P48

PRESCRIBING PATTERNS OF ANTI-ASTHMA MEDICATION IN CHILDREN AND ADOLESCENTS IN PRIMARY CARE IN FRANCE

¹I Naimi, ²F Tubach, ³S Guillo, ²A Ajrouche, ¹V Houdouin, ²Y De Rycke, ³F Kaguelidou*. ¹Department of Pediatric Pneumology, Hôpital Robert Debré, APHP, Paris, France; ²Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, IPLESP UMR-S1136, CIC 1421, AP-HP, Hôpital Pitié-Salpêtrière, Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacopépidémiologie, PARIS; ³Department of Pediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, APHP; Université Paris VII Diderot – ECEVE – Pres Sorbonne Paris Cité; INSERM CIC1426, APHP – University Paris 7, Paris, France

10.1136/archdischild-2019-esdppp.88

Background Little is known about the short and long-term therapeutic management of asthmatic children. The aim of this study was to assess the prescribing patterns of antiasthma drugs in primary care.

Methods This is a retrospective cohort study performed between January 2011 and December 2017 using the EGB (Echantillon Généraliste de Bénéficiaires) database, a 1/97th sample of the French national healthcare insurance system. Claims data for all individuals aged from 5 to 18 years' old who had received at least one antiasthma drug in the study period without any delivery in the previous 24 months and with 24 months of follow-up after first delivery, were analysed.

Results A total of 7,680 children and adolescents (68.6% aged 5–11, 31.4% aged 12–18 years) were delivered at least one antiasthma drug (ATC code R03) during study period. The majority (66%) did not redeem another prescription in the following year (occasional users), when 18.4% redeemed prescriptions twice (low users) and 15.6% ≥ 3 times (high users). Most users (67%) were delivered only one class of R03 per dispensing in the first year and short-acting β_2 -agonists (SABAs) were the most frequently dispensed drugs. However, 33.4% of users were not prescribed SABAs. During the second year, only 27% of first-year users redeemed R03 prescriptions: 15.8% among occasional users, 35.5% of low users and 64.7% of high users. Among low and high first-year users who redeemed R03 drugs during the second year, 39.7% did not use inhaled corticosteroids alone or in association to LABAs.

Conclusions A high proportion of children and adolescents that used antiasthmatic drugs, even on a regular basis, were not prescribed these drugs in the long term. This finding may correspond either to the widespread use of antiasthmatic drugs in indications other than asthma or to an important undertreatment of asthmatic children and adolescents.

Disclosure(s) Nothing to disclose

P49

A PHARMACOKINETIC EVALUATION OF ORAL CLAVULANIC ACID IN TERM NEWBORNS

¹FM Keijl*, ¹RF Kornelisse, ²NG Hartwig, ³J van der Sluijs, ⁴A van Driel, ²S Kenter, ⁵J Heidema, ⁶P den Butter, ⁷BCP Koch, ¹IKM Reiss, ¹K Allegaert, ¹GA Tramper-Stranders. ¹Erasmus MC – Sophia Children's Hospital; ²Franciscus Gasthuis and Vlietland, Rotterdam; ³Maxima Medical Center, Veldhoven; ⁴IJsselland Hospital, Capelle a/d IJssel; ⁵Sint Antonius Hospital, Nieuwegein; ⁶Ikazia Hospital; ⁷Erasmus Medical Center, Rotterdam, The Netherlands; ⁸KU Leuven, Leuven, Belgium

10.1136/archdischild-2019-esdppp.87

Background Clavulanic acid is an irreversible beta-lactamase inhibitor which has a weak antibacterial action. When combined with a beta-lactam antibiotic such as amoxicillin, it is

effective against a broad range of bacteria. Despite its widespread use, little is known on the mechanism of action and target levels. A few studies on oral clavulanic acid in adults are available reporting great variance (AUC median 4.99 mg·h/L [0.44–8.31])¹ and a short elimination half-time (1.08h).² Observations in neonates are currently lacking. We therefore evaluated the pharmacokinetics of oral clavulanic acid co-administered with amoxicillin in term newborns.

Methods As part of a multicenter RCT (Clinicaltrials.gov: NCT03247920) evaluating neonatal intravenous-to-oral switch therapy in probable bacterial infection, we measured serum levels in patients allocated to the intervention group. They switched to amoxicillin/clavulanic acid suspension (25/6.25 mg/kg tid), after 48 hours of intravenous penicillin/gentamicin. Two blood samples from different dosing intervals, were obtained and directly stored at -80°C. Initially, and to ensure that amoxicillin levels were attained as safety marker, levels in the second part of the timeframe (4–8 h after administration) were collected. For the second batch, peak levels (1–2 h after administration) were collected. Analysis was performed using Liquid Chromatography and Mass Spectrometry.

Results At submission, samples of the first 15 patients were analysed (first batch). Samples were collected 6.0 $\pm$ 1.3 h (mean, S.D.) after antibiotic administration. Clavulanic acid levels were detected in all patients but a great variance was observed (median: 1.4 mg/L; range: 0.20–4.82 mg/L). Extrapolation would lead to an AUC of at least 8.4 mg·h/L.

Conclusions Oral clavulanic acid is absorbed in term newborns, but great variance is seen in trough levels (4–8 h after administration). Extrapolation predicts at least an AUC comparable to those of adults. Peak levels in the first part of the time interval (0–4h) are needed to further build confidence on this conclusion.

REFERENCES

1. De Velde F, De Winter BCM, Koch BCP, Van Gelder T, Mouton JW, Consortium C-N. Highly variable absorption of clavulanic acid during the day: a population pharmacokinetic analysis. *J Antimicrob Chemother.* 2018;**73**(2):469–76.
2. Vree TB, Dammers E, Exler PS. Identical pattern of highly variable absorption of clavulanic acid from four different oral formulations of co-amoxiclav in healthy subjects. *J Antimicrob Chemother* 2003;**51**(2):373–8.

Disclosure(s) Nothing to disclose

P50

INDIVIDUAL VARIATIONS IN FENTANYL PHARMACOKINETICS AND PHARMACODYNAMICS IN PRETERM INFANTS

¹J Kindblom*, ²E Norman, ³A Rane, ²A-C Berg, ⁴U Schubert, ⁴B Hallberg, ^{2,5}V Fellman. ¹Sahlgrenska Academy, Institute of Medicine, Sahlgrenska University Hospital, Gothenburg; ²Clinical Science, Lund, Lund; ³Division of Clinical Pharmacology, Karolinska University Hospital Huddinge; ⁴Department of Neonatology, Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden; ⁵Children's Hospital, Helsinki, Helsinki, Finland

10.1136/archdischild-2019-esdppp.88

Background Fentanyl pharmacokinetics and pharmacodynamics are lacking in preterm infants. Our aim was to study these and their relation with a new formulation of fentanyl 5 mg/mL for procedural pain.

Methods Preterm infants were given 0.5 (n=20, median gestational age 26.5; range 23.3–34.1 weeks) and 2 mg/kg (n=8, 27.4; 25.3–30.7 weeks) fentanyl, respectively, before skin-breaking procedures or tracheal intubation. Blood samples were collected after ten minutes, two, four, eight and 24

hours. Physiologic parameters were monitored and pain scores assessed.

Results The median fentanyl concentrations were 0.18, 0.15, 0.15 and 0.57, 0.37, 0.35 ng/mL at 15–31 minutes, two and four hours and the half-lives were 1.6 to 20.5 or 4.1 to 32.6 hours for the low and high dose groups, respectively. A significant correlation was seen between weight at study inclusion and half-life (Spearman's $r = -0.9$, $p < 0.001$), volume of distribution ($r = -0.8$, $p < 0.01$) and clearance ($r = -0.9$, $p < 0.01$) in the low dose group ($n=9$). Pain assessment results were not correlated to pharmacokinetic variables. Fentanyl was well tolerated.

Conclusion The inter-individual variation of fentanyl pharmacokinetics is large in preterm infants and the dose of 0.5 mg/kg seems too small for skin-breaking procedures.

Disclosure(s) Nothing to disclose

P51

A COMBINED EXPERIMENTAL APPROACH TO ASSESS INTESTINAL DRUG ABSORPTION IN EARLY CHILDHOOD

¹M Kiss*, ²J Nicolai, ¹JMM van den Heuvel, ³R Mbasu, ⁴SM Botden, ¹JB Koenderink, ¹FGM Russel, ²A-L Ungell, ^{1,5}SN de Wildt. ¹Department of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, The Netherlands; ²Development Science, UCB Biopharma SPRL, Braine-l'Alleud, Belgium; ³Development Science, UCB Celltech, Slough, UK; ⁴Department of Surgery-Division of Pediatric Surgery, Radboud UMC-Amalia Children's Hospital, Nijmegen; ⁵Intensive Care and Department of Pediatric Surgery, ErasmusMC-Sophia Children's Hospital, Rotterdam, The Netherlands

10.1136/archdischild-2019-esdppp.89

Background Drug transporters and metabolizing enzymes located in the epithelial lining of the intestine limit or enhance systemic drug exposure. During child development, the abundance and activity of these transporters and enzymes - determining how fast and how much of a drug is being absorbed into the circulation - changes from birth to adolescence. As most drugs given to children are taken by mouth, the aim of this project is to study the abundance and activity of transporters and metabolizing enzymes, involved in the intestinal absorption of drugs.

Methods The *ex vivo* Ussing chamber with pediatric small intestinal tissue is applied to evaluate intestinal drug absorption and metabolism.¹ Transport and metabolism of a selection of drug molecules is assessed across these tissues by sampling the donor and receiver compartment at different intervals and sample analysis by LC-MS/MS. Viability, functionality and integrity of the tissues are monitored using electrophysiological parameters (dP, R, I). Ussing chamber experiments are combined with a targeted proteomics approach to quantify drug transporter and metabolizing enzyme abundance in these tissues.

Results An Ussing chamber method has been successfully set up using both adult and pediatric intestinal tissue. To date samples from three children of different ages have been evaluated and show promising results. Tissue from the same patients has been stored for proteomics analysis.

Conclusion The Ussing method presents an innovative, feasible approach to study active intestinal transport in children. Further studies are now underway to elucidate age-related variation in intestinal transport and metabolism.

REFERENCE

1. Sjöberg Å, Lutz M, Tannergren C, Wingolf C, Borde A, Ungell AL: Comprehensive study on regional human intestinal permeability and prediction of fraction

absorbed of drugs using the Ussing chamber technique. *Eur J Pharm Sci* 2013 Jan 23;48(1-2):166–80.

Disclosure(s) The collaboration project is financed by the Ministry of Economic Affairs by means of the PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public-private partnerships. Johan Nicolaï, Richard Mbasu and Anna-Lena Ungell are employees of UCB Biopharma SPRL.

P52

LOW AND ERRATIC EXPOSURE OF ORAL ACETAMINOPHEN IN CRITICALLY ILL CHILDREN DETERMINED WITH A ¹⁴C MICROTRACER STUDY: A CASE FOR IV ACETAMINOPHEN FOR ACUTE PAIN MANAGEMENT?

¹N Kleiber*, ²E Calvier, ³MG Mooij, ²EHJ Krekels, ⁴WH Vaes, ⁵AD Windhorst, ⁶H Hendrikse, ³D Tibboel, ²CAJ Knibbe, ⁷SN de Wildt. ¹Pediatrics and Clinical Pharmacology Unit, CHU Sainte-Justine, Montréal, QC, Canada; ²Leiden Academic Centre for Drug Research, Leiden University, Leiden; ³Erasmus MC – Sophia Childrens Hospital, Rotterdam; ⁴TNO, Zeist; ⁵Amsterdam University Medical Center; ⁶Vrije Universiteit Amsterdam (VU), Amsterdam; ⁷Department of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, The Netherlands

10.1136/archdischild-2019-esdppp.90

Background Despite being the most commonly used analgesic and antipyretic, oral APAP bioavailability has not been determined in children.

The aim of this study is to compare exposure after oral vs iv APAP using the PK data of the first pediatric oral bioavailability ¹⁴C microtracer study.

Methods

Design bioavailability microtracer population PK study

Participants patients < 6 yrs old in the pediatric ICU who received 15 mg/kg iv APAP q6h

Intervention a single microdose of ¹⁴CAPAP (3 µg/kg) given orally at the same time as a therapeutic iv dose

Data collection Blood was sampled 8 times up to 24 h post-dose

Data analysis population PK analysis using NONMEM. Based on the model, exposure after oral vs iv was compared by simulating the concentration-time profiles and C_{ss} (targeted: 10 mg/L ± 20% deviation).

3 doses were simulated: 15 mg/kg q6h oral and iv and 22.5 mg/kg oral q6h. 1000 simulations were performed and the percentage of patients reaching the targeted mean C_{ss} of 10 mg/L ± 20% were compared.

Results Oral bioavailability was 72% (range:11–91%). After 15 mg/kg APAP, the median simulated oral C_{ss} was subtherapeutic (6.5 mg/L), but therapeutic (10 mg/L) for IV dosing (15 mg/kg). Patients were 2.5 times less likely to reach therapeutic plasma concentrations with 15 mg/kg oral vs iv APAP.

With the maximal recommended oral doses of 22.5 mg/kg 6 h aimed to overcome the 72% bioavailability, median mean C_{ss} were therapeutic but overexposure and underexposure were more common than with iv (37 vs 32% C_{ss} < 8 mg/L and 30 vs 21% C_{ss} > 12 mg/L).

Conclusion Compared to IV, the usual (15 mg/kg) oral APAP doses result in low systemic exposure with subsequent risk of therapeutic failure. When oral doses are increased to overcome the low bioavailability, underdosing still occurs and over-dosing was observed in patients with high bioavailability. IV