September 22nd, 2023 08:00 - 09:00

POSTER WALK – PHARMACOLOGY

ID 671. Grading the level of evidence of neonatal pharmacotherapy: midazolam and phenobarbital as examples

Liam Mahoney[1], Genny Raffaeli[2,3], Serdar Beken[4], Sezin Ünal[5], Charalampos Kotidis[6,7], Giacomo Cavallaro[3], Felipe Garrido[8], Aomesh Bhatt[9], Eugene M. Dempsey[10,11,12], Karel Allegaert[13,14,15], Sinno H.P. Simons[16], Robert B. Flint[13,16], **Professor Anne Smits**[14,17]

[1]University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom, [2]Department of Clinical Sciences and Community Health, Università Degli Studi Di Milano, Milan, Italy, [3]Neonatal Intensive Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [4]Department of Pediatrics, Section of Neonatology, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey, [5]Department of Neonatology, Ankara Etlik City Hospital, University of Health Sciences, Ankara, Turkey, [6]Department of Women's and Children's Health, University of Liverpool, Liverpool Health Partners, Liverpool, United Kingdom, [7]University of Liverpool, Liverpool Womens Hospital, Liverpool, United Kingdom, [8]Clínica Universidad de Navarra, , Spain, [9]Department of Paediatrics, University of Oxford, Oxford OX3 9DU, United Kingdom, [10]INFANT Research Centre, University College Cork, Cork, Ireland, [11]Department of Neonatology, Cork University Maternity Hospital, Cork, Ireland, [12]Department of Paediatrics and Child Health, University College Cork, Cork, Ireland, [13]Department of Hospital Pharmacy, Erasmus MC, Rotterdam, the Netherlands, [14]Department of Development and Regeneration, KU Leuven, Leuven, Belgium, [15]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [16]Department of Pediatric and Neonatal Intensive Care, Division of Neonatology, Erasmus University Medical Center – Sophia

Children's Hospital, Rotterdam, The Netherlands, [17]Neonatal intensive care unit, University Hospitals Leuven, Leuven, Belgium

Background

Drugs are commonly used off-label or unlicensed in neonates. This does not mean they are used without evidence or knowledge. Drugs administered to neonates have usually been studied, ranging from retrospective observational studies up to high quality prospective trials mimicking drug registration trials. However, a clear overview on the level of evidence for individual drugs, their dosing, efficacy and safety in neonates is lacking. As European Society for Pediatric Research Pharmacology section, we aimed to apply and evaluate the Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies (GAPPS) scoring system [1], for the level of evidence of two commonly used anti-epileptic drugs, as proof of principle compounds.

Methods

Midazolam and phenobarbital as anti-epileptics were evaluated with a systematic literature search on neonatal pharmacokinetic (PK) and/or pharmacodynamic [PD, (amplitude-integrated) electroencephalography effect] studies. With the GAPPS system, two evaluators graded the current level of evidence. Inter-rater agreement (Kappa) was assessed for dosing evidence score (DES), quality of evidence (QoE), and strength of recommendation (REC).

Results

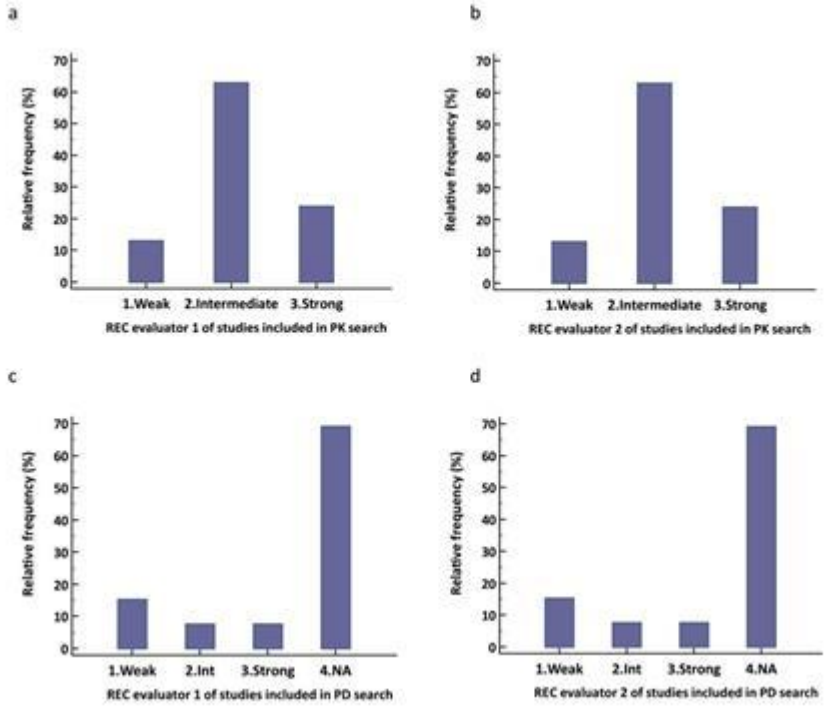
Seventy-two studies were included. DES scores 4 and 9 were most frequently used for PK, and scores 0 and 1 for PD. Inter-rater agreements on DES, QoE, and REC ranged from moderate to very good. A final REC was provided for all PK studies, but only for 25% (midazolam) and 33% (phenobarbital) of PD studies. Distribution of

relative frequencies of REC for the included PK studies for both evaluators are provided in Figure 1a and 1b, and for the PD studies in Figure 1c and 1d.

Conclusion

There is a reasonable level of evidence concerning midazolam and phenobarbital PK in neonates, although using a predefined target without integrated PK/PD evaluation. Further research is needed on midazolam use in term neonates with therapeutic hypothermia, and phenobarbital treatment in preterms, due to the limited observations in these subgroups.

[1] Gastine S. et al, Expert Review of Clinical Pharmacology, 2019;12,1091–1098.



Distribution of strength of recommendations (REC) of both evaluators for studies in the pharmacokinetic (PK) literature searches (Fig.1a–1b respectively), and the pharmacodynamic (PD) searches (Fig.1c–1d). Int: intermediate; NA: not applicable.

Distribution of strength of recommendations (REC) of both evaluators for studies in the pharmacokinetic (PK) literature searches (Fig.1a–1b respectively), and the pharmacodynamic (PD) searches (Fig.1c–1d). Int: intermediate; NA: not applicable.

None declared

ID 286. Pharmacovigilance of nephrotoxic drugs in neonates: the Pottel score for signal detection in ELBW neonates

Mrs Mathilde Dumoulin[1], Mr. Hans Pottel[2], Mrs Djalila Mekahli[3,4], Mrs Annouschka Laenen[5], Mrs Anne Smits[6,7], **Mr Karel Allegaert**[7,8,9]

[1]Department of Paediatrics, Leuven University Hospitals, Leuven, Belgium, [2]Department of Public Health and Primary Care, KU Leuven Campus Kulak, Kortrijk, Belgium, [3]Department of Pediatric Nephrology, Leuven University Hospitals, Leuven, Belgium, [4]PKD research group, Department of Cellular and Molecular medicine, KU Leuven, Leuven, Belgium, [5]Leuven Biostatistics and Statistical Bioinformatics Center (L–BioStat), KU Leuven, Leuven, Belgium, [6]Department of Development and Regeneration, KU Leuven, Leuven, Belgium, [7]Neonatal Intensive Care Unit, Leuven University Hospitals , Leuven, Belgium, [8]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [9]Department of Hospital Pharmacy, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Background

Extreme low birth weight (ELBW) neonates (⩽1000 grams) are at high–risk to develop acute kidney injury (AKI). As exposure to nephrotoxic drugs is very common, early and consistent pharmacovigilance has the potential to reduce or prevent AKI. However, due to the physiologic serum creatinine (SCr) changes and complex pathophysiology of AKI we lack a pragmatic tool for its detection. Pottel et al. suggested rescaling SCr by dividing SCr with the mean SCr–value of the age and sex specific healthy population. (1) In the present study we investigated if this Pottel method can detect a drug–related nephrotoxic signal in ELBW neonates.

Methods

In previous work we showed a shift of SCr of about 1 standard deviation (SD) in ibuprofen–exposed neonates as well as a modest increase of SCr when treated with the antibiotics vancomycin and amikacin. (2,3) We updated this existing dataset, calculating Pottel scores for every available SCr value in the first 28 postnatal days, based on previous calculated 50th centile values in an ELBW population. We used linear mixed models modelling the Pottel score as response variable and continuous time (day), treatment, and the interaction thereof in the explanatory model. We also analysed the combined effects of ibuprofen and antibiotics, allowing us to estimate the effect of ibuprofen corrected for antibiotics and vice versa.

Results

We had 3231 SCr observations in 201 ELBW neonates. When calculating Pottel scores in function of consecutive days of ibuprofen administration we observed a significant increase in scores starting from day one after exposure, but with still some further increase afterwards showing a cumulative effect. Results remained comparable when corrected for antibiotics with mean Pottel score on day 0 of 1.020 and on day 3 of 1.106 (95% CI 1.068–1.145, p <0.0001) (Figure 1). Antibiotic administration showed a small but statistical significant difference up until day 5.

Conclusion

While using the rescaled SCr biomarker using the Pottel method we showed a clear signal in ibuprofen–exposed ELBW neonates, proving the method to be a possible pragmatic tool to detect AKI bedside.

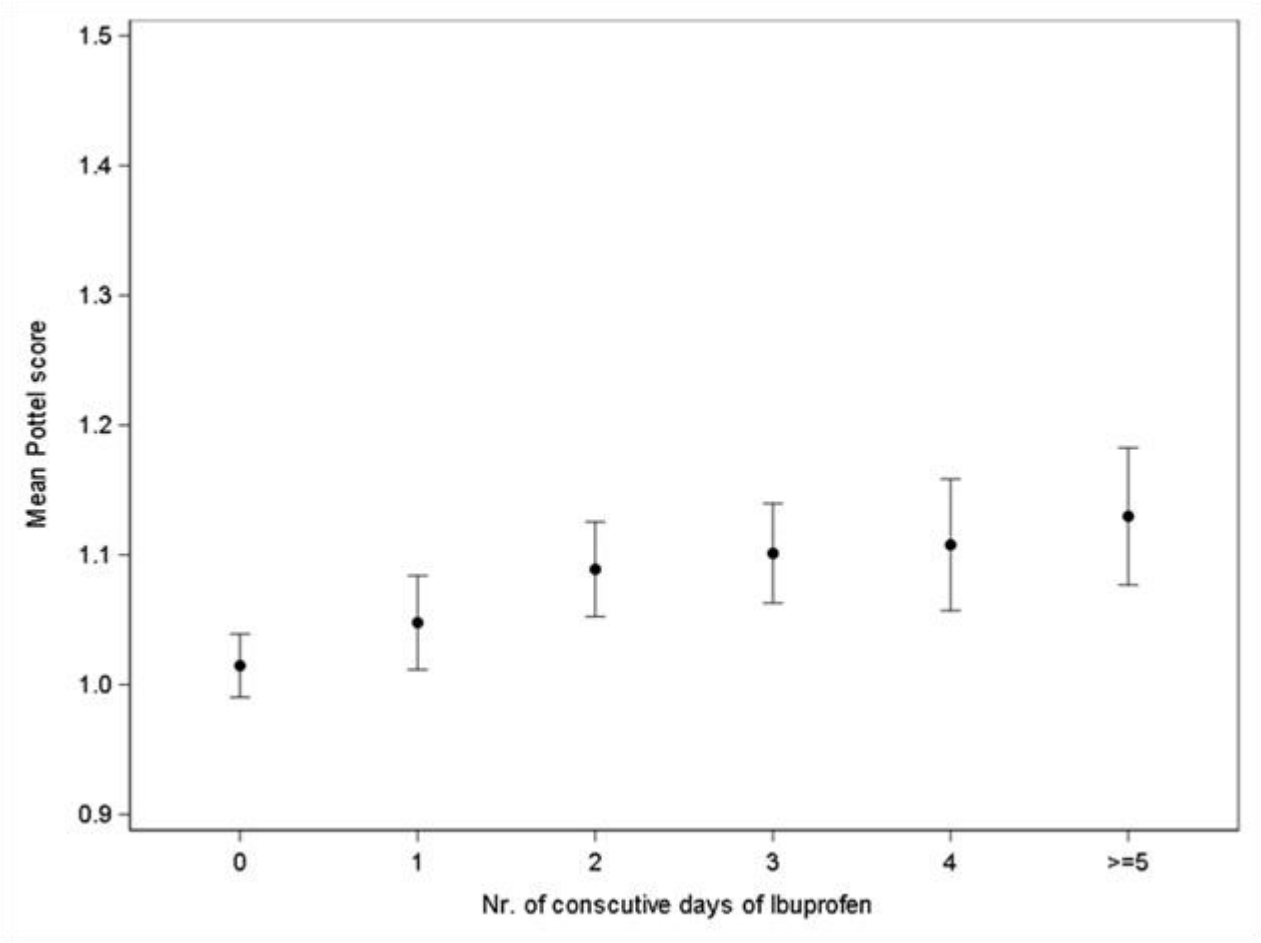


Fig 1: Mean Pottel score in function of number of consecutive days of administration of Ibuprofen, corrected for influence of antibiotics.

Fig 1: Mean Pottel score in function of number of consecutive days of administration of Ibuprofen, corrected for influence of antibiotics.

None declared

ID 48. USE OF COLISTIN IN PREMATURE INFANTS: EFFICACY AND SIDE EFFECTS

Médecin Saida Mecheri[1], Master assistant Faiza Benmati[1], Associate profesors Djamel Chelirem[1], Master assistant Abdeldjalil Brahimi[1], Professor Kamel Boudhar[1]
[1]NICU – Central Hospital of Army, Algeries, Algeria

Background :
Nosocomial infections are a major problem in neonatal intensive care units (NICUs). Colistin is an antibiotic from the group of polymyxins and is particularly essential in the elimination of multidrug–resistant Gram–negative bacteria.
Several side effects, particularly nephrotoxicity, were associated with intravenous administration of colistin; However, there are few studies involving preterm infants, and this study aimed to investigate the efficacy and side effects of colistin in this particular group of patients.
The aims is the analyze the efficacy of intravenous colistin use in preterm infants with nosocomial sepsis in the intensive care unit, and describe the side effects observed during treatment.

Methods:
Retrospective review of the records of preterm infants who received colistin with positive cultures. Patients were evaluated for response to treatment and side effects observed.

Results: A total of 52 preterm infants with medians of 30 weeks (28–36) gestational age and 1200 g (950–2950) birth weight were included. The most frequently isolated pathogens were Klebsiella pneumoniae, Acinetobacter baumannii and Enterobacter cloacae. The mean duration of treatment with colistin was 10 days (3 – 20) and the

dose ranged from 100000 to 150000 IU/kg/day. All patients treated with colistin were put on at least one other antibiotic.
While a complete clinical response was achieved in 36 patients (69.2%), 11 patients (21.1%) died during treatment. 5 patients (9.6%) died from another medical condition. The main side effects observed in our patients were hypomagnesemia and hypokalemia in 50 patients (96.1%), acute renal injury was observed in 6 patients (11.5%).

Conclusion: Administration of colistin appears to be effective in the treatment of nosocomial infections in preterm infants; nevertheless, it should be remembered that close monitoring of renal function tests and serum electrolytes including magnesium should be done during treatment with colistin in preterm infants.

None declared

ID 1045. conect4children: service development and delivery by the pan-European paediatric clinical research network

Professor Mark Turner[1,2], Ms Heidrun Hildebrand[3], Dr Katharine Cheng, Dr Sabah Attar[1,2], Dr Fenna Mahler[1,4], Dr Francesca Rocchi[5], Ms Rebecca Leary[6], Dr Ricardo Fernandes[1,7], Prof Saskia de Wildt[4], Prof Gilles Vassal[8], Dr Ron Portman[9], Ms Begonya Nafria[10,12], Ms Laura Mangiarini[11], Prof Carlo Giaquinto[11]

[1]Conect4children Stichting, Utrecht, Netherlands, [2]University of Liverpool, Liverpool, United Kingdom, [3]Bayer AG, Research & Development, Pharmaceuticals, Berlin, Germany, [4]Radboud University Medical Centre, Nijmegen, Netherlands, [5]OPBG, Rome, Italy, [6]Newcastle University, Newcastle, United Kingdom, [7]Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal, [8]Gustave Roussy Comprehensive Cancer Center, , Paris Saclay, Villejuif, France, [9]Novartis, Newark, United States of America, [10]Patient Engagement in Research Department, Institut de Recerca Sant Joan de Déu, , Esplugues de Llobregat, Spain, [11]Fondazione Penta, Padova, Italy, [12]Innovation Department Hospital Sant Joan de Déu, Esplugues de Llobregat, Esplugues de Llobregat, Spain

Introduction: Paediatric clinical research has specific features that can make research difficult. The conect4children partnership aimed to address some of the difficulties in paediatric clinical research by co-creating several services for academic and industry research.

Methods: A public private partnership was funded by the Innovative Health Initiative involving 10 large pharmaceutical companies and 33 academic organizations. The partnership identified key services, co-developed and tested processes, implemented a suite of standard operating procedures, including quality control, and built business models for each service.

Results: An Expert Advice service was built around over 400 selected experts working in 24 clinical and methodology groups, embedding patient and public involvement. The service has managed 50 requests for advice (12 involving children and young people, 10 academic requests) and 3 multi-stakeholder meetings. Services for site finding and feasibility and support to study setup and conduct were built around 20 National Hubs (most of which which were developed by the project) involving 250 sites through a single point of contact. The services were tested using 3 academic studies and 8 industry studies. Education and Training was built around a Moodle-based platform. The c4c Academy includes a suite of 7 core courses (related to GCP) was supplemented by 25 short courses and an Advanced Course in Paediatric Drug Development. 2243 people have used the Education and Training portal. A paediatric data dictionary was developed and used to create the Paediatric User Guide (PUG) by CDISC, the leading data standards organization for clinical research in drug development. The PUG includes 91 paediatric terms. A non-profit foundation, conect4children Stichting has been incorporated to provide these services to academia and industry in a sustainable manner.

Conclusion: A public private partnership provided a platform for the development and testing of services to facilitate patient-centric paediatric clinical research. These services will be available to academic and industry drug developers through the c4c Stichting

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU), Europe's biggest Public-Private Partnership, under grant agreement No 777389

All the authors are paid employees of Beneficiaries to the c4c project (IMI2 JU No 777389. MT, SA, FM, RF are officers of conect4children Stichtinhg.

ID 1055. ASSOCIATIONS OF OPIOID EXPOSURE WITH BRAIN SIZE AMONG EXTREMELY PRETERM INFANTS

Doctor Seh Hyun Kim[1], Yvonne Sheldon[1], Doctor Katherine Bell[1], Kaitlyn Roddy[1], Sara Rostas[1,2], Debra Marks[1], Tina Steele[1], Elizabeth Singh[1], Kirsten Thiim[1], **Doctor Aisling Garvey**[1], Doctor Mohamed El-Dib[1], Doctor Terrie Inder[1,3]
[1]Brigham Women's Hospital, Boston, United States, [2]New York Presbyterian Hospital, New York, United States, [3]Children's Hospital of Orange County, Irvine, United States

Background: Morphine and Fentanyl are commonly used in extremely preterm infants in the neonatal intensive care unit (NICU) but may impair brain growth. This study aims to evaluate the relationship between opioid exposure and brain size in extremely preterm infants.

Methods: This is a retrospective cohort study of preterm infants (<28 weeks gestation) admitted to Brigham Women's Hospital NICU who were exposed to opioids and underwent term-equivalent brain magnetic resonance imaging between 2017 and 2020. We quantified morphine and fentanyl exposure as total mg/kg received and total days of exposure to opioids during NICU hospitalization. Brain size was quantified using biparietal diameter (cBPD) and transverse cerebellar diameter (cTCD), corrected for postmenstrual age.

Results: This study included 62 preterm infants. The median for total received fentanyl was 2.1 mcg/kg (IQR 1.0–6.0 mcg/kg), total received morphine was 0.2 mg/kg (IQR 0.0–5.1 mcg/kg) and opioid duration was 5 days (IQR 2.0–15.0 days). In multivariate linear regression analysis, total received morphine was associated with lower cBPW (regression coefficient –0.052, 95% CI –0.104 , –0.001). Opioid duration was associated with lower cBPW (regression coefficient –0.083, 95% CI –0.145, –

0.020) and cTCD (regression coefficient −0.049, 95% CI −0.089, −0.009). Total received fentanyl did not correlate with cBPW and cTCD.

Conclusion: Higher morphine doses and longer duration of opioid exposure in the NICU were associated with smaller brain size at term equivalent age. While we cannot ascribe causality in this observational study, exposure to opioids may be a modifiable risk factor for poor brain growth among extremely preterm infants.

	β*	SE	95% CI	p-value
cBPW				
Total received fentanyl	-0.0004	0.004	[-0.009 , 0.008]	0.933
Total received morphine	-0.052	0.026	[-0.104 , -0.001]	0.047
Opioid duration	-0.083	0.031	[-0.145 , -0.020]	0.010
cTCD				
Total received fentanyl	-0.001	0.003	[-0.007 , 0.004]	0.661
Total received morphine	-0.023	0.017	[-0.056 , 0.011]	0.180
Opioid duration	-0.049	0.020	[-0.089 , -0.009]	0.017

*Adjusted for gestational age, birth weight z score, and PMA at MRI.

β, regression coefficient; SE, standard error; CI, confidence interval; PMA, post–menstrual age; MRI, magnetic resonance imaging.

*Adjusted for gestational age, birth weight z score, and PMA at MRI.

β, regression coefficient; SE, standard error; CI, confidence interval; PMA, post–menstrual age; MRI, magnetic resonance imaging.

None declared

ID 14. Pharmacotherapy-related practices and skills as reported by attendees of the Neonatal Online Training and Education (NOTE) course on neonatal clinical pharmacology

Professor Karel Allegaert[1,2], Pharm Dotan Shaniv[3], MD, PhD Sinno Simons[4], PharmD, PhD Robert Flint[2,4], prof Anne Smits[1,5], Nurse Susan Smith[6], MD Mike Hall[6]
[1]KU Leuven , Leuven , Belgium, [2]Hospital Pharmacy, Erasmus MC, Rotterdam, Rotterdam, the Netherlands , [3]Kaplan Medical Center, Clalit Health Services, Rehovot, Israel, [4]Division of Neonatology, Erasmus MC Sophia's Children's Hospital , Rotterdam, the Netherlands , [5]Neonatal Intensive Care Unit, UZ Leuven, Leuven, Belgium, Leuven , Belgium, [6]School of Health Sciences, Southampton , United Kingdom

Background: We intended to get a snapshot of pharmacotherapy–related practices at the initiation of the 2022 clinical pharmacology NOTE course[1]. Besides guiding education, this also informs us of contemporary practices, research or additional needs of early career colleagues.

Methods: The online questionnaire was developed by the NOTE content coordinator of the pharmacology module (KA), subsequently distributed to the NOTE pharmacology faculty for input. Topics covered were: (1)Who do you contact with drug–related questions? (2)Does a pharmacist visit your unit? (3)Have you ever reported an adverse drug reaction (ADR)? (4)What information sources do you use? (5)Have you ever assisted in a trial as (co)investigator? (6)What are the top 5 prescribed drugs in your unit?

Results: Fifty three (77%) responses were received from 69 participants (United Kingdom 15, Qatar 7, India 5, Trinidad/Tobago 5, Ireland 5, Emirates 5, Palestinian Authority 4, Norway 4, Nigeria 3, Denmark 2, Canada 2, Zambia 2, Mauritius 2, and

Bahrain, Japan, Kenya, Iceland, Indonesia, Malta, Portugal, United States), mainly doctors (64). On Q1, colleague–neonatologists (39), external sources/formularies (5), or pharmacists (9) were mentioned. Q2: 27 (39%) reported regular/daily visits of a pharmacist, 9 weekly, 17 had no structured visits. Q3: 17 (32%) have reported an ADR on at least one occasion. Q4: Information sources (formulary) used by the respondents were BNFc (22), NeoFax (through Micromedex) (21) Neonatal Formulary (3) or Lexicomp (through UpToDate) (5). Others (25) mentioned local, regional or national formularies. Q5: Six respondents had assisted at least in one drug research trial. Q6: The top 5 drugs prescribed by the respondents were caffeine, gentamicin, benzylpenicillin, ampicillin, amikacin.

Discussion: This snapshot reflects large heterogeneity in practices (who to consult for drug–related questions, access to pharmacist, information sources) and experiences (ADR reporting, trial involvement), and provides guidance on needs (pharmacists, ADR reporting, information sources awareness) on pharmacotherapy. The top 5 drugs reflect the common use of antibiotics.

Conclusions: The results of this questionnaire reflect needs to improve our practices, by raising awareness of formularies, ADR reporting or a broader involvement in clinical trials. Questionnaires are useful to learn from and interact with NOTE participants.
[1]: https://moodle.neonataltraining.eu/

none declared

ID 221. HAIR AS AN ALTERNATIVE MATRIX TO ASSESS EXPOSURE OF PREMATURE NEONATES TO PHTHALATE AND ALTERNATIVE PLASTICIZERS IN THE NEONATAL INTENSIVE CARE UNIT

Doctor Lucas Panneel[1,2], PharmD Paulien Cleys[3], Prof. Dr. Adrian Covaci[3], Prof. Dr. Antonius Mulder[1,2], Prof. Dr. Philippe G Jorens[2,4]

[1]Neonatal Intensive Care Unit, Antwerp University Hospital, Edegem, Belgium, [2]Laboratory for Experimental Medicine and Pediatrics, University of Antwerp, Wilrijk, Belgium, [3]Toxicological Centre, University of Antwerp, Wilrijk, Belgium, [4]Department of Intensive Care Medicine and Clinical Pharmacology, Antwerp University Hospital, Edegem, Belgium

Background

Phthalates, plasticizers used to soften plastic materials, can leach from plastic medical devices (PMD) into the human body. Di–(2–ethylhexyl)–phthalate (DEHP) has long been the most popular plasticizer, but its use was restricted in PMDs due to endocrine disrupting properties, being gradually replaced by alternative plasticizers (APs). Up to this date, urine was the sole matrix to study plasticizer exposure in the neonatal intensive care unit (NICU). The primary aim of this study was to assess simultaneous measurement of phthalate and AP metabolites in neonatal scalp hair. In addition, we aimed to use this matrix to investigate cumulative exposure of premature neonates to plasticizers during NICU stay.

Methods

Patients were included from a prospective cohort study (Plastic–NICU, Clinicaltrials.gov NCT05404815) at the Antwerp University Hospital NICU (Belgium). Scalp hair samples (⩾3mg) from premature neonates (n=45), born at <31 weeks gestational age and/or <1500g birthweight, were collected at term age. Hair samples

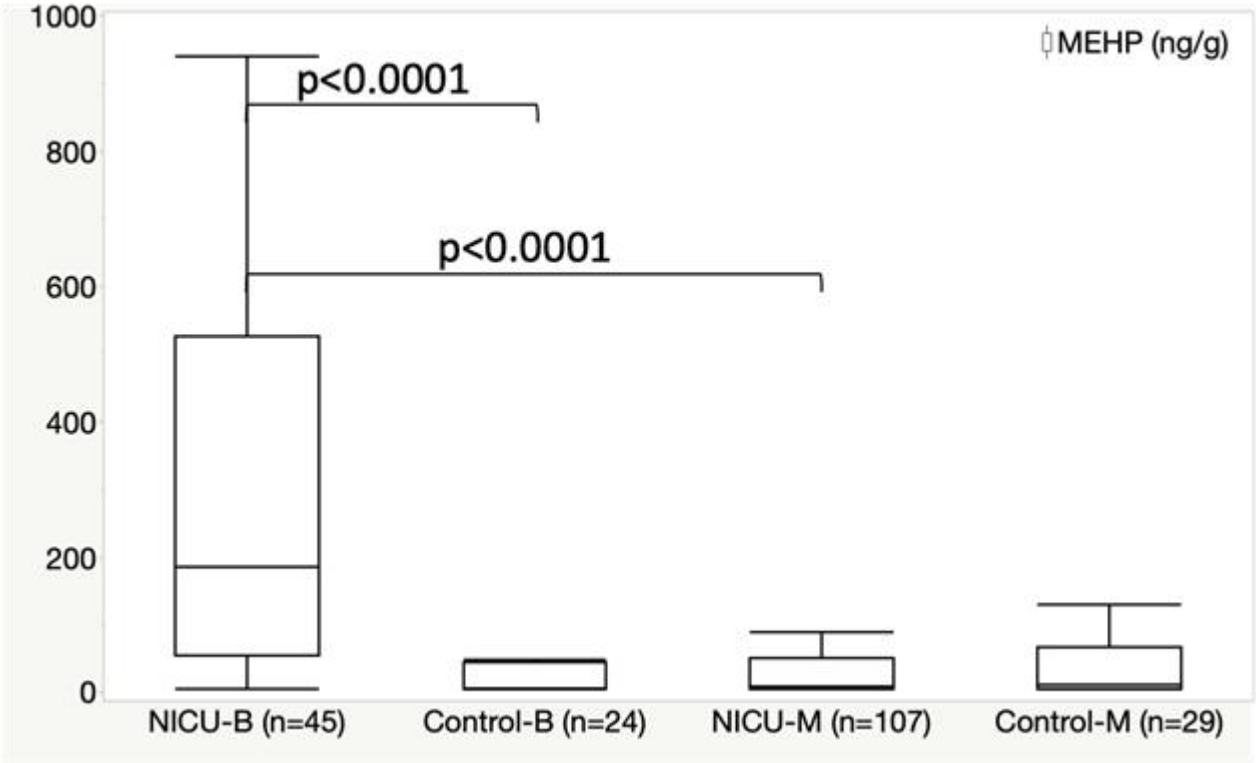
from their mothers were collected 48 hours after birth reflecting gestational exposure. Term neonates (n=24) were recruited as a control group from the well baby maternity ward. Samples were analyzed with liquid–chromatography coupled to tandem mass spectrometry. Statistics are derived from univariate non–parametric tests.

Results

Three phthalate and three AP metabolites were detected in ±90% of NICU neonatal samples. Hair sampled after NICU stay contained significantly higher metabolite concentrations of both classic phthalates (DEHP, DiBP, and DnBP) and alternative plasticizers (DEHA, DEHT, and TOTM), than in control neonates ($p<0.0001$). Neonatal concentrations were also 5–10 higher than in hair samples from previous healthy adult and pediatric populations ($p<0.0001$). Maternal phthalate metabolite concentrations in our NICU mother cohort were higher compared to a healthy pregnant population in Greece ($p=0.02$). Lastly, continuous NICU exposure to non–invasive respiratory support and a gastric tube is correlated with increased concentrations in hair samples (rho=0.4), indicating accumulation in this alternative matrix.

Conclusions

This is the first study to detect biomarkers of exposure to phthalate and alternative plasticizers in neonatal hair. Our data indicate that preterm neonates are still highly exposed to these endocrine disrupting chemicals during NICU stay, despite the EU Medical Devices Regulation (MDR 2017/745).



Comparison of the primary DEHP–metabolite (MEHP, ng/g) in hair samples from NICU–neonates (NICU–B), control–neonates (control–B), NICU–mothers (NICU–M), and control–mothers (control–M). P–values are derived from the Wilcoxon Rank Sums Test.

Comparison of the primary DEHP–metabolite (MEHP, ng/g) in hair samples from NICU–neonates (NICU–B), control–neonates (control–B), NICU–mothers (NICU–M), and control–mothers (control–M). P–values are derived from the Wilcoxon Rank Sums Test.

None declared

ID 442. DO INFANT BEHAVIORS MEDIATE THE RELATIONSHIP BETWEEN PRENATAL COCAINE EXPOSURE AND DEFICITS IN PERCEPTUAL REASONING SKILLS IN YOUNG ADULTS?

Doctor lynn Singer[1], Dr. Jeffrey Albert[1], Dr. Sonia Minnes[1], Dr. Meeyoung Min[2], Dr. Juneyung Kim[3], Ms. Sunyung Kim[1]

[1]Case Western Reserve University, Cleveland, United States, [2]University of Utah, Cleveland, United States, [3]University of North Dakota, Grand Forks, USA

Background: Understanding the relationship of prenatal drug exposures to adult outcomes is difficult due to the lack of cohort studies post adolescence and the confounding of environmental factors over time. Perceptual reasoning (PR), a nonverbal executive function reflecting abstract reasoning, has been negatively related to PCE from 4–21 years of age. We sought to assess whether deficits in PR were mediated or indirectly related to behaviors identified in infancy to be negatively affected by PCE, controlling for prenatal alcohol, marijuana and tobacco exposure, maternal psychological distress, the HOME environment and elevated lead.

Methods: 388 infants (195 PCE; 48 % male), primarily African–American, low socioeconomic status, were followed from birth to 21 years. PRIQ was assessed with the Wechsler Scales at 4, 9, 15, and 21 years. At 0–1 month, infants were administered a neonatal visual preference test, and a Neurobehavioral Assessment (NB). The Fagan Test of Infant Intelligence (FTII) was given at 6.5 and 12 months., the Bayley MDI at 6, 12, 24 months. Two path models were conducted, 1 for the entire sample and a second to include those with lead levels (n=287), with PRIQ as a latent variable, and head circumference (HC) and infant behaviors as mediators.

Results: Both models were consistent in demonstrating significant indirect effects of HC (beta = 0.882, S.E. = 0.282, p < 0.002) and MDI (beta =0.481, S.E. = 0.056, p < 0.000) on the intercept of PRIQ after control for covariates. PCE was related to HC (beta = −0.757, S.E. = 0.320, p< 0.018) FTII (beta = −1.959, S.E.= 0.994, p< 0.049) and, after control for HC, MDI (beta= −3.161, S.E.= 1.777, p< 0.075). HC was related to NB abnormalities, (beta= −0.069, S.E.= 0.035, p< 0.048). In the model with lead, there was no relationship of lead or HOME to PCE but lead also decreased the PRIQ intercept (beta = −4.609, S.E.= 1.352, p< 0.001).

Conclusions: Negative effects of PCE on PRIQ can be linked to early physical and behavioral deficits independent of environmental factors, suggesting a causal biologic relationship of PCE to adult deficits in perceptual reasoning,

NIDA R01–07957 and R01–42747.

None declared

ID 789. PILOT-PHASE RESULTS OF HYDROCORTISONE SUCCINATE SUPPLEMENTATION DURING HYPOTHERMIA TREATMENT IN INFANTS WITH NEONATAL ENCEPHALOPATHY

Doctor Marianna Dobi[1], Anna Vamos[1], Doctor Gellert Balazs Karvaly[2], Doctor Robert Farkas[2], Doctor Eniko Szakmar[1], Doctor Unoke Meder[1], Doctor Agnes Jermendy[1], Professor Miklos Szabo[1], Doctor Kata Kovacs[1]

[1]Division of Neonatology, Pediatric Center, MTA Center of Excellence, Semmelweis University, Budapest, Hungary, [2]Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary

Background: Hemodynamic instability is a frequent complication in infants with neonatal encephalopathy (NE) during hypothermia treatment, and relative adrenal insufficiency (RAI) could be considered as an underlying etiology. We previously showed that low–dose hydrocortisone succinate supplementation (HCSS) is effective in raising blood pressure in infants with NE, however, it is still unknown if hydrocortisone influences neurodevelopmental impairment, so it is paramount that this therapy should be administered at the lowest effective dose and for the shortest possible duration. Both hypothermia and perinatal asphyxia are expected to alter hydrocortisone exposure and data regarding optimal dose ranges are unknown.

Methods: To determine the exposure to hydrocortisone succinate, hydrocortisone and cortisone following the supplementation under lower body temperatures, we are conducting a prospective clinical study including hypotensive infants with NE at the NICU of the Department of Paediatrics Semmelweis University, Budapest, Hungary. For the pilot–phase, patient enrollment was started in September 2021. Arterial blood samples for serum cortisol and cortisone measurements, determined using liquid

chromatography–tandem mass spectrometry, were taken every 6 hours from the start of standard, 0.5 mg/kg/6 hours HCSS during hypothermia treatment.

Results: Currently, data of 13 patients (160 samples) are available. The baseline (endogenous) cortisol levels, assayed before beginning the treatment, were lower than 15 µg/dl (median 0.89 [IQR 0.72; 9.15] µg/dl), the threshold of RAI, in 85% of the cases. After the first HCSS, cortisol levels increased significantly from the baseline (median 22.2 [IQR 10.7; 40.9] µg/dl; p=0.001), and remained elevated thereafter. We found great interindividual variability in the cortisol (range 2.42–148 µg/dl) and cortisone levels (range 1.3–16.6 µg/dl). Furthermore, a trend of higher cortisone levels were measured after HCSS in NE infants with hepatic impairment.

Conclusion: Based on this pilot study we found low baseline serum cortisol levels before HCSS and high variability and wide ranges of cortisol and cortisone levels after HCSS in infants with NE during hypothermia treatment without reaching steady state. Personalized hydrocortisone succinate dosing is still lacking in cooled infants with NE and, based on our preliminary results, hepatic impairment may further alter drug metabolism in this population.
The research was funded by ESPR Young Investigator START-UP GRANT 2021, OTKA PD_142288 and RRF-2.3.1-21-2022-00011 grants.

ID 146. PAIN AND HEART RATE VARIABILITY IN NEONATES RECEIVING DEXMEDETOMIDINE

Miss Catarina Sevivas[1], Mrs Marta Camprubí, Miss Ruth Ibañez, Miss Melisa Fontalvo

[1]Hospital Sant Joan De Deu, Barcelona, Spain

BACKGROUND: Newborns admitted to a NICU experience pain and discomfort. Based on the cardiovascular and nociceptive systems link, a monitor that assess the parasympathetic response to pain by the analysis of heart rate variability was conceptualised – Newborn Infant Parasympathetic Evaluation (NIPE). Concurrently, the use of alpha–2 agonists in pain management has increased in neonates. Considering its effect on the autonomic nervous system, we have hypothesised that it may alter the NIPE's measurement capacity. Our aim was to demonstrate this possible interference and the correlation between the NIPE index and comfort related variables.

METHODS: Sixteen newborns requiring sedoanalgesia in the NICU were included, who underwent a total of 84 simultaneous assessments of the NIPE index and comfort–related variables (including the COMFORT–neo scale).

RESULTS: The analysis of all the assessments carried out showed a strong correlation between NIPE index and the COMFORT–neo (p=0.014), as well as other related variables. The postmenstrual age was considered a confounding variable and it was not possible to obtain a good correlation between the scale and the NIPE index in premature infants. When analysing results by sedation group, a good correlation was stablished in patients receiving dexmedetomidine/clonidine.

CONCLUSION: Our results indicate that NIPE is reliable to assess prolonged pain/discomfort in term newborns. More studies are required to validate it in prematures. In patients receiving dexmedetomidine/clonidine the correlations remain strong, suggesting that it does not alter NIPE's measurement capacity. A correlation between the NIPE index and rScO2 has also been demonstrated for the first time.

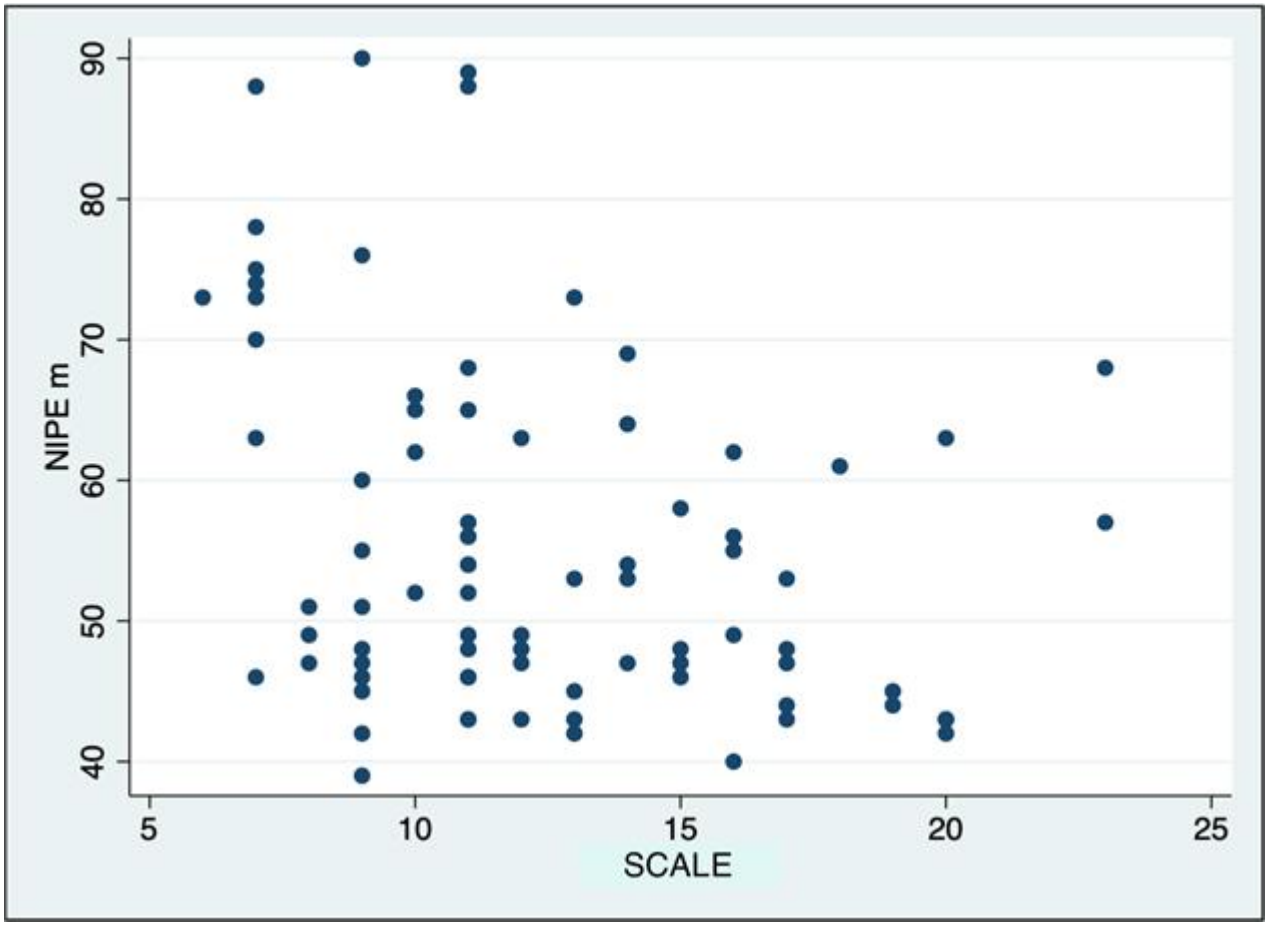


Figure 1. NIPEm and Comfort neo correlation (rho=–0.3433; p=0.014)

Figure 1. NIPEm and Comfort neo correlation (rho=–0.3433; p=0.014)

None declared

ID 267. CAFFEINE THERAPY FOR APNEA OF PREMATURITY: REAL WORLD DATA ON EFFECTIVITY

Miss Kelly Storm[1], Dr. Robert Flint[1,2], Dr. Wes Onland[3,4], Prof. Anton van Kaam[3,4], Prof. Irwin Reiss[1], Dr. Jeroen Hutten[3,4], Dr. Sinno Simons[1]

[1]Department of Neonatal and Pediatric Intensive Care, Division of Neonatology, Erasmus University Medical Center – Sophia Children's Hospital, Rotterdam, The Netherlands, [2]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Department of Neonatology, Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands, [4]Amsterdam Reproduction & Development, Amsterdam, The Netherlands

Background.

Caffeine is the cornerstone of pharmacologic treatment for apnea of prematurity and is the most frequently used drug in preterm infants. Caffeine has been well studied in randomized controlled trials and pharmacokinetic studies. We hypothesize that the clinical application of caffeine differs from the initial evidence-based therapy and therefore aimed to describe daily clinical practice of caffeine use in preterm infants in a single center.

Methods.

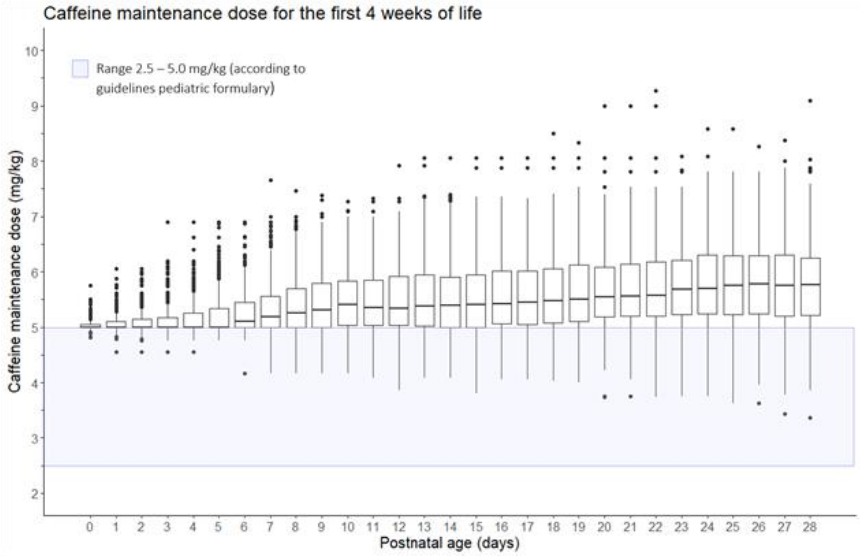
We performed a retrospective study in infants born before 30 weeks gestational age (GA), admitted to the NICU of the Erasmus MC Rotterdam from January 2018 to December 2021. Patients were included if they received treatment with caffeine base. The primary outcome was treatment failure, defined as the need for an additional caffeine loading dose or co-treatment with doxapram.

Results.

A total of 554 patients with a median GA of 27 (IQR 26 to 28) weeks and a median birthweight of 980 (IQR 781 to 1200) grams were included. The median caffeine maintenance dose was 5.3 mg/kg/day (IQR 5.0 to 5.7). In 374 patients (68%), therapy failed with a median time to treatment failure of 11 days (IQR 6 to 21 days). No correlation was found between postnatal age or birthweight and the caffeine maintenance dose at the time of treatment failure.

Conclusion.

Caffeine was used independent of apnea as standard of care from the first day of life in high maintenance dosages. A relatively low effectivity of caffeine was found, especially in preterm infants < 28 weeks of gestation, in contrast to what would be expected based on pharmacological maturation. Despite the high dosages of caffeine, additional therapy was still needed for nearly 70% of patients, indicating the necessity for the development of new dosing strategies or alternative therapies.



Caffeine maintenance dose for the first four weeks of life

Caffeine maintenance dose for the first four weeks of life

None declared

ID 730. Prescribing Behavior of Analgosedatives for Extremely Premature Neonates: A Retrospective Analysis

Mr Samir El Abdouni[1], Dr Gerbrich van den Bosch[2], Ms Jonne Uiterwijk[1], Ms Jolette Straatman[1], Dr Floor van Rosse[1], Dr Sinno Simons[2], **Dr Robert Flint**[1,2]
[1]Department of Hospital Pharmacy, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [2]Department of Neonatal and Pediatric Intensive Care, Division of Neonatology, Erasmus MC, University Medical Center–Sophia Children's Hospital, Rotterdam, The Netherlands

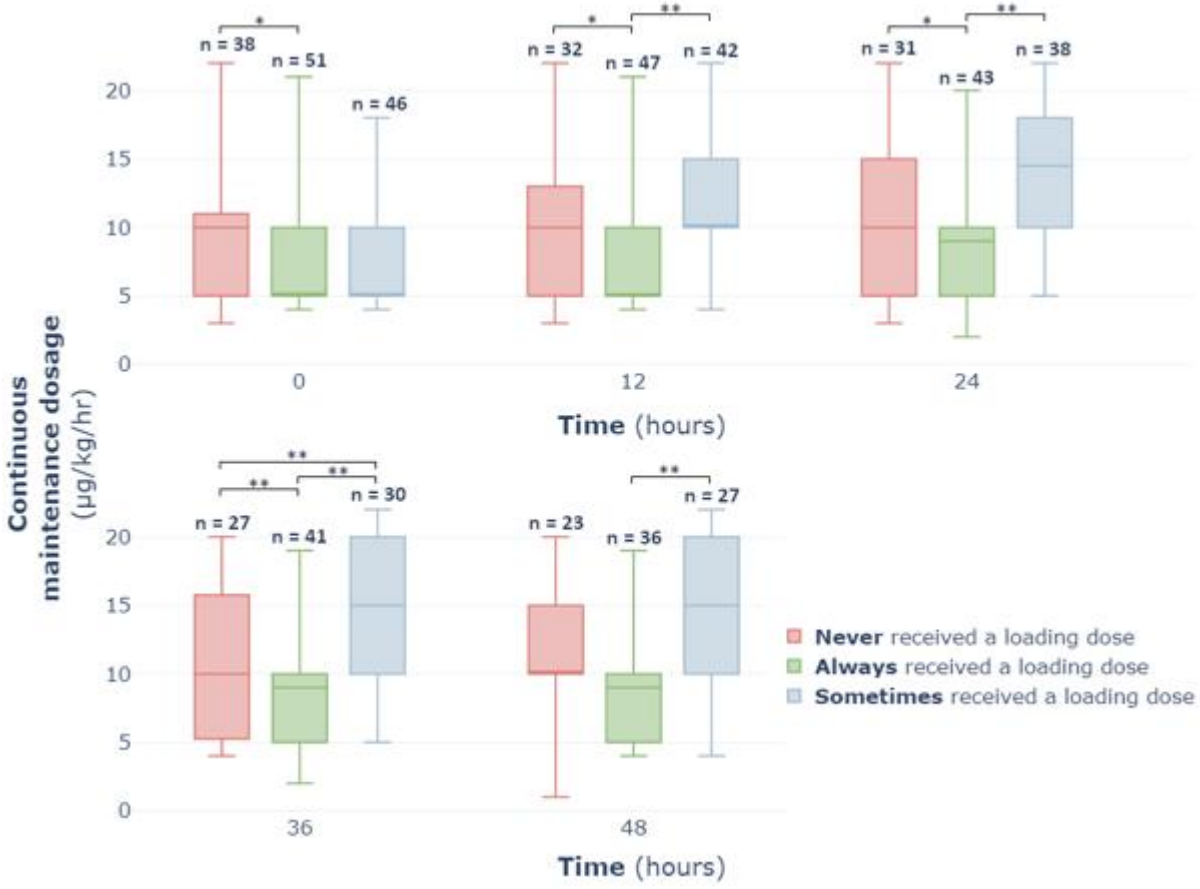
Background: Managing pain in extremely premature (EP) neonates is complex, and protocols at NICUs often lack tailored advice for different indications or patient characteristics, increasing the risk of insufficient pain management. This study aims to examine clinician prescribing behavior, identify areas for improvement, and suggest modifications to existing protocols, which enables the improvement of analgosedative therapy for EP neonates.

Methods: In this single center, retrospective study, we analyzed data from all EP neonates (gestational age below 28 weeks) admitted to our level III–IV NICU between 2017 and 2021, comparing baseline characteristics and drug administration data.

Results: Of the 2633 neonates admitted to the NICU, 10% (n=268) was EP. Of these, 59% (n=142) received analgosedative therapy and ‘Pain’ was the most common therapeutic indication (52%), followed by respiratory–related indications (20%). Morphine, fentanyl, and acetaminophen were prescribed most frequently, with 98% being used intravenously (IV).
At initiation of continuous infusion, loading doses were administered for morphine and midazolam in 68% and 59% of cases, respectively. At dose escalation, this

decreased to 40% and 33% for morphine and midazolam, respectively. Morphine continuous infusion patients who always received a loading dose required significantly lower median dosages during the first 36 hours after continuous infusion initiation than those who did not (Figure 1). The median starting dosage of patients who never received a loading dose was significantly higher than those who did (10 vs. 5 μg/kg/h; p = 0.03) and remained constant throughout the 48–hour period. Patients who sometimes received a loading dose, had a significantly higher median dosage after 12 hours.

Conclusion: The higher maintenance dosages required by EP neonates who did not receive a loading dose highlights the need for a critical evaluation of the use of loading doses surrounding continuous infusions. Administering a loading dose can improve pain management by providing faster therapeutic effects, while starting at a lower maintenance dosage and allowing for dose titration which can reduce unnecessary opiate exposure.



Median morphine dosages within the first 48 hours after therapy (re–)initiation for extremely premature neonates in the presence or absence of a loading dose. * = p<0.05. ** = p<0.01

Median morphine dosages within the first 48 hours after therapy (re–)initiation for extremely premature neonates in the presence or absence of a loading dose. * = p<0.05. ** = p<0.01

All authors declare no conflict of interest.

ID 45.THE EFFECT OF MASSAGE THERAPY BEFORE HEEL STICK EXTRACTION ON NEONATES ADMITTED IN A PRIVATE TERTIARY HOSPITAL IN DAVAO CITY

Doctor Arvin Gallardo[1], Doctor Joel Gallardo[1]

[1]San Pedro Hospital of Davao Inc., Davao City, Philippines

Background: Pain is a unique experience that every single person has felt in their lifetime, some more intense than others. It has been suggested that hospitalized infants born at 25 to 42 weeks of gestation experience an average of 14 painful procedures a day for the duration of their first two weeks of life. One of the common procedures is the heel stick, done prior to discharge for the routine expanded newborn screening test. Neonates are affected by pain during these practices, which may impair their adaptability to the outside world and result in strain and physiological imbalance. Hence, this study is aimed at identifying the effect of massage therapy on the neonatal pain score prior to heel stick extraction on expanded new–born screening.

Methods: The study used a prospective randomized controlled trial design. Sampling was done via the closed envelope method. The setting was a private tertiary hospital in Davao City. The study included 56 term neonates with more than 24 hours of life, an APGAR score of more than or equal to 7 at 5 minutes after birth, no painful intervention other than the routine Vitamin K; Hepatitis B and BCG vaccinations given after birth; and delivered in the tertiary private hospital. The Neonatal Infant Pain Scale was used in the study. Patients in the massage group were given a foot massage involving stroking and gentle kneading on the outer aspect of the ipsilateral leg, done for 2 minutes prior to performing the heel stick procedure. Data were analyzed using descriptive statistics such as mean and standard deviations for the

demographic profile. An independent T–test was used for continuous variables and a chi–square test for categorical variables.

Results: The Neonate Infant Pain Scale score was lower for the massage group during the heel stick procedure (P 0.68) and 1 minute after the procedure (P .000).

Conclusions: Massage therapy has a positive and favorable effect on reducing the amount of pain in neonates prior to heel stick extraction for expanded newborn screening using the neonatal pain scale in a tertiary hospital in Davao City.

Comparison in the Pain Scores of Neonates between Groups

Screening	Control Group	Massage Group	p-value
Pain scale during heel stick	6.89 ± .416	6.32 ± 1.541	.068
Pain scale 1 minute after	3.79 ± 2.394	1.71 ± 1.584	.000

***Interpretation: Minimum score 0; Maximum score 7*

none declared