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ABS 1

UNDERSTANDING THE RELATIONSHIP BETWEEN DOPAMINE CONCENTRATION AND BLOOD PRESSURE IN NEONATES: INCUBATORS VERSUS COT

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INTRODUCTION

Dopamine is a commonly used drug to correct hypotension affecting up to 50% of neonates admitted to the neonatal intensive care unit (NICU). Our local unit in Brighton anecdotally reports instances of rapidly fluctuating mean arterial pressure (MAP) around the changeover of dopamine infusions, which may be attributed to dopamine stability. Current literature, albeit limited, suggests that temperature and light are stability factors but have failed to study dopamine stability in conditions comparable to a NICU setting. This study aimed to investigate the effects of temperature and light on dopamine concentration in incubator and cot simulated models and their potential influence on MAP.

METHODS

An audit on 56 patients who have received dopamine infusions in the past three years was conducted to inform the development of our experimental models and to visualise reported MAP fluctuations. Dopamine infusion solutions (n = 20) were prepared in 5% glucose to either a concentration of 1.6 mg/mL, kept at either room temperature or 35°C (incubator simulation) or 5.5 mg/mL, kept at room temperature (cot simulation) in the absence and in the presence of light. Concentration was measured using cyclic voltammetry at 0, 0.5, 1 and 24 hours.

RESULTS

Random sampling of MAP traces from 10 patients demonstrated that neonates in incubators

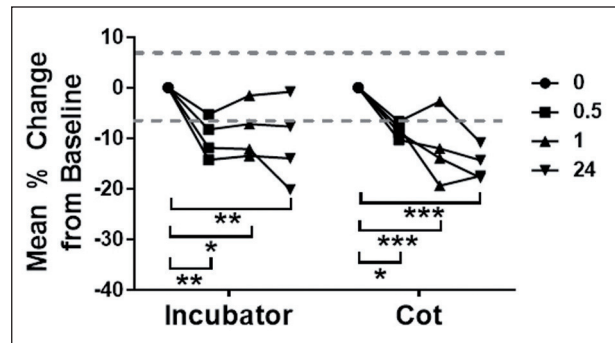


Figure 1 (ABS 1). Mean percentage of change from baseline in the 2 groups.

(mean gestational age 26 weeks SD 1.73 weeks, mean birthweight 773 g SD 220 g) consistently experienced rapid MAP fluctuations at the start of a dopamine infusion, whereas neonates in cots (mean gestational age 37 weeks SD 1.67 weeks, mean birthweight 3,419 g SD 545 g) did not experience such changes. This appeared to coincide with a fall in dopamine concentration (~10%) observed within the first thirty minutes of preparation of infusions followed by a very gradual decline in concentration (~5% further) at 24 hours (**Fig. 1**). This trend was persistent across all study conditions with no significant differences found between concentration, temperature and light.

CONCLUSIONS

Rapid decline in dopamine concentration within 30 minutes of preparation were associated with MAP fluctuations exclusive to incubated neonates. This may be attributed to their prematurity and thus poor ability to auto-regulate blood pressure. To minimise MAP fluctuations associated with a risk of intraventricular haemorrhage, our local unit has now opted to delay administration of dopamine infusions by 30 minutes post preparation.

ABS 2

IBUPROFEN PHARMACOGENETIC STUDY IN HUMAN MILK SAMPLES

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INTRODUCTION

Ibuprofen is one of the analgesic the most given to breastfeeding women. We have recently showed that whatever the stage of lactation is, the mid relative infant dose (RID) remains inferior to 1% (RID = 0.38% [0.04-1.53]). Recently, a breastfed newborn died from an intoxication to morphine, while his mother was given codeine. This fatal case led us to study the cytochrome P450 polymorphism involved in the ibuprofen metabolism.

METHODS

DNA was extracted from 13 frozen milk samples (by using QiaSymphony DSP DNA, following the recommendation of the Qiagen, Courtaboeuf society, France). These milk samples came from 13 women who received an ibuprofen treatment during breastfeeding (1,200 mg/day). A study of the CYP2C8 and CYP2C9 polymorphism was made by using Taqman® method.

RESULTS

Allelic variants were equivalent to those known in the caucasian population. Whatever the polymorphism is, the RID remains inferior to 1.56%.

CONCLUSIONS

Milk is rarely used, although it is reliable, as a matrix in pharmacogenetic studies. Frozen milk can be a good alternative to blood sample for analyzing DNA polymorphism. Unlike morphine, whatever the CYP2C8 and CYP2C9 polymorphism may be, the ibuprofen RID remains inferior to 1%. Ibuprofen can be given to breastfeeding women, regardless of their pharmacogenetic profile.

ABS 3

EFFECT OF POSTNATAL CORTICOSTEROID ON BROWN ADIPOSE TISSUE THERMOGENESIS IN NEONATAL RAT

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INTRODUCTION

Corticosteroids have been used to prevent or treat bronchopulmonary dysplasia (BPD), refractory hypotension or facilitate extubation in preterm infants. Growth retardation is a common phenomenon encountered during corticosteroid treatment. Blunted body weight gain may be related to disturbance in energy expenditure. Brown adipose tissue (BAT) plays an important

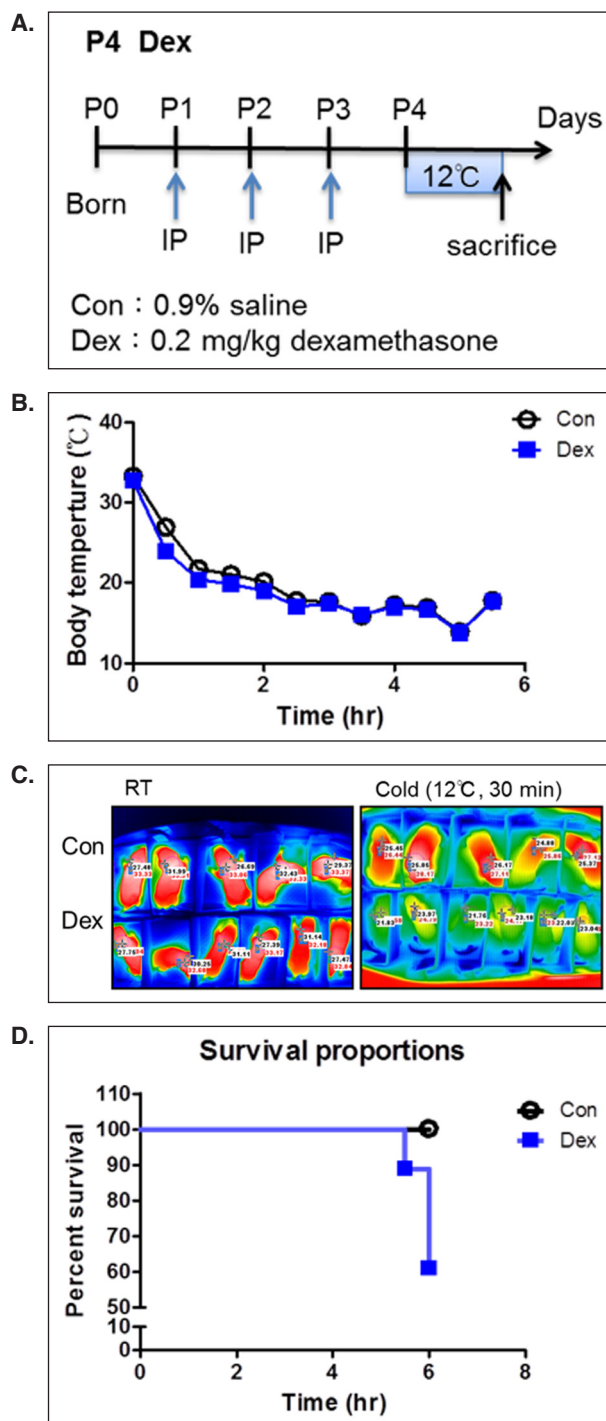


Figure 1 (ABS 3). Methods and results in neonatal rats with and without dexamethasone (Dex).

role in thermogenesis and energy metabolism in human newborn. UCP1 is the key protein in BAT thermogenesis. We hypothesize that exposure to postnatal corticosteroids in neonatal rat attenuate UCP1 function in brown adipose tissue, resulting in intolerance to cold stress.

METHODS

Rat pups received either saline (Con) or dexamethasone (0.2 mg/kg/day, Dex) injection daily

from postnatal day 1 (P1) to P3 and were sacrificed on P4 (**Fig. 1A**). The body weight/length, weights of major organs and BAT were recorded. BAT was stained and examined histologically. Next, we challenged rat pups receiving the above treatment with 12°C cold exposure for 6 hours on P4. Changes of body surface temperature and survival curve were plotted. We also measure the mRNA and protein level of UCP1.

RESULTS

The drop in body temperature was more significant in Dex group during the first 30 minutes of cold exposure (**Fig. 1B**). Comparing with Con group, almost all the major organs in Dex group were decreased in size. BAT, however, was enlarged and showed whitening histologically (**Fig. 1C**). The survival rate of cold exposure pups was significantly lower in Dex group compared with Con group (60% vs. 100%) (**Fig. 1D**). In addition, UCP1 mRNA transcription and protein translation were also decreased after cold stress exposure.

CONCLUSIONS

Early postnatal dexamethasone attenuates the transcription and translation of UCP1 after cold stress exposure, resulting in cold intolerance and increased mortality.

ABS 4

URINARY 17- α -HYDROXY-PROGESTERONE AS A POTENTIAL MARKER OF NEONATAL PAIN

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INTRODUCTION

Despite the widespread use of pain scales on neonatal wards the quantification of pain in neonatal patients is fairly subjective. The inability of verbal communication with preterm or term infants adds to the problem.

METHODS

Urinary concentrations of prostaglandin-e, leukotriene-b4, glutamate and 17- α -hydroxy-progesterone of patients with any kind of tissue damage potentially causing pain were analysed and compared to those of a healthy control group. For quantification enzyme linked immunosorbent assays, tandem-mass-spectrometry and ultra

performance liquid chromatography were applied.

RESULTS

88 preterm and term infants were included in the study. No differences were found for the parameters prostaglandin-e, leukotriene-b4 and glutamate. Concentrations of 17- α -hydroxy-progesterone were significantly higher in patients with tissue damage (5,030.68 pmol/mol creatinine) as compared to healthy controls (189.36 pmol/mol creatinine), t-test $p < 0.04$.

CONCLUSIONS

Although this needs to be shown in a larger number of neonates, 17- α -hydroxy-progesterone may have the potential to be used as an objective marker of pain in this age group.

ABS 5

PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES AIMING FOR RATIONAL DRUG DOSING IN PRETERM NEONATES: THE DINO STUDY

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INTRODUCTION

The DINO-study (Drug dosage Improvement in preterm NeOnates) simultaneously collects pharmacokinetic and pharmacodynamic data of nine frequently used drugs, namely Doxapram, Fentanyl, Levetiracetam, Midazolam, Paracetamol, Phenobarbital, Sildenafil, Fluconazole and Ibuprofen in preterm neonates. Seven of these drugs are still used off-label. It aims to increase safety and efficacy by improving dosing recommendations in this vulnerable population.

METHODS

By using sparse opportunistic blood sampling using limited sample volumes of 200 μ L, the burden to the individual child is minimal. The study is performed in 4 centres in the Netherlands, enabling the DINO team to collect 1,456 samples until mid-May 2017. In about one third of these samples more than one drug can be quantified as children received multiple study drugs simultaneously. The development of assays with a sample volume of 10-50 μ L allows for the use of all these data. Cell pellets of the respective samples were stored after centrifugation and can be used for genotyping in case additional permission is given by the parents/guardians.

RESULTS

Population pharmacokinetic models are being developed using non-linear mixed effects modelling. Pharmacodynamics are investigated through effect measurements such as pain scores or second-to-second monitor read-outs of oxygen saturation to relate the concentration to a certain effect. This model-based approach enables us to evaluate current dosing advises and to propose new dosing regimen where necessary. Thereby, it aims at substantially increasing the proportion of newborns in the therapeutic window, potentially resulting in higher success rates of treatment and less side-effects. Besides prospective collection of samples through the DINO study, data previously collected for other analyses are considered for analysis. By doing so, data sharing supports clinical dose optimizations, as typically data in preterm neonates is sparse and data collected prospectively may not be sufficient.

CONCLUSIONS

The design of the DINO-study serves as a suitable example on how to perform pharmacokinetic-pharmacodynamic research in preterm infants and can be extended to the whole pediatric research field. Current collaborations will enable us to use the network for future research, such as the

prospective evaluation of the developed dosing recommendations or for new drugs.

ABS 6

VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION IMPAIRS ACETYLCHOLINE-INDUCED CONTRACTION IN NEONATAL PORCINE CORONARY ARTERIES

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INTRODUCTION

Veno-arterial extracorporeal membrane oxygenation (ECMO) is known to alter endothelial function in arteries exposed to the treatment. In porcine coronary artery, acetylcholine causes vasoconstriction, independently of endothelium integrity. Acetylcholine-induced vasoconstriction is the result of a balance between the relaxing action on endothelial nitric oxide release and the contraction derived from the stimulation of the M3 muscarinic receptors on smooth muscular cells.

METHODS

Two groups of newborn piglets were used for the study: one was exposed to veno-arterial ECMO for 8 hours (n = 2) and the other one (n = 2) was used as control. Coronary arteries were dissected, removing the loose connective tissue, cut into 3-5-mm rings and kept in ice-cold Krebs-Ringer buffer. The rings were pre-contracted with U46619 (10⁻⁷ M), a thromboxane A2 mimetic and then acetylcholine (10⁻⁶ M) was added (**Fig. 1A** and **Fig. 1B**). After, the rings were washed out from Ach and papaverine (10⁻⁴ M), an endothelium-independent vasodilator was added to ascertain whether complete relaxation had been obtained (**Fig. 1C**).

RESULTS

The contractile response to U46619 was not significantly different between the two groups. A very mild contraction on the coronary artery rings, from the ECMO, group was induced by Ach compared to the ones of the control group (p < 0.05).

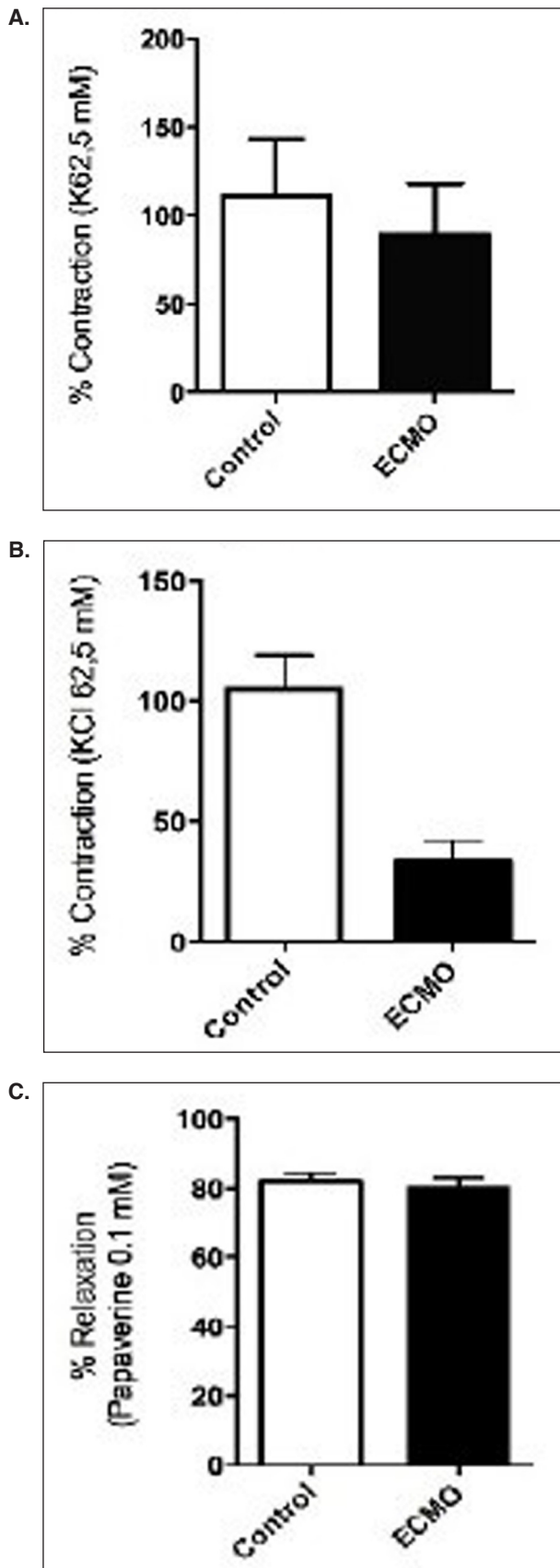


Figure 1 (ABS 6). **A.** Contractile response of coronary artery rings to U46619. **B.** Contractile response of coronary artery rings to acetylcholine. **C.** Relaxation after acetylcholine wash-out (relaxant ability of coronary artery rings).

No differences in relaxations after acetylcholine neither in endothelium – independent relaxations to papaverine were observed in the two groups.

CONCLUSIONS

Extracorporeal membrane oxygenation with its continuous, not pulsatile flow, can impair the vascular response to acetylcholine. ECMO can lower the contractile response to acetylcholine in vessels underwent to treatment. Our data suggested that ECMO could interfere with Ach pathway, altering the balance between the endothelial and smooth muscular components of its mechanism of action. Further experiments are needed to confirm these data.

ABS 7

β3-ADRENOCEPTOR REGULATION OF NITRIC OXIDE IN THE CORD VASCULAR SYSTEM

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INTRODUCTION

Normal vascular reactivity of cord vessels is fundamental to maintain an adequate supply of oxygen and nutrients to the fetus during pregnancy, labor, and delivery. The human umbilical vessels have not autonomic innervations; therefore, their tone can be adjusted only by circulating or locally released vasoactive substances.

METHODS

Isolated rings from umbilical arteries and veins were mounted in organ chambers for isometric tension recording. Umbilical artery and vein rings were contracted with K⁺ (62.5 mM), 5-HT (1 nM-10 μM) or U44069 (1 nM-10 μM) to evaluate

their contractile activity. The relaxation induced by the β_3 -adrenoceptor agonist BRL 37344 was investigated performing cumulative dose-response curves, after pre-contraction obtained with a single dose of U44069 (1 μ M). The role of endothelium in vascular reactivity was studied in denuded vessels or in the presence of NO synthase inhibitor L-NAME (0.1 mM), the sGC inhibitor ODQ (10 μ M), the AC inhibitor DDA (10 μ M) or the cyclooxygenase inhibitor indomethacin (10 μ M).

RESULTS

The contractile response to U44069 and 5-HT was higher than the standard contraction induced by K^+ in both umbilical vessels. In particular, the contraction was higher in veins than in the arteries. There were no statistically significant differences in terms of efficacy and potency between the two vascular districts. The selective β_3 -adrenoceptor

agonist BRL 37344 was able to relax U44069-contracted vessels in a concentration-dependent manner with no statistically significant differences between arteries and veins. The endothelium denudation or pretreatment with L-NAME or ODQ markedly inhibited the relaxant response to BRL 37344. Conversely, neither DDA nor indomethacin affected BRL 37344-induced relaxation (**Fig. 1**).

CONCLUSIONS

The response evoked by the β_3 -adrenoceptor agonist BRL 37344 was endothelium and NO-dependent since it was inhibited by endothelium removal or by the presence of NOS or sGC inhibitors, but not by the presence of AC or cyclooxygenase inhibitors. The study showed that the relaxation induced by β_3 -adrenoceptor agonists was minimal compared to the contractile ability of the same vascular district

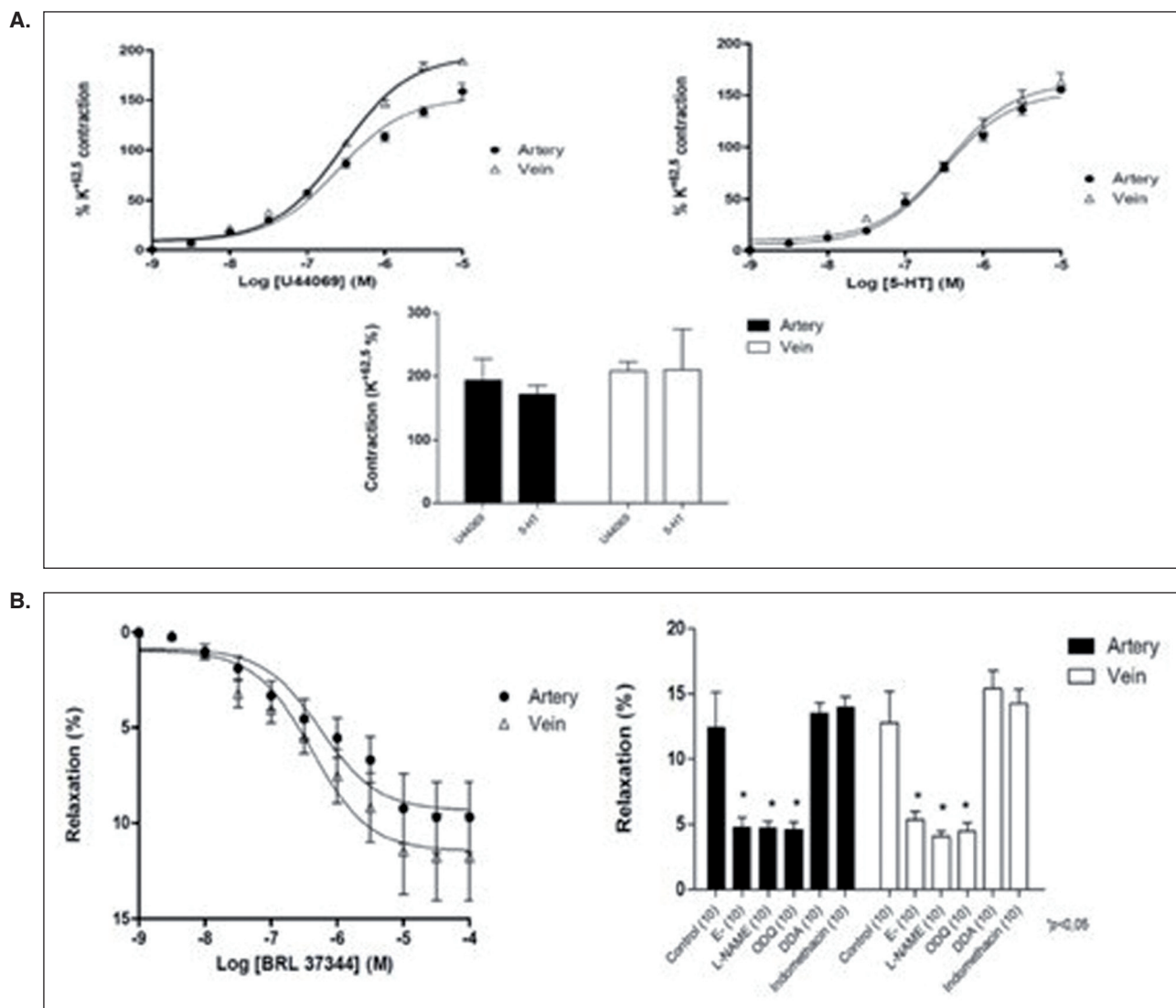


Figure 1 (ABS 7). Contractile response of human umbilical vessels (A) and relaxant responses of human umbilical vessels after U44069-induced pre-contraction (B).

submitted to U44069. These data demonstrate that umbilical vessels have a high contractile ability, which is certainly greater than their releasing capability.

ABS 8

BIG DATA ANALYSES FOR CONTINUOUS EVALUATION OF PHARMACOTHERAPY: A PROOF OF PRINCIPLE WITH DOXAPRAM FOR PRETERM INFANTS

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INTRODUCTION

Drug effect evaluation is often based on human interpretation of a selection of patient data. While clinical use of “big data” remains mostly limited to the traditional “snapshot” assessment of a patient’s health status, analysis of continuous data brings new opportunities to improve care. Continuous quantitative analyses of high frequency patient data could not only allow proper timing of interventions, but also monitor and evaluate the effects of these interventions. We aim to evaluate the usefulness and applicability of high frequency physiological data for analyses of pharmacotherapy.

METHODS

As a proof of principle, the effects of doxapram, a respiratory stimulant, on the oxygenation in

preterm infants were studied. Second-to-second physiological data on arterial oxygen saturation (SpO₂), respiratory rate and heart rate were collected from bedside monitors from 12 hours before to 36 hours after start of doxapram loading dose followed by continuous maintenance dose in seven preterm infants. The effect of doxapram was determined comparing the mean of each parameter during for each hour four hours before start of doxapram in comparison with the first four hours after start, as well as with a four-hour time window 24 hours after the start of doxapram, using a paired T-test. Besides physiological data, plasma concentrations of doxapram and keto-doxapram were measured.

RESULTS

Arterial oxygen saturation increased immediately after the start of doxapram treatment alongside an increase in heart rate, indicated by decreased variation of heart rate at the lower percentiles. The respiratory rate remained unaffected. The number of saturation dips and the time below a saturation of 80%, as well as the area under the 80%-saturation-time curve (AUC), were significantly lower during four hours after the start of doxapram compared to four hours before start, $p = 0.016$, $p = 0.014$, $p = 0.011$, respectively. The AUC under 90% oxygen saturation also significantly improved after start of doxapram. The improvement of respiratory parameters was sustained with maintenance dosage, comparing four hours before, with the timeframe 24-28 hours after start of doxapram ($p < 0.05$). Plasma concentrations of doxapram and keto-doxapram were quantified. Results are presented in **Fig. 1**.

CONCLUSIONS

Using high-frequency monitoring data, we showed detailed effects of pharmacotherapy over time. We could objectively determine the respiratory condition and the effects of doxapram treatment in preterm infants, by-passing discussions on the definition of apnea and interpretation of subjective parameters. This type of analysis might help to develop individualized drug treatments with tailored dose adjustments based on a closed-loop algorithm.

ABS 9

ADRIN 1 METHODOLOGY STUDY: ADVERSE DRUG REACTIONS IN NEONATES: WHAT ARE THE BEST WAYS TO EVALUATE SUSPECTED ADVERSE DRUG REACTIONS IN NEONATES?

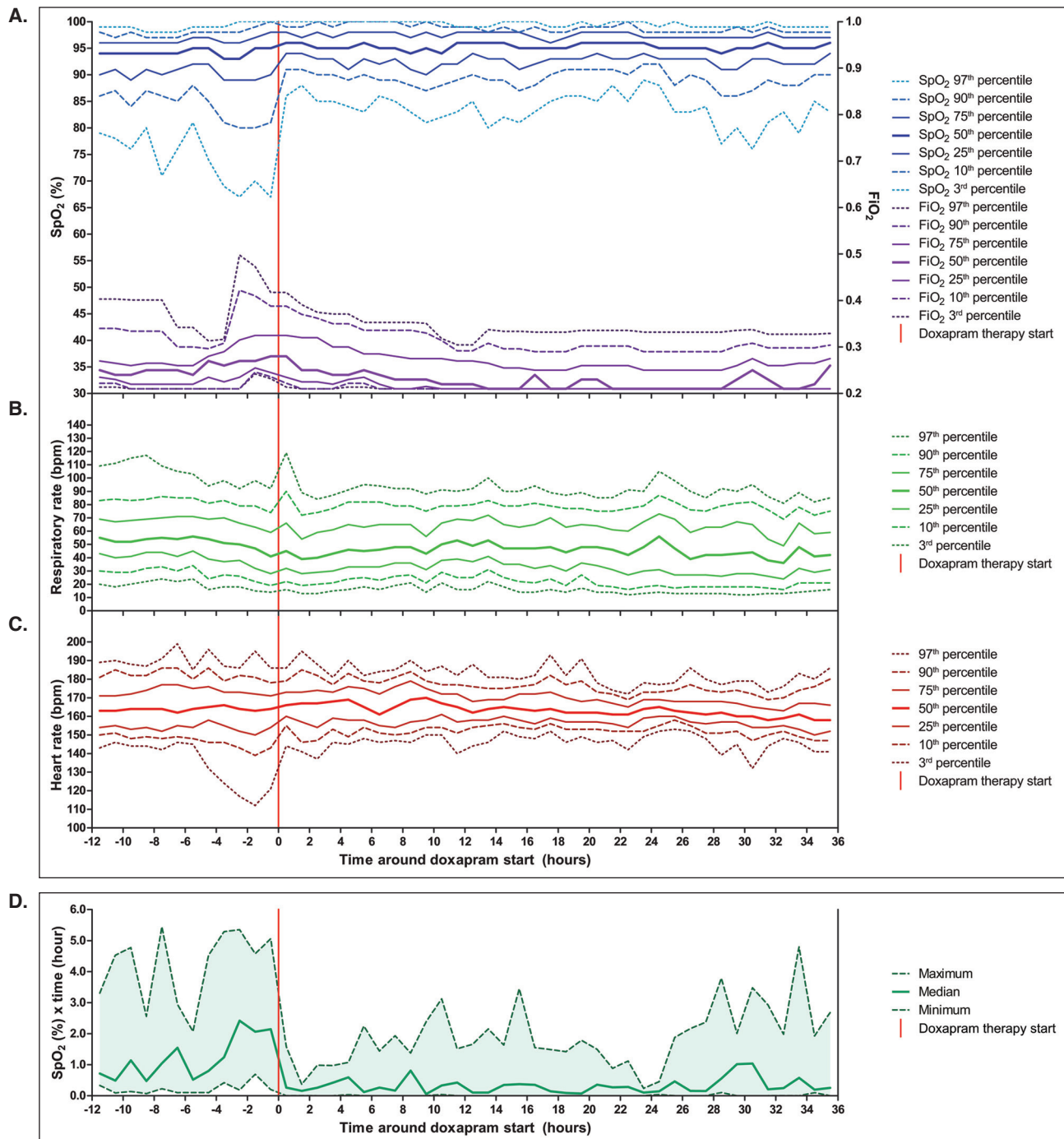


Figure 1 (ABS 8). A-C. SpO₂, respiratory rate and heart rate around doxapram therapy start. D. Area under the curve (SpO₂ x hour) during SpO₂ dips under 90%.

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INTRODUCTION

Many of the thousands of babies admitted to UK neonatal care units annually will require medications; up to 90% of these will be prescribed

unlicensed or off-label [1]. The incidence of adverse drug reactions (ADRs) in children has been estimated to be between 0.6% and 16.8%, but the data for neonates is limited [2]. Of the existing tools that help clinicians to assess the causality of ADRs, few have been validated in a neonatal setting. This study aims to evaluate the use of three existing tools for assessing causality of neonatal ADRs, and to compare the outcomes between tests and raters.

METHODS

Following ethical approval, data were collected prospectively on suspected ADRs occurring in a tertiary neonatal care unit in the north of England over a nine week period. Structured summaries of these cases were presented to five experienced neonatal clinicians who each undertook three separate causality assessments of each case using the Karch and Lasagna algorithm (KL), the Liverpool ADR Causality Assessment Tool (LCAT), and the New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units (NAINICU) [3-5]. Inter-rater and inter-test statistical analyses were performed – this was done by calculating kappa scores, weighted kappa scores, % exact agreement and % extreme disagreement.

RESULTS

Causality assessments have been undertaken on 34 ADR cases reported from the unit. Inter-rater reliability weighted kappa scores ranged from 0.207 to 0.454 for the KL algorithm, 0.121 to 0.428 for LCAT and 0.240 to 0.483 for NAINICU. The NAINICU method showed the highest % exact agreement between assessors ranging from 44.12 to 58.82%. In reference to Altman's statistical literature [6], a kappa score of 0.2-0.4 suggests fair inter-rater reliability. The LCAT method showed the lowest % extreme disagreement between assessors. This ranged from 0 to 17.65%. Inter-test reliability (measured by non-weighted kappa score) varied from -0.022 to 0.257 between the KL algorithm and NAINICU, 0.122 to 0.580 between the KL algorithm and the LCAT and from 0.030 to 0.319 between NAINICU and LCAT.

CONCLUSIONS

The three tools evaluated produced varied causality assessment outcomes when used on neonatal ADRs. Marked inter-test and inter-rater variability was noted. The study demonstrated that a neonate-specific method may need to be designed and validated to accurately and reliably assess causality in this population.

REFERENCES

- [1] Choonara I, Conroy S. Unlicensed and off-label drug use in children: implications for safety. *Drug Saf.* 2002;25(1):1-5.
- [2] Smyth RM, Gargon E, Kirkham J, Cresswell L, Golder S, Smyth R, Williamson P. Adverse drug reactions in children – a systematic review. *PLoS One.* 2012;7(3):e24061.
- [3] Karch FE, Smith CL, Kerzner B, Mazzullo JM, Weintraub M, Lasagna L. Adverse drug reactions—a matter of opinion. *Clin Pharmacol Ther.* 1976;19(5 Pt 1):489-92.
- [4] Gallagher RM, Kirkham JJ, Mason JR, Bird KA, Williamson PR, Nunn AJ, Turner MA, Smyth RL, Pirmohamed M. Development and inter-rater

reliability of the Liverpool adverse drug reaction causality assessment tool. *PLoS One.* 2011;6(12):e28096.

[5] Du W, Lehr VT, Lieh-Lai M, Koo W, Ward RM, Rieder MJ, Van Den Anker JN, Reeves JH, Mathew M, Lulic-Botica M, Aranda JV. An algorithm to detect adverse drug reactions in the neonatal intensive care unit. *J Clin Pharmacol.* 2013;53(1):87-95.

[6] Altman DG. Statistics in medical journals: developments in the 1980s. *Stat Med.* 1991;10(12):1897-913.

ABS 10

LARGE DIFFERENCES IN OFF-LABEL AND NEONATAL DRUG USE STILL EXIST: TIME FOR CONSENSUS?

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INTRODUCTION

Treatment of critically ill and preterm neonates includes the use of multiple drugs. Many drugs are off-label for neonates and evidence for neonatal use is sparse. Consequently, because of the variable interpretation, large differences may occur in prescriptions of drugs for neonates between neonatal intensive care units (NICUs). This may reflect the drugs and indications on which the least consensus has been reached, and should therefore be prioritized for expert-interpretation of current evidence, and for future research. We aimed to investigate the current neonatal drugs used in four Dutch NICUs, determine the variability, and relate this to the proportion off-label drug use for neonates.

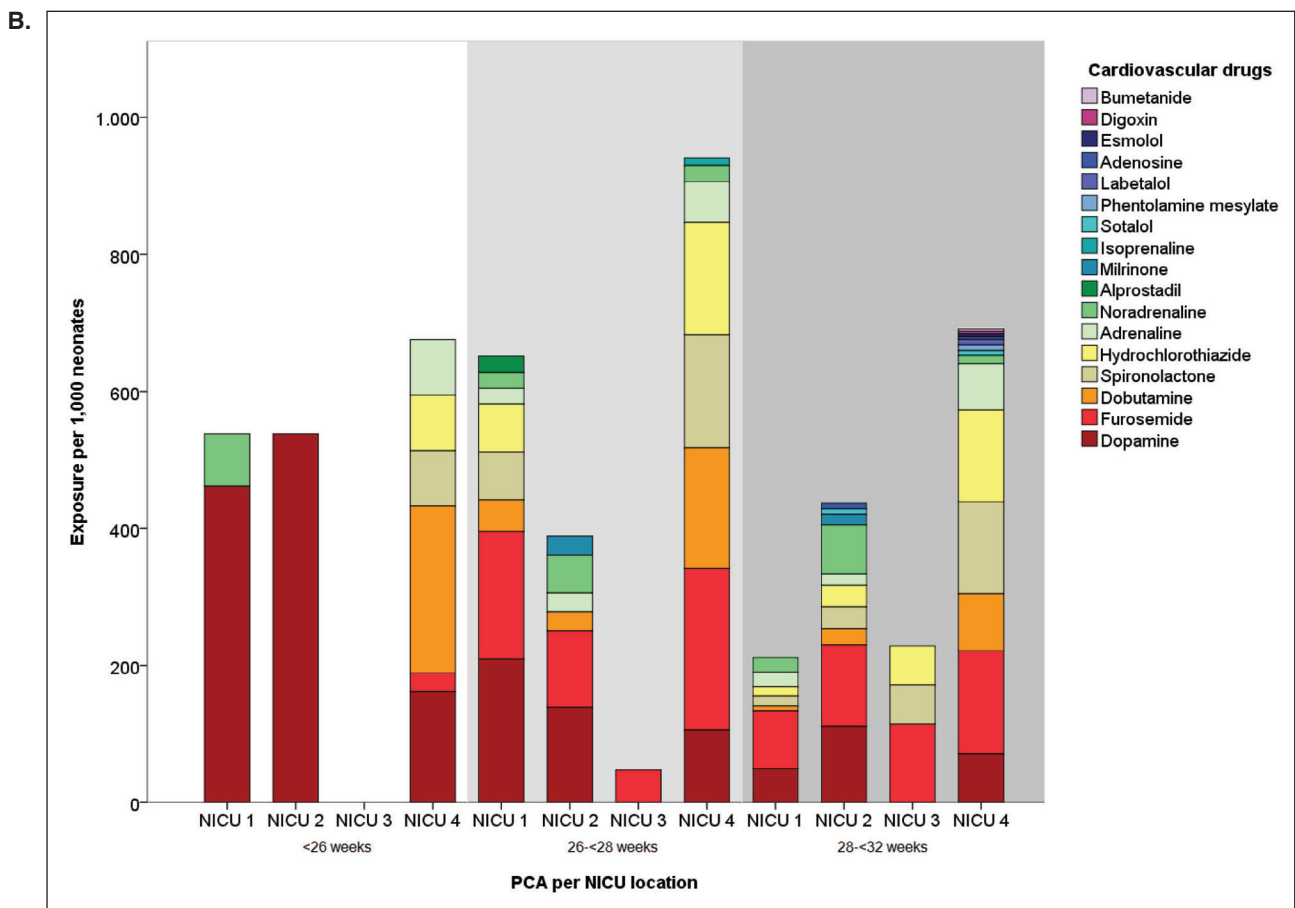
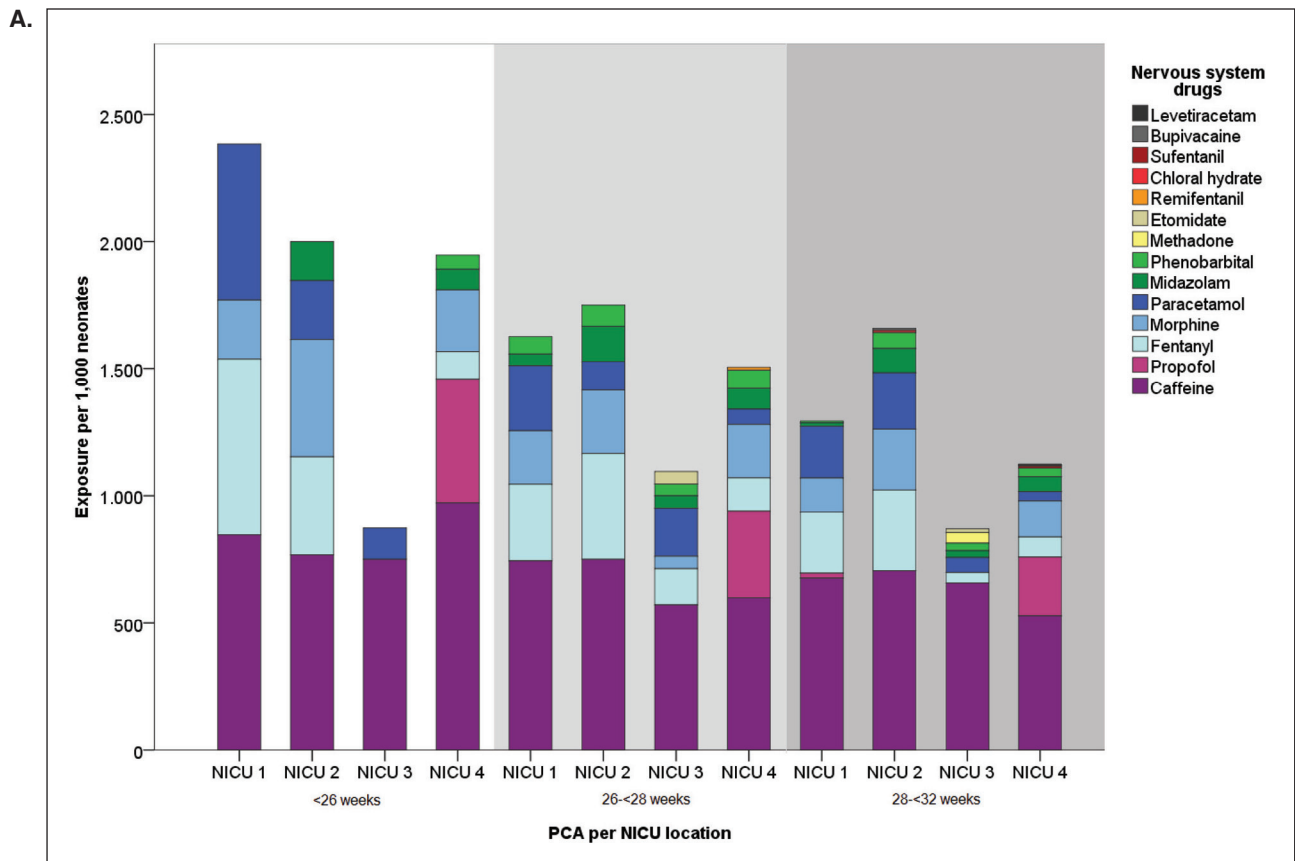


Figure 1 (ABS 10). Differences in prescription frequency between NICUs and Postconceptional Age-groups in nervous system drugs (A) and cardiovascular drugs (B).

METHODS

This was a retrospective cohort study on drug use in all neonates admitted to four different Dutch NICUs between the 1st of September 2014 until the 31st of August 2015. Basic characteristics related to prescribed drug use were compared between hospitals with respect to gestational age, postconceptional age, proportion off-label (OL) for neonatal age. All drugs were classified in accordance with the Anatomical Therapeutic Chemical (ATC) classification system and were assessed for on/off-label status for neonatal age. Five common indications for neonatal care were selected of which the treatment protocols were compared to give insight in the cause of potential differences; pain, intubation, convulsions, sedation, and haemodynamics.

RESULTS

1,491 neonates (GA-range 23⁺⁶-42⁺² weeks) were included in the study with a total of 32,182 patient days, 181 different drugs and 10,895 prescriptions, of which 39% was off-label for neonatal age. Overall, anti-infective drugs were most frequently used with a total of 3,161 prescriptions, of which

a small proportion of 17% was OL for neonatal age. The nervous system drugs included 2,500 prescriptions of which 47% was OL for neonatal age. Main differences in prescriptions between NICUs are presented in **Fig. 1**; no cardiovascular drugs in one NICU below a PCA of 26 weeks, compared to 6 different ones in another NICU; nervous system drugs showed large variety in frequency as well as variety of drugs. This may partly be due to the largest differences shown between pain treatment protocols of the NICUs. Median duration of drug treatment was 36 days; 28 days; 18 days; and 13 days, at the four NICUs respectively.

CONCLUSIONS

We showed that drugs used for neonatal clinical practice were very different between four Dutch NICUs. The drug classes with the highest proportion of off-label drugs for neonatal age showed the largest differences between NICUs, i.e. for cardiovascular and nervous system drugs. We believe that drug research in neonates should have high priority to access safe and appropriate medicines, and optimal drug therapy in newborns.