 days (IQR: 3-6) in the study group and 3 days in the control group (IQR: 3-5; $p = 0.31$). Maximum predicted trough serum levels of gentamicin during treatment, cumulative area under the curve and gentamicin clearance were similar between cases and controls. Besides SNHL, other severe neurodevelopmental impairments occurred in 44% of the patients from the study group and 12% of the patients from the control group ($p = 0.002$).

CONCLUSIONS

SNHL remains a serious complication of prematurity and is associated with other neurodevelopmental disabilities. Gentamicin administered in therapeutically controlled doses is not associated with SNHL in VLBW infants.

ABS 20

QUANTIFICATION OF THE IMPACT OF PHARMACOGENETICS ON TRAMADOL DISPOSITION IN EARLY INFANCY

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INTRODUCTION

Tramadol (M) is metabolized by cytochrome P40 (CYP)2D6 to O-demethyl tramadol (M1). M1 formation depends on maturational CYP2D6 activity and its polymorphism CYP2D6 activity score. These covariates only in part explain the variability in log M/M1 plasma concentrations observed. Recently, it has been suggested that drug transporter polymorphism on Organic Cation Transporter 1 (OCT1, active uptake from plasma to hepatocyte) also affect the log M/M1 in adults, but data on *in vivo* OCT1 ontogeny are unreported.

PATIENTS AND METHODS

An earlier published dataset on 250 plasma log M/M1 values in young infants was linked with clinical characteristics and data on pharmacogenetic polymorphisms (OCT1, CYP2D6 activity score) to quantify the impact of pharmacogenetics on the variability in plasma log M/M1 values in early infancy (multiple regression).

RESULTS

The impact of the CYP2D6 activity score and postmenstrual age were confirmed, but neonates with 2 active OCT alleles had higher plasma log M/M1 values (**Fig. 1**). In a multiple regression model, postmenstrual age, CYP2D6 and OCT allele frequency explained 51% of the plasma log M/M1 variability observed. When limited to the pharmacogenetic markers, 33% of the variability was explained.

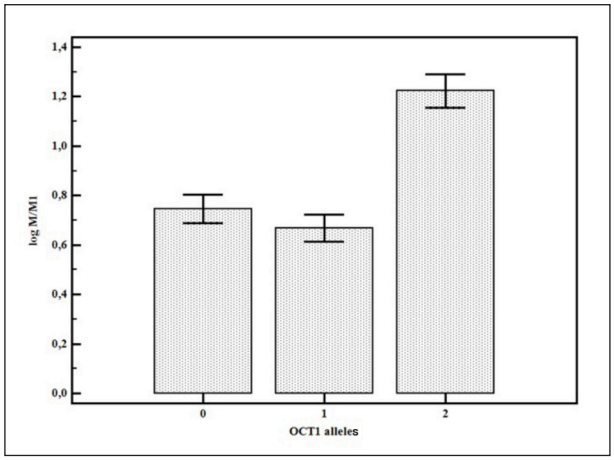

Figure 1 (ABS 20). Log M/M1 in plasma, 250 observations, OCT allele number (a higher OCT allele = higher uptake = higher log value).

CONCLUSIONS

At preliminary analysis, both the CYP2D6 activity score and OCT allele frequency already in part explained the variability in plasma log M/M1, supporting the relevance to further explore this dataset. This illustrates the relevance of pharmacogenetics and provides evidence for phenotypic OCT1 activity in early infancy.

ABS 21

PHARMACOKINETICS OF ANTENATAL MAGNESIUM SULFATE IN PRETERM INFANTS FOR NEUROPROTECTION

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INTRODUCTION

Antenatal magnesium sulfate has been shown now in large randomised studies to confer neuroprotection to the preterm infant and decreases the risk of cerebral palsy. Although guidelines for this have been developed, there is still variation in the doses used. Evidence from neonatal studies is critical in understanding developmental variations in drug pharmacokinetics and can guide dosing adjustments and reduce adverse effects. The objective of this study was to characterise the pharmacokinetics of antenatally given magnesium sulfate in preterm infants.

PATIENTS AND METHODS

Data were collected from a single tertiary centre in the Netherlands. Blood samples (n = 132) were taken postnatally at various timepoints from 43 neonates whose mothers received intravenous magnesium sulfate for treatment and/or prevention of eclampsia or preterm labour. All the mothers had received a similar dosing schedule i.e. IV 4 g bolus followed by 1 g/hr infusion of $MgSO_4$. Population pharmacokinetics was carried out using nonlinear mixed-effect modelling (NONMEM). NONMEM

was performed using first-order conditional estimation (FOCE) with interaction. The classical 1-compartment model was used.

RESULTS

The estimated pharmacokinetics (PK) parameters are shown in **Tab. 1**. The initial model was considered a base model on which the addition of various covariates was tested. The weight was included in all models as a priori covariate affecting neonatal Ke by use of allometric scaling. When other covariates were tested, forward inclusion revealed gestational age as a significant covariate as it resulted in 4.3 unit decrease in the OFV (p = 0.038) and hence included in the final model as shown in **Tab. 2**.

Table 1 (ABS 21). Model-building process to reach the final pharmacokinetic model of Mg.

Model	1-compartment Ke (allometric)	1-compartment Ke-WT –GA (allometric)
OFV	**-315.93**	**-320.20**
ΔOFV	-	-4.270
p-value	-	0.0387
PK parameter		
Mother's θ_{Ke} (hr^{-1})	0.1477	0.1498
Child's θ_{Ke} (L)	0.0599	0.0636
$t_{1/2\ mother}$ (hr)	4.69	4.63
$t_{1/2\ neonate}$ (hr)	11.57	10.90
B_{GA}	-	0.199
Baseline conc. (mmol/L)	0.595	0.602
$IIV_{Ke\ mother}$	33.9%	36.0%
$IIV_{Ke\ neonate}$	36.8%	33.1%
ε (CV%)	11.9%	11.6%

ΔOFV indicates a change in OFV relative to the previous model; a ΔOFV of -3.84 is significant at p < 0.05 (1 df). Weight (WT) was scaled to a median of 65 kg.
IIV: inter-individual variability; ε: residual variability.

CONCLUSIONS

Preterm infants have delayed clearance and prolonged half-life of magnesium sulfate. Further analyses are necessary according the underlying cause of prematurity, duration of therapy in relation to PK. However, this data can be used for simulation of future dose studies of antenatal magnesium sulfate for neuroprotection.

ABS 22

DETERMINATION OF OPTIMAL DOSING OF RECOMBINANT HUMAN IGF-1/IGFBP-3 TO ESTABLISH AND MAINTAIN PHYSIOLOGICAL INTRAUTERINE SERUM IGF-1 LEVELS IN PRETERM INFANTS

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INTRODUCTION

rhIGF-1/IGFBP-3 is currently being investigated for the prevention of retinopathy of prematurity (ROP) in preterm infants. A population pharmacokinetic model was developed using data from Phase 1 and 2 (Sections A-C) studies of rhIGF-1/IGFBP-3 in preterm infants in order to predict optimal dosing to establish and maintain serum IGF-1 within the range of physiological intrauterine levels. Section D of the Phase 2

Table 2 (ABS 21). Allometric model for all patients.

	PK parameter	RSE	IIV	RSE	Residual variability	RSE
Mother Ke (hr^{-1})	0.1498	0.279	36.0%	0.760	11.6%	0.365
Mother $t_{1/2}$ (hr)	4.626					
Child Ke (hr^{-1})	0.0636	0.191	33.1%	1.165		
Child $t_{1/2}$ (hr)	10.90					
Effect of GA	0.199	0.556				
Baseline conc.	0.602	0.260				

PK parameters are scaled to a median weight of 65 kg (median mothers weight prior to pregnancy).
IIV: inter-individual variability; RSE: relative standard error of parameter estimates.

study, which aims to evaluate dosing and efficacy of rhIGF-1/IGFBP-3, was initiated using the predicted dosing regimen. We report serum IGF-1 levels for the first 10 infants treated in Section D in order to assess the appropriateness of this regimen.

PATIENTS AND METHODS

The Phase 2 Section D study is currently ongoing in infants with gestational age (GA; wk^{+d}) 23^{+0} to 27^{+6} at birth, randomised to receive rhIGF-1/IGFBP-3 or standard neonatal care (control); target enrolment is 120 infants. rhIGF-1/IGFBP-3 is administered at a dose of 250 μg/kg/day by continuous intravenous infusion from birth up to a postmenstrual age of 29 wk + 6 d. An interim review of serum IGF-1 data was conducted once 10 treated infants had completed the dosing phase of the study in order to assess suitability of the dosing regimen to reach and maintain serum IGF-1 target levels of 28-109 μg/L (estimated physiological intrauterine levels for GA 23 to 28 wk based on published literature). Serum IGF-1 levels were measured using a validated radioimmunoassay at a central laboratory.

RESULTS

Serum IGF-1 data were reviewed for 10 treated (50.0% female, 50.0% male) and 9 control infants (33.3% female, 66.7% male). At birth, GA (wk^{+d}) ranged from 24^{+4}-27^{+5} for treated and 23^{+3}-27^{+6} for control infants; birth weight ranged from 0.5-1.1 kg and 0.6-1.2 kg, respectively. Duration of therapy in treated infants ranged from 1-34 days. At baseline, mean (SD) serum IGF-1 was 19.2 (8.0) μg/L for treated and 15.4 (4.7) μg/L for control infants. Mean (SD) serum IGF-1 levels increased to 45.9 (19.6) μg/L at 12 h in treated infants, and remained within target levels for all subsequent timepoints. In control infants, mean serum IGF-1 remained below target levels for all timepoints (**Fig. 1**). Over the course of the study, 88.8% of serum IGF-1 measurements were within target levels for treated infants compared with 11.1% for control infants (intent-to-treat analysis).

CONCLUSIONS

Using the selected dose of rhIGF-1/IGFBP-3 250 μg/kg/day continuous intravenous infusion, serum IGF-1 levels were within targeted, physiological intrauterine levels for the majority of measurements

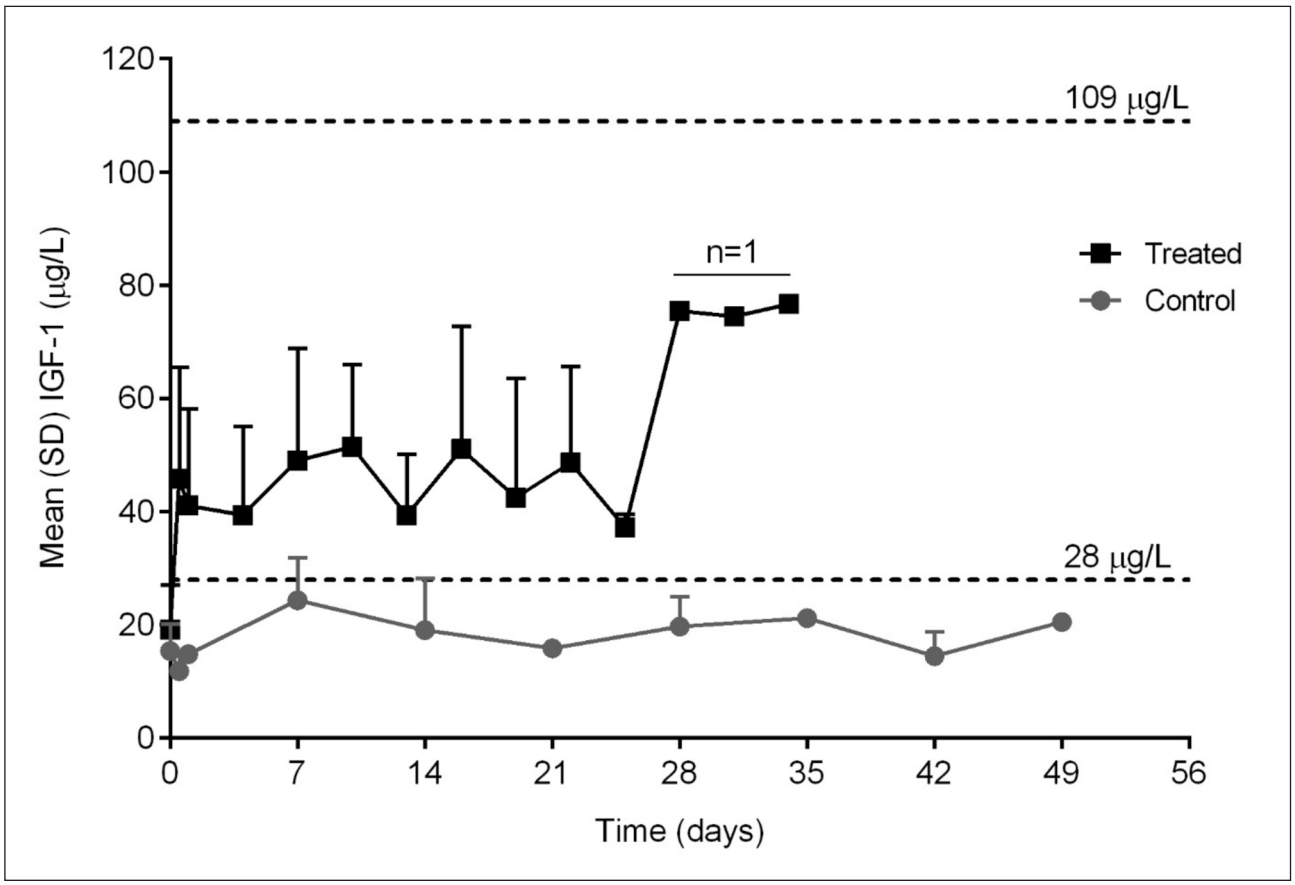

Figure 1 (ABS 22). IGF-1 profile (mean [SD]; treated vs. control infants).

during therapy in treated infants. This analysis validates the population pharmacokinetic model and confirms the appropriateness of the predicted dosing regimen for the Phase 2 Section D study.

Testing medicines in children

ABS 23

EARLY INTRAVENOUS PARACETAMOL CLOSES DUCTUS ARTERIOSUS IN VERY PREMATURE INFANTS: A RANDOMIZED, CONTROLLED TRIAL

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INTRODUCTION

Symptomatic patent ductus arteriosus (PDA) complicates the recovery of a very preterm infant (VLGA, gestation < 32 wk). Approved PDA treatments, like COX inhibitors and surgical ligation are associated with adverse effects. Administration of paracetamol, an inhibitor of prostaglandin synthase, has been shown to induce the closure of PDA (Hammermann et al., 2011). This result has been repeated in several non-randomized trials. In the present study we tested the hypothesis that paracetamol causes early closure of ductus arteriosus when given intravenously to preterm infants shortly after birth. We further prospectively evaluated whether treatment was associated with serious adverse effects.

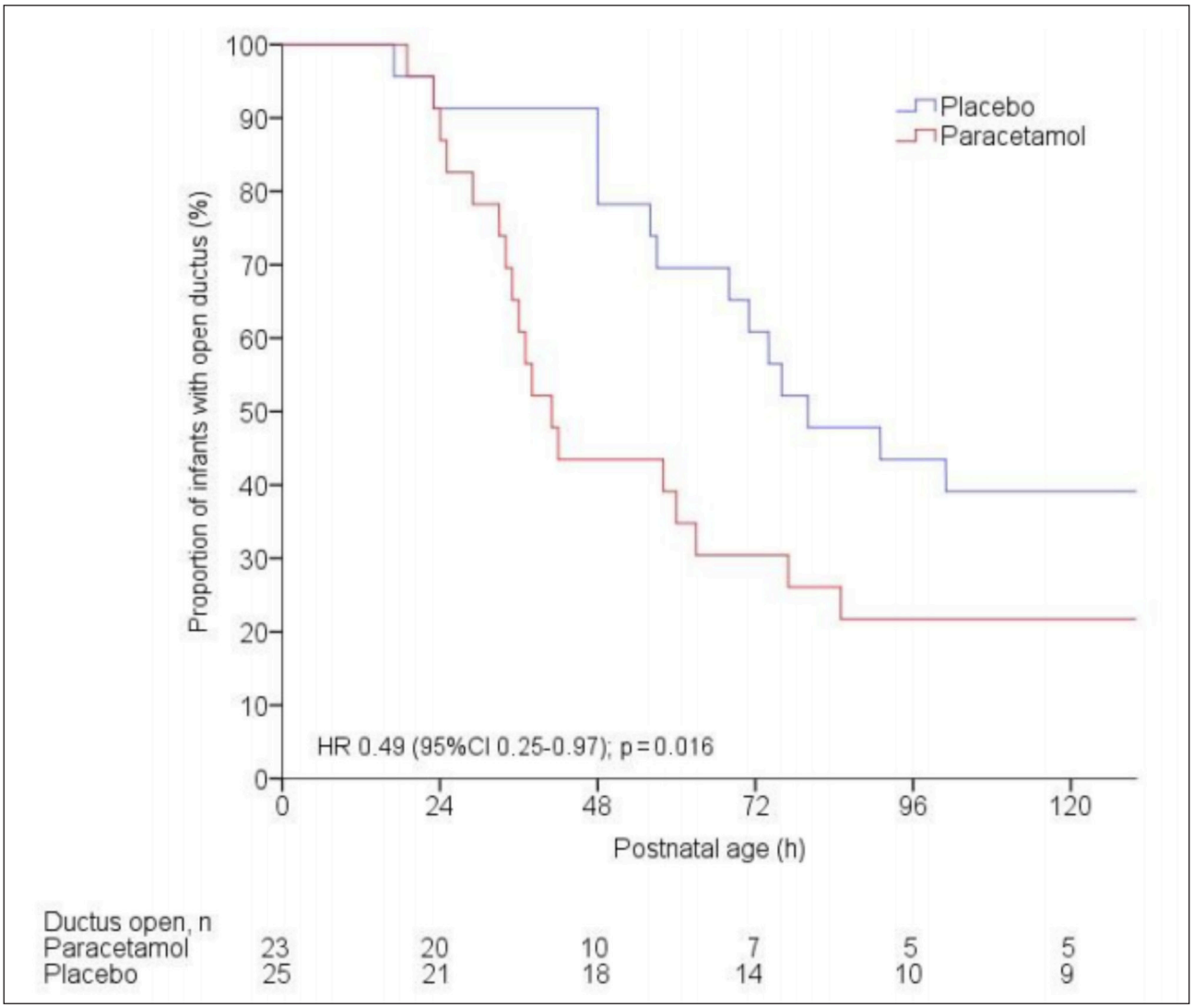

Figure 1 (ABS 23). Kaplan-Meier survival curve for ductal closure.

PATIENTS AND METHODS

Based on 40% clinical difference between paracetamol treated and control infants, the sample size was calculated as 48. Infants born < 32 weeks GA without lethal disease became eligible to the randomized double blinded clinical trial, after signing of the informed consent from the parents. Study drug was started before 24 hours' of age. The loading dose was 20 mg/kg followed by 7.5 mg/kg for every 6 hours for 4 days. Placebo was 0.45% NaCl. Cardiac ultrasound (CU) was performed daily, first CU was done before the study drug, and on daily basis until one day after the end of study drug. Thereafter, infants with open ductus were examined until ductus was closed. All had CU at the time of discharge from NICU. Data was prospectively collected for evaluation of possible side-effects of paracetamol.

RESULTS

Originally 63 infants born at < 32 weeks GA were prospectively screened from Sep 2013 to Nov 2014. Of them, 48 underwent randomization; 23 assigned to paracetamol and 25 to placebo. Mean (SD) gestational age in paracetamol group was 28.4 (2.4) vs. placebo group 28.3 (2.1) wk, mean (SD) birth weights were 1,224 (428) g and 1,123 (340) g, respectively. There were no differences in the baseline characteristics between the study groups. The caliber of the ductus was similar before the onset of treatment (paracetamol 1.57 mm, placebo 1.39 mm, p = 0.38). During the treatment the ductus closed faster in the paracetamol exposed than in the placebo group (**Fig. 1**, p = 0.016, Kaplan-Meier). In infants born before < 27 weeks there was no detectable response of ductus to paracetamol. No side-effects were detected, and there were no differences in serious adverse events (i.e. death, BPD, NEC) between the groups.

CONCLUSIONS

Early IV paracetamol for 4 days induced closure of ductus arteriosus in very preterm infants. No adverse effects were detected. This RCT provided evidence on the biological efficacy and safety of paracetamol to PDA of preterm infants. The optimal duration and dosage of paracetamol remains to be studied. A large randomized trial is required to demonstrate the safety and efficacy of paracetamol remain to be studied.

ABS 24

NEW PERSPECTIVES IN NEONATAL ANALGO-SEDATION: DEXMEDETOMIDINE

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INTRODUCTION

Dexmedetomidine is a centrally acting α2-adrenoceptor agonist with sedative, anxiolytic and analgesic properties and no effect on respiratory function. Currently, dexmedetomidine is not approved for pediatric use, but adult and pediatric literature have been mostly in favour of its use for mechanically ventilated patients. In these populations, dexmedetomidine infusion is associated with reduction in the duration of mechanical ventilation, reduction in the use of narcotics and/or adjunctive sedation, reduction in the incidence of intensive care unit length of stay, delirium/organic brain dysfunction and sepsis. Data regarding neonatal population are few, but they are encouraging.

PATIENTS AND METHODS

Twelve mechanically ventilated neonates (with gestational age ≥ 26 weeks) that needed analgosedation for their underlying conditions, performed dexmedetomidine infusion. The initial rate was 0.3 μg/kg/hour without loading dose and it was increased 0.1 μg/kg every 4-12 hours, if required.

We assessed effectiveness by regular Neonatal Pain, Agitation, and Sedation Scale (N-PASS) performace and by comparing them with 12 retrospective matching controls (treated with a traditional sedation approach) for the need for adjunctive fentanyl and/or midazolam.

Safety was assessed through hemodynamic parameters and concomitant inotropes use records. Weaning was performed decreasing the rate of 0.1 μg/kg every 6-12 hours. Withdrawal was assessed through Sophia Observation withdrawal Symptoms-scale (SOS).

RESULTS

Maximum dose was 0.64 ± 0.26 μg/kg/h. The dose at extubation time was 0.48 ± 0.27 μg/kg/h. The lenght of therapy was 149.3 ± 93.4 hours.

Eleven patients (91.7%) required the administration of an adjunctive drug; the total doses of both fentanyl and midazolam were significantly reduced respect to controls.

Hemodynamic profile associated with dexmedetomidine infusion revealed insignificant changes in mean heart rate, systolic and diastolic

Table 1 (ABS 24). Hemodynamic profile associated with dexmedetomidine infusion.

Time	SBP (mmHg)	DBP (mmHg)	HR (bpm)
Baseline[a]	64.1 ± 15.2	38.1 ± 12.6	149.9 ± 16.0
1 hour after DEX start[a]	64.5 ± 15.9	39.6 ± 10.5	149.5 ± 15.6
2 hours after DEX start[a]	63.3 ± 15.6	39.0 ± 8.9	150.2 ± 18.5
24 hours after DEX start[a]	68.8 ± 16.4	42.5 ± 9.1	138.5 ± 14.9
72 hours after DEX start[a]	66.5 ± 18.3	41.1 ± 13.0	144.4 ± 19.6
2 hours before stop infusion[a]	67.3 ± 9.6	46.5 ± 11.1	
2 hours after stop infusion[a]	71.2 ± 15.7	44.9 ± 14.2	
24 hours after stop infusion[a]	73.6 ± 15.2	47.6 ± 9.5	

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; bpm: beats per minute; DEX: dexmedetomidine.
[a]Data are presented as means ± standard deviation.

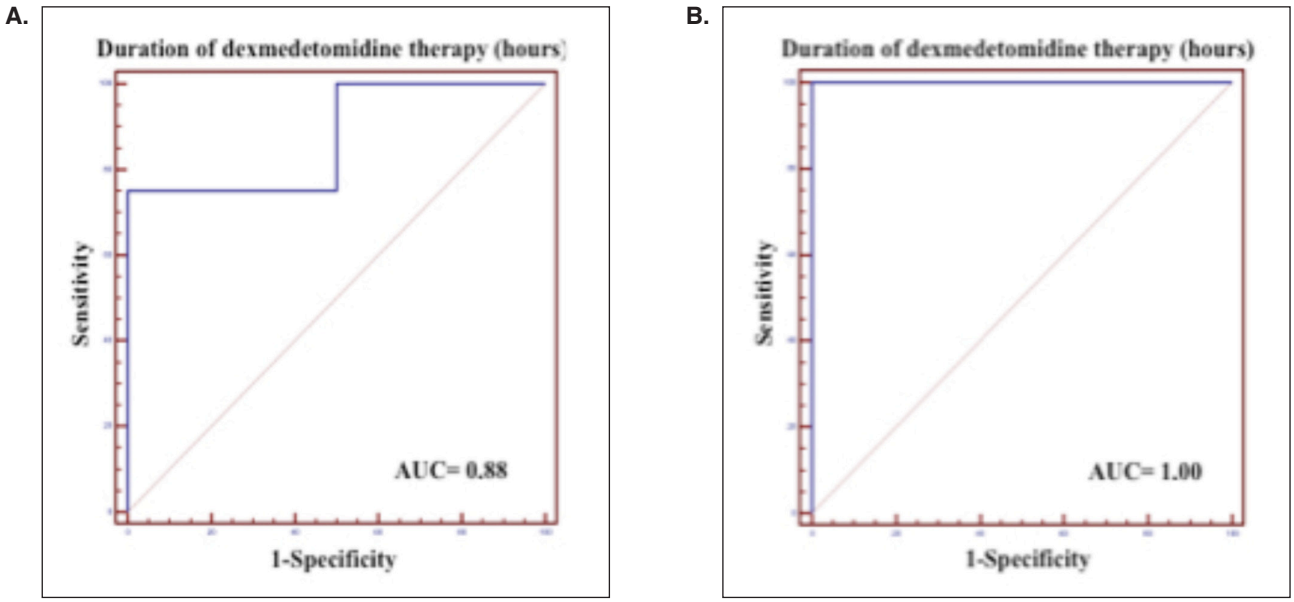

Figure 1 (ABS 24) . Correlation between the duration of dexmedetomidine therapy and signs of potential withdrawal (SOS score ≥ 4). **A.** ROC analysis of the duration of therapy for predicting potential withdrawal during tapering. **B.** ROC analysis of the duration of therapy for predicting potential withdrawal anytime in the 72 hours following discontinuation.

blood pressure (**Tab. 1**); no differences in the duration of dopamine and dobutamine therapies were observed. One patient presented a hypotensive episode within the first two hours of dexmedetomidine infusion that resolved after a saline bolus.

Five patients (41.7%) presented a positive SOS score. The detection of a positive score was dependent from the duration of infusion (≥ 122 hours) and not from a higher mean dose (**Fig. 1**).

CONCLUSIONS

Dexmedetomidine was effective in neonates, as demonstrated by the significant reduction in other drugs requirement. Its lack of any respiratory effect, allowed us to extubate patients during dexmedetomidine infusion.

Regarding safety, our study showed that it is a reliable drug and its prolonged use is not associated with increasing side-effects, but only with the risk for withdrawal.

Dexmedetomidine is a very promising perspective.

ABS 25

RISK ASSESSMENT BASED ON AN EXPERIMENTAL MODEL TO EVALUATE COM-

PATIBILITY OF RECOMBINANT IGF-1/IGFBP-3 WITH INTRAVENOUS MEDICATIONS COMMONLY ADMINISTERED IN THE NEONATAL ENVIRONMENT

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INTRODUCTION

Despite extensive co-administration of drugs to neonates, drug-drug compatibility has not generally been tested before medicines are introduced to this population. Recombinant human (rh)IGF-1/IGFBP-3 (a protein complex) is being studied for the prevention of retinopathy of prematurity as a continuous intravenous (IV) infusion in preterm infants. A comprehensive risk assessment based on *in vitro* testing is evaluating the compatibility of rhIGF-1/IGFBP-3 with medications routinely administered intravenously in the neonatal intensive care unit (NICU). We report initial physical/chemical compatibility results from *in vitro* studies performed as part of this assessment.

PATIENTS AND METHODS

Medications most likely to be co-infused with rhIGF-1/IGFBP-3 were identified at the start of the risk assessment by consulting sites for an ongoing trial. *In vitro* mixing of rhIGF-1/IGFBP-3 with each test medication (predominantly small molecules) was performed based on different volumes and/or mass ratios to mimic different dose ranges. Duration of mixing was based on average infusion rates of rhIGF-1/IGFBP-3 with each test medication at the highest dose, and an estimated volume for an umbilical catheter. Physical compatibility was assessed by visual observation, optical density at 320 nm, pH, and osmolality for each mixed solution and corresponding controls. The concentration of each test medication post-mixing was assessed using reversed phase high performance liquid chromatography.

RESULTS

In vitro studies have been completed for rhIGF-1/IGFBP-3 with dopamine, total parenteral nutrition (TPN), TPN + intralipid 20%, intralipid 20%, dobutamine, vancomycin, morphine, fentanyl and midazolam. No precipitation, turbidity or gas evolution was observed for any mixture. No color, pH or osmolality changes were observed vs. controls except for: 1) a pH decrease of ~0.6 units with dopamine at 20 µg/kg per minute (attributed to the higher buffering capacity of the buffer in the dopamine formulation vs. rhIGF-1/IGFBP-3 formulation buffer); 2) an osmolality decrease of ~19% for fentanyl at 5 µg/kg per hour (attributed to dilution of rhIGF-1/IGFBP-3 formulation buffer) (**Tab. 1**). A risk assessment is ongoing for each medication to determine probability and

Table 1 (ABS 25). Results of rhIGF-1/IGFBP-3[a] *in vitro* compatibility studies to date.

Test medication	Mixing dose for test medication[b]	Results based on physical panel and RP-HPLC assessment
Dopamine[c]	2, 10, and 20 µg/kg/min with a flow rate of 0.26 ml/hr	• Compatible under the simulated study (*in vitro* for 60 min at room temperature) • A pH decrease was observed for the highest dose • No loss of dopamine
TPN (with and without electrolytes)[c]	1, 4, and 10 ml/hr	• Compatible under the simulated study (*in vitro* for 60 min at room temperature)
TPN + intralipid 20%[c]	0.5 and 3 g/kg/24 hr with 10 ml/hr TPN	
Intralipid 20%[c]	0.5 and 3 g/kg/24 hr	
Dobutamine	2, 10, and 25 µg/kg/min	• Compatible under the simulated study (*in vitro* for 90 min at room temperature) • An osmolality change of ~19% was observed with the highest fentanyl dose[e] • No loss of small molecule drug
Vancomycin	15 and 25 mg/kg/24 hr[d]	
Morphine	5, 10, and 50 µg/kg/hr	
Fentanyl	0.5, 2, and 5 µg/kg/hr	
Midazolam	20 and 60 µg/kg/hr	

RP-HPLC: reversed-phase high performance liquid chromatography; TPN: total parenteral nutrition.
[a]The compatibility studies were conducted with an rhIGF-1/IGFBP-3 dose of 250 µg/kg/24 hr, calculated for a 0.5 kg premature neonate.
[b]The calculations were performed for a 0.5 kg premature neonate. [c]Osmolality was not included in testing panel. [d]Continuous infusion. [e]The decrease is not considered clinically significant (Jackson JK and Derleth DP. Arch Dis Child Fetal Neonatal Ed. 2000;83:F130-4).

severity of any risk, which will support a risk management strategy developed with clinicians.

CONCLUSIONS

In vitro data indicate rhIGF-1/IGFBP-3 compatibility with medications commonly utilised in the NICU. Further work is ongoing to evaluate compatibility with other IV drugs and develop assays to test chemical compatibility of rhIGF-1/IGFBP-3. We believe this work will establish a new benchmark for compatibility testing of drugs utilised in neonates. Contributions from clinicians and cross-functional disciplines will be key to the process.