September 22nd, 2023 15:00 - 17:00

PARALLEL SESSION 30 - PHARMA 2

ID 217. PERSISTING EXPOSURE TO ENDOCRINE DISRUPTING PHTHALATES AND ALTERNATIVE PLASTICIZERS IN NEONATAL INTENSIVE CARE UNIT PATIENTS

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

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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). Premature neonates in the neonatal intensive care unit (NICU) rely on invasive PMDs, and may be exposed to high amounts of plasticizers. This study investigated current phthalate and AP exposure in the NICU using longitudinal urine samples and identified patients at a higher risk.

Methods

This prospective cohort study (NCT05404815) included patients at the Antwerp University Hospital NICU. Throughout hospitalization, 840 urine samples were

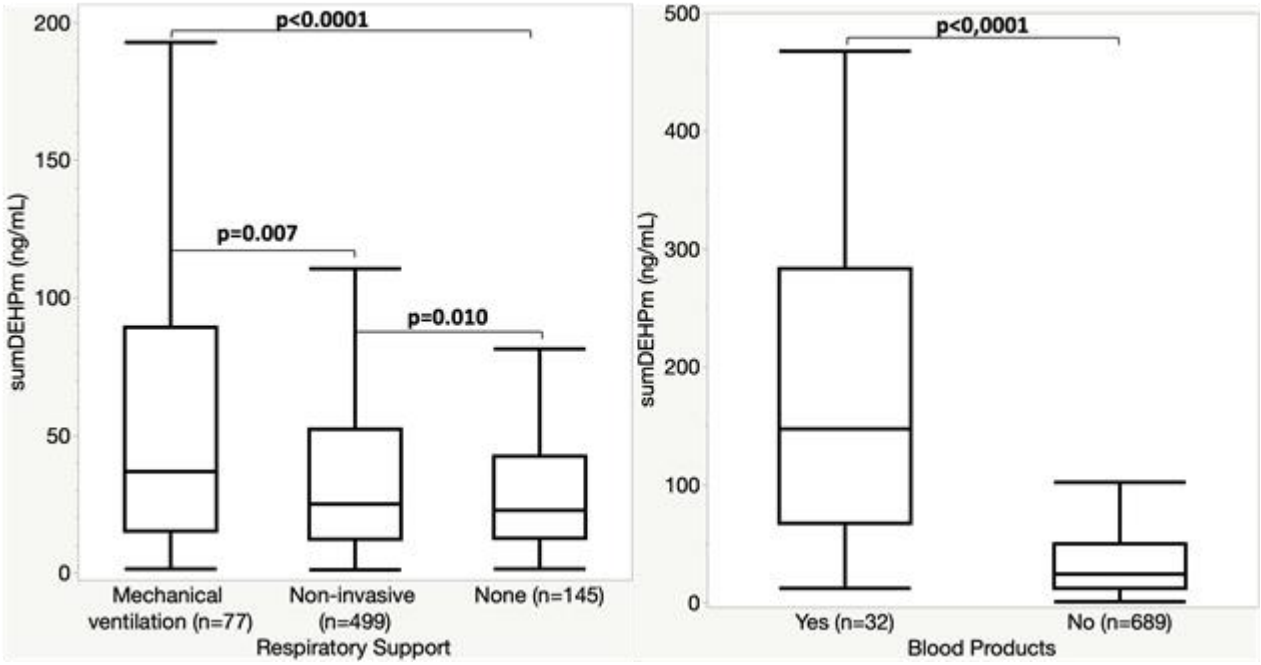
collected from 100 preterm (gestational age (GA) 24–31w) and 20 control neonates, and analyzed for phthalate and AP metabolites by LC–MS/MS. Birth characteristics, sampling time, and PMD exposure (defined in a 2–day window before each urine collection) were analyzed as predictors for urinary metabolites using univariate non–parametric tests.

Results

Phthalate metabolites were detected in ⩾90% of neonatal samples, AP metabolites in ±50%. Median urinary phthalate metabolite concentrations were lower compared to previous NICU studies (2005–2019). DEHP–metabolites were significantly higher in preterm than in control neonates ($p=0.0497$) and compared to NICU/control mothers ($p<0.0001$). Within the preterm group, DEHP–metabolites were negatively correlated with GA (rho=–0.37) and birthweight (rho=–0.26). DEHP–metabolite concentrations gradually increased after birth until week three postnatal age, then decreased until discharge. Concerning parenteral nutrition and a central catheter, no significant differences were observed in exposed compared to unexposed preterms. Respiratory support ($p=0.0003$) and blood products ($p<0.0001$) were associated with significantly higher urinary DEHP–metabolites. Post–hoc analysis showed higher concentrations with invasive ($p<0.0001$) and non–invasive ventilation ($p=0.010$) than without respiratory support. After blood transfusion, ±50% had an estimated daily intake of DEHP above the tolerable daily intake (36µg/kg/d).

Conclusions

This study shows persisting NICU exposure of premature neonates to endocrine disrupting phthalates, despite changing legislation (MDR 2017/745). We’re the first to map neonatal exposure to APs. More immature children, especially with respiratory support and/or receiving blood products are at increased risk of phthalate exposure above reference levels.



DEHP metabolite concentrations (sumDEHPm) in neonatal urine samples after different medical equipment exposure. P–values are derived from the Mann–Whitney U test when comparing 2 groups, the Kruskal–Wallis for more groups.

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None declared

ID 188. RANDOMIZED CROSSOVER TRIAL TO COMPARE EFFECT OF DURATION OF SKIN TO SKIN CARE ON PRETERM NEONATAL PAIN CONTROL

Professor Vivek Shukla[2], Dr Pratik Trivedi[1], Dr Jaimin Patel[1], Professor Archana Nimbalkar[1], Professor Dipen Patel[1], Mr Ajay Phatak[1], **Professor Somashekhar Nimbalkar**[1]
[1]Bhaikaka University, Karamsad, India, [2]University of Alabama, Birmingham, USA

Background:
Preterm neonates who receive intensive care undergo multiple painful procedures as a part of their medical management. Skin–to–skin care (SSC) for 30 minutes before the painful procedure has been shown to provide effective pain control in preterm neonates. We tested the hypothesis that SSC for shorter durations will be as effective as that for 30 minutes for preterm neonatal pain control.

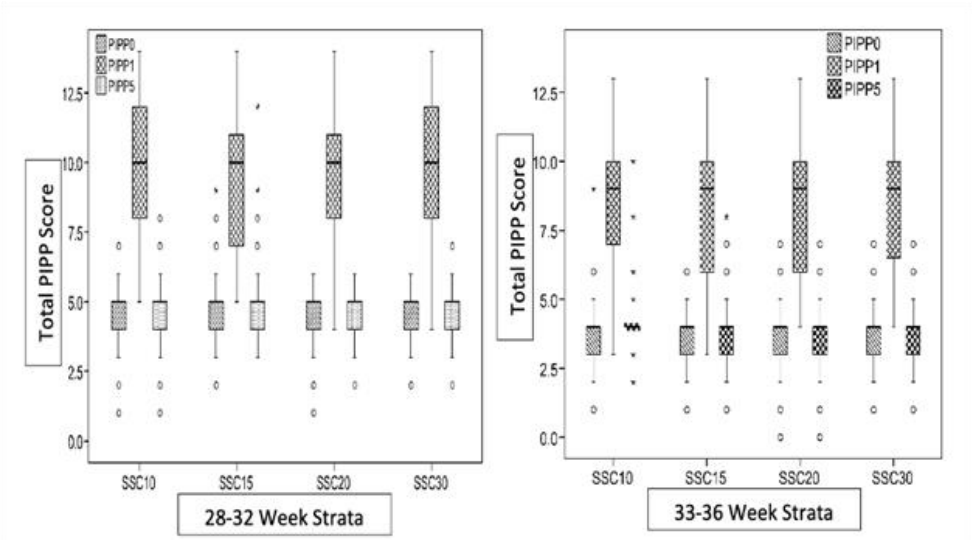
Methods:
Study participants were stratified as per the gestational age into two strata, 28–32 weeks and 33–36 weeks. All neonates requiring heel–stick for glucose monitoring admitted to the study NICU from January 2019 to December 2022 were eligible. Those on the ventilator, hemodynamically unstable, exposed to analgesic/sedative medications within the last 24 hours of the procedure, and neurologically impaired were excluded. SSC was given by mothers by crossover design for 10, 15, 20, and 30 minutes by random sequence allocation generated by a computer–based randomization software. Blinded PIPP scores assessments at 0, 1, and 5 minutes of heel–stick were done using video recording. A clinically significant PIPP score difference was defined as a difference of ⩾1 in the total PIPP score. The trial was registered at the Clinical Trials Registry of India, registration number: CTRI/2019/05/019428.

Results:

A total of 136 neonates (68/stratum) were enrolled. One infant in the 28–32 week strata was excluded as the later 2 heel–stick procedures were not clinically indicated. The male: female ratio was 1.4:1. The mean (SD) days after birth was 17.6 (11.5) days in the 28–32 and 8.3 (5.8) days in the 33–36 weeks strata. The mean (SD) birthweight was 1.38 (0.33) and 1.68 (0.27) kg in the 28–32 and 33–36 weeks strata, respectively. There was no clinically significant difference between groups for PIPP score at 0,1 and 5 minutes in both strata (Figure 1). The PIPP score at 5 minutes was not significantly different from that at 0 minutes in all groups in both strata.

Conclusion:

Skin–to–skin care for 10, 15, and 20 minutes were as effective as that for 30 minutes. The result of this study will help in providing effective pain control in preterm neonates for moderately painful procedures.



PIPP Score Distribution

PIPP Score Distribution

None Declared

ID 160. OBSERVATIONAL COHORT STUDY OF USE OF CAFFEINE IN PRETERM INFANTS AND ASSOCIATION BETWEEN EARLY CAFFEINE USE AND NEONATAL OUTCOMES

Dr Lisa Szatkowski[1], **Miss Sheeza Fateh**[1], Janine Abramson[1], Dr T'ng Chang Kwok[1], Dr Don Sharkey[1], Dr Helen Budge[1], Dr Shalini Ojha[1,2]

[1]University Of Nottingham, Nottingham, United Kingdom, [2]Neonatal Unit, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom

Objective

To quantify trends in caffeine use in infants born at <32 weeks' gestational age (GA), and to investigate the effects of early vs late caffeine on neonatal outcomes.

Study design

Retrospective propensity score matched cohort study using routinely recorded data from the National Neonatal Research Database of infants born at <32 weeks' GA admitted to neonatal units in England and Wales (2012—2020).

Results

89% (58 913/66 081) of infants received caffeine. In 70%, caffeine was started early (on the day of birth or the day after), increasing from 55% in 2012 to 83% in 2020. Caffeine was given for a median (IQR) of 28 (17—43) days starting on day 2 (1—3) and continued up to 34 (33—34) weeks postmenstrual age.

In the propensity score matched cohort of 13 045 pairs of infants, the odds of preterm brain injury (early caffeine, 2306/13 045 (17.7%) vs late caffeine, 2528/13 045 (19.4%), OR=0.89 (95% CI 0.84 to 0.95)) and bronchopulmonary dysplasia (BPD) (early caffeine, 4020/13 045 (32.8%) vs late caffeine, 4694/13 045 (37.7%), OR=0.81

(95% CI 0.76 to 0.85)) were lower in the group that received early caffeine compared with those who received it later.

Conclusions

Early use of caffeine has increased in England and Wales. This is associated with reduced risks of BPD and preterm brain injury. Randomised trials are needed to find the optimal timing of caffeine use and the groups of infants who will benefit most from early administration of caffeine.

None declared

ID 1044. IMPACT OF BEING BORN SMALL FOR GESTATIONAL AGE ON RENAL DRUG CLEARANCE

Doctor Anne van Rongen[1], Miss Pheline X.M. Remijn[1], Miss Nicole ter Laak[1], Doctor Elke H.J. Krekels[1], Doctor Swantje Völler[1], Professor Karel Allegaert[2,3,4], Professor Anne Smits[2,5], Doctor Elisabet I Nielsen[6], Professor Catherine M.T. Sherwin[7], Professor Michiel F. Schreuder[8], Doctor Robert B. Flint[4,9], Doctor Sinno H.P. Simons[9], Professor Catherijne A.J. Knibbe[1,10]

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Background:

The pharmacokinetics of drugs in neonates vary largely, as a result of variation in for instance gestational age (GA), birthweight, and postnatal age (PNA). Current research has not paid specific attention to neonates born small for gestational age (SGA) as compared to appropriate for gestational age (AGA) counterparts. We aim to determine the influence of being born SGA on the clearance (CL) and volume of distribution (Vd) of gentamicin and amikacin in neonates.

Methods:

We used already available datasets of patients treated with gentamicin or amikacin (Table 1). For both drugs, we used the previously published two compartment model [1,2] in NONMEM 7.4 and a covariate analysis was performed in which the influence of SGA (i.e. a birthweight less than the 10th percentile of the birthweight for their GA) and Z–score of birthweight for GA were tested, in addition to birthweight or GA and PNA, on CL and bodyweight on Vd.

Results:

After including SGA in the covariate model, in addition to birthweight and PNA, CL proved to be 19% higher in SGA neonates compared to AGA neonates for both gentamicin and amikacin ($p<0.001$, respectively). When SGA was added as covariate in the GA and PNA model, gentamicin and amikacin CL was significantly decreased with 30% and 32% ($p<0.001$), respectively, for SGA compared to AGA neonates. Overall, the birthweight and PNA + SGA model described the data significantly better than the GA and PNA + SGA model for both gentamicin and amikacin CL ($p<0.001$). In addition to bodyweight, SGA was not a covariate for Vd.

Conclusion:

Being small for gestational age has an important impact on the clearance of gentamicin and amikacin. If dosing is based on birthweight, CL for SGA neonates is 19% underestimated, potentially because the maturation for SGA neonates is further developed than predicted by their birthweight. If dosing is based on GA, CL for SGA neonates is 30% overestimated, probably because the maturation for SGA neonates is behind as predicted by their GA. These results imply that SGA should be included into dosing guidelines for renally cleared drugs in neonates.

Table 1: Patient demographics of the gentamicin and amikacin dataset.

	Gentamicin [4,5]	Amikacin [6–9]
Number of patients (n)	733	944
Gestational age (weeks)	35 (23-42.1)	32 (24-42)
Postmenstrual age (weeks)	35.29 (23.1-43.3)	33 (24-55)
Postnatal age (days)	3 (1-30)	3 (1-30)
Birthweight (g)	2390 (440-5240)	1780 (420-5420)
Bodyweight (g)	2385 (440-5420)	1920 (420-5420)
Co-administration of ibuprofen (n(%))	76 (10.4%)	52 (5.5%)
Small for gestational age (n(%))	84 (11.5%)	121 (12.8%)
Birthweight Z-score	0.11 (-4.1 - 4.8)	-0.17 (-3.4 - 4.0)

Values are expressed as median [range].

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None declared

Acknowledgements: This research is sponsored by STIMAG (Stichting Management Apothekers en de Gezondheidszorg)