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Oral Presentations

O-1 DOSING FOR TWO: PLACENTAL TRANSFER AND FETAL DARUNAVIR EXPOSURE

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Background Fetal drug exposure during pregnancy can be a determinant of fetal drug toxicity or efficacy. Fetal exposure is usually derived from the cord-to-maternal (ctm) concentration ratio. This static parameter does not provide information on the pharmacokinetics in utero, limiting the assessment of a fetal exposure-effect relationship. Pregnancy physiologically-based pharmacokinetic (p-PB-PK) modelling could provide a solution, although incor-poration of placental transfer remains challenging. Here, we aimed to include placental transfer parameters de-rived from an *ex vivo* human cotyledon perfusion model into a p-PBPK model, to quantitatively simulate fetal ex-posure to the antiretroviral agent darunavir, co-adminis-tered with ritonavir, at term.
Methods An existing and validated p-PBPK model of ma-ternal darunavir/ritonavir exposure was coded in Berkeley Madonna syntax to allow expansion with a feto-placental unit. Bidirectional placental transport of darunavir at term was included. In order to parameterize the model, we determined maternal-to-fetal (mtf) and fetal-to-maternal (ftm) darunavir/ritonavir placental clearances with an *ex vivo* human cotyledon perfusion model. Simulated ma-ternal PK profiles were compared with observed clinical data to verify the validity of the maternal model aspect. Next, population fetal PK profiles were simulated for different darunavir/ritonavir dosing regimens. These profiles were compared with available cord blood concen-trations *in vivo*. Additionally, we explored the influence of different DRV/r dosing regimens on fetal exposure and antiviral effects.
Results An average (±SD) mtf cotyledon clearance of 0.91 ±0.11 mL/min and ftm of 1.6±0.3 mL/min was de-termined (n=6 perfusions). Scaled placental transfer was included into a feto-placental unit and integrated in the p-PBPK model. For darunavir 600/100 mg twice daily, the simulated fetal plasma Cmax, Ctrough, Tmax and T1/2 at steady state were; 1.1 mg/L, 0.57 mg/L, 3 hours, and 21 hours, respectively. This indicates that the fetal population Ctrough is above the protein-adjusted EC90 for inhibit-ing the replication of wild type (0.20 mg/L) and around the EC90 for resistant virus (0.55 mg/L). The simulated ftm plasma concentration ratio (range) over a dosing interval was 0.30 (0.16–0.37), compared to a median (range) ratio for observed darunavir ctm plasma ratio of 0.18 (0–0.82; 0 reported if cord blood concentrations were below the lower limit of quantification [<0.09 mg/L] and hence no ratio could be determined).
Conclusion A p-PBPK model for maternal darunavir exposure was extended with a feto-placental unit. The simulated fetal darunavir plasma concentrations were in the range of observed cord blood concentrations. This advanced model provides a valuable tool in assessing the implications of new dosing regimens, optimising the safety of maternal pharmacotherapy and fetal antiretro-viral treatment.

O-2 POPULATION AND DEVELOPMENTAL PHARMACOKINETIC ANALYSIS TO EVALUATE AND OPTIMISE CEFOTAXIME DOSING REGIMEN IN NEONATES AND YOUNG INFANTS

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Background Cefotaxime is one of the most frequently prescribed antibiotics for the treatment of Gram-negative bacterial sepsis in neonates. However, the dosing regi-mens routinely used in clinical practice vary considerably. The objective of the present study was to conduct a population pharmacokinetic study of cefotaxime in neonates and young infants in order to evaluate and optimise the dosing regimen.
Methods An opportunistic sampling strategy com-bined with population pharmacokinetic analysis using NONMEM software was performed. Cefotaxime concentrations were measured by high-performance liquid chromatography tandem mass spectrometry. Developmental pharmacokinetics-pharmacodynamics, the microbiological pathogens, and safety aspects were taken into account to optimise the dose.
Results The pharmacokinetic data from 100 neonates (gestational age [GA] range, 23 to 42 weeks) were modeled with an allometric two compartment model with first-order elimination. The median values for clearance and volume of distribution at steady state were 0.12 litre/h/kg of body weight and 0.64 litre/kg, respectively. The covariate analysis showed that current weight, GA, and postnatal age [PNA] had significant impacts on ce-fotaxime pharmacokinetics. Monte Carlo simulations demonstrated that the current dose recommendations underdosed the older newborns. A model-based dosing regimen of 50 mg/kg twice a day to four times a day, according to GA and PNA, was established. The associated risk of overdose for the proposed dosing regimen was 0.01%.
Conclusion We determined the population pharma cokinetics of cefotaxime and established a model based dosing regimen to optimise treatment for neonates and young infants.

O-3 POPULATION PHARMACOKINETICS AND DOSING OPTIMISATION OF CEFTRIAXONE IN BURN INFANTS AND CHILDREN

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10.1136/archdischild-2017-esdppp.3

Background Ceftriaxone, a broad spectrum cephalosporin, used as first-line empirical antimicrobial therapy in burn children. Burn injury had shown significant impact on pharmacokinetics of antimicrobials. As paediatric data are limited, our aim was to evaluate the population pharmacokinetics of

ceftriaxone in burn infants and children and define the appropriate dose in order to optimise antimicrobial treatment.

Methods Blood samples were collected from paediatric patients treated with ceftriaxone and concentrations were quantified by HPLC-UV. Population pharmacokinetic analysis was performed using NONMEM software.

Results The data from 50 paediatric patients (age range: 0.6–4.8 years) were available for population pharmacoki-netic analysis. A one-compartment model with first-order elimination showed the best fit with the data. A covariate analysis identified that age and weight had significant im-pact on ceftriaxone pharmacokinetics. A dose regimen of 50 mg/kg/day every 12 hour for infants and 75 mg/kg/day every 12 hour for young children produces satisfactory target attainments, using the standard MIC of 0.5 mg/litre.

Conclusion The population pharmacokinetics of ceftri-axone was evaluated in burn infants and young children and an optimal dosing regimen was established based on simulation.

O-4 ANALYSIS OF VORICONAZOLE MONITORING DATA IN CHILDREN WITH ONCO-HAEMATOLOGICAL DISEASES

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10.1136/archdischild-2017-esdppp.4

Background Voriconazole (VCZ) is a triazole antifungal agent widely used in immunocompromised patients with suspected or proved invasive fungal infection. The achievement of therapeutic range (1–5 mg/L) is clinically important to maximise VCZ efficacy. Many factors are known to influence its pharmacokinetics characterised by a wide inter and intra-individual variability in trough concentrations (age, genotype, comedications.). VCZ is metabolised primarily by CYP2C19 producing the main metabolite, N-oxide VCZ, pharmacologically inactive but potentially responsible for the occurrence of toxicities. Polymorphisms on 2 C19 gene induce different phenotypes impacting the VCZ plasma levels. Our objectives are to evaluate the variability of voriconazole trough concentrations and identify practical issues to optimise and interpret such monitoring data in children and adolescents with oncohaematological disease.

Methods Children (<18 years old) with oncohaematological disease treated with VCZ for documented or suspected invasive fungal infection who had samples drawn for VCZ monitoring from January 2014 to December 2016 were included in the study. Demographic data (age, sex, weight, initial disease and biological parameters) were collected for each patient from medical prescription or informatic extraction. Indication of VCZ, detailed treatment and monitoring data were also collected. The statistical analyses were performed using SPSS v24.0. For some analysis, patients were divided in two group based on prescription recommendations: Group 1 (G1) included children<2 years, 2–12 years and 12–14 years<50 kg and Group 2 (G2) included adolescents>12–14 years>50 kg (instead of 40 kg) and adolescents>14 years>40 kg.

Results A total of 380 trough concentrations at steady state (C0,ss) were identified in 79 patients (46 girls and 33 boys), 126 concentrations had to be excluded (66 were not at steady state, 22 were not trough levels, 38 had incomplete medical or biological information). Median age at the initiation of VCZ was 9 (1–16.5) years. The majority of patients had acute leukaemia (60.8%) and received VCZ after allogenic hematopoietic stem cell transplantation. Median oral doses in G1 was 8.1 (2.5–13.8) mg/kg (n=38) vs 3.9 (2.4–6.0) mg/kg (n=13) in G2. Median intravenous doses in G1 was 7.8 (4.2–13.3) mg/kg (n=22) vs 3.7 (2.8–4.6) mg/kg (n=6) in G2. In the global cohort, 45.6% attain therapeutic range at first monitoring, 46.8% had C0,ss below 1 mg/L and 7.6% had C0,ss over 5 mg/L. Forty-one patients were treated with recommended doses but only 53% of them reach therapeutic range. There was no impact of age, sex, biological parameters, indication of VCZ on C0,ss values. The number of C0,ss in the therapeutic range increases with the number of monitoring per pa-tient following dosage adaptation.

Conclusion There is a wide variability in VCZ trough con-centrations and our data shows that conditions should be precisely defined. for optimal monitoring. It is necessary to identify factors which contribute to this variability to individualise treatment for each patient and to take them into consideration for establishing a standardised thera-peutic drug monitoring.

O-5 AMIKACIN DISPOSITION AND DOSING RECOMMENDATIONS IN NEONATES WITH PERINATAL ASPHYXIA TREATED WITH THERAPEUTIC HYPOTHERMIA (AMICOOL STUDY)

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Background Aminoglycosides are administered to treat (suspected) neonatal sepsis. The pharmacokinetics (PK) of this antibiotic class are expected to be different in neonates with perinatal asphyxia (PA) treated with therapeutic hypothermia (TH). Effective exposure of the aminoglycoside amikacin in neonates is achieved using a prospectively validated population PK mod-el-derived dosing regimen.[1] However, dosing adjustments in case of PA with TH are lacking. The aim of the current (AMICOOL) study was to further explore amikacin disposition in neonates by quantifying the impact of PA treated with TH on amikacin clearance and to provide dosing recommendations for this specific patient population.

Methods Amikacin therapeutic drug monitoring data were retrospectively collected from term neonates with PA treated with TH and admitted to the neonatal inten-sive care units of VUmc Amsterdam and the University Hospitals Leuven between 2010–2015. Data were added to the original published amikacin population PK dataset.[2] A data-driven covariate analysis was performed to assess the impact of PA treated with TH on amikacin clearance. Monte Carlo simulations facilitated the comparison of simulated amikacin exposures using the current dosing guidelines.[1] and proposed dosing adaptations for PA treated with TH. We hereby aimed to achieve optimal amikacin trough (<5 mg/L) and peak (>24 mg/L) levels. Stochastic simulations were used to investigate the differ-ences in exposure among typical neonates with PA and TH with varying birth weights (1965–4220 g).

Results Data of 55 neonates with PA treated with TH were added to the original amikacin population PK dataset of 930 neonates.[2] A 40.6% (RSE 9%) decrease in amikacin clearance for neonates with PA with TH was documented. Based on Monte Carlo simulations, the current dosing guidelines resulted in 40%–57% of neonates with PA and TH displaying amikacin trough concentrations

above the toxic trough level (>5 mg/L), while an additional increase of the dosing interval with 12 hours decreased this percentage to 14%. Stochastic simulations showed that among typical neonates the percentage of patients with trough concentrations>5 mg/L ranges 14% to 25%.

Conclusion In neonates with perinatal asphyxia treated with therapeutic hypothermia, amikacin clearance is reduced with 40.6%. Based on simulations, an additional prolongation of the dosing interval with 12 hours results in optimised amikacin exposure and reduces toxicity in this specific population. As a future perspective, the model-based dosing proposal needs prospective validation. Since amikacin can be used as a surrogate for glomerular filtration, clearance of other drugs using the same elimination route could also be reduced in case of perinatal asphyxia treated with therapeutic hypothermia and may require further dosing adaptations.

Co-authors * Both authors A. Smits and S. Cristea contributed equally

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O-6 HYPERFILTRATION IN THE PAEDIATRIC INTENSIVE CARE UNIT (HYPIC) A PILOT STUDY

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Background Hyperfiltration refers to the enhanced re-nal elimination of circulating solute. It is an increasingly recognised phenomenon in critically ill adults, leading to subtherapeutic treatment of renally cleared drugs. Although its existence has also been suggested in critically ill children, concrete data are currently lacking.

Objectives The primary aim of this pilot study was to investigate the incidence and risk factors of hyperfiltration in a paediatric intensive care setting. Additionally, a comparison of different methods for glomerular filtration rate (GFR) assessment in critically ill children was made.

Methods The HYPIC study was a single centre, prospective, observational study, conducted at the paediatric intensive care unit (PICU) and the cardiac surgery intensive care unit (CSICU) of the Ghent University Hospital, Belgium, enrolling patients between 1 month and 15 years of age. GFR was estimated by means of a calculated 24 hour creatinine clearance (24 hour CrCL). Creatinine in serum and urine were determined using the Jaffe's reaction, and corrected for interfering total protein concentration accord-ing to Speeckaert et al.[1] The Larsson formula was used for cystatin C-based estimation of GFR.[2] Hyperfiltration was defined as a GFR exceeding normal values for age plus two standard deviations. Logistic regression analysis was used to evaluate risk factors for hyperfiltration. GFR assessment methods (24 hour CrCl, modified Schwartz formula and Larsson formula) were compared using Bland-Altman plots.[3]

Results Data were collected from 58 patients (median age: 20 months; age range: 1 month to 15 years). Hyper-filtration was present in 80.8% of patients. Body length was identified to be an independent risk factor for hyper-filtration (p=0.05). Although not statistically significant, body surface area (p=0.12) and a neurological admission reason (p=0.12) also seem related to the development of hyperfiltration. A systematic difference between calcu-lated creatinine clearance (24 hour CrCL) and the estimated GFR (eGFR) using the modified Schwartz formula was observed (mean difference 28.9 ml/min/1.73 m²; SD60.4 ml/min/1.73 m²). The Schwartz formula was accurate at low GFR, but underestimated the GFR at higher values. The mean difference of GFR between the Larsson formula and the 24 hour CrCl was very low (3.67 ml/kg/m²; SD66.9 ml/min/1.73 m²).

Conclusion Hyperfiltration is a common phenomenon in critically ill children. The modified Schwartz formula is likely to underestimate GFR in case of hyperfiltration. Cystatin C seems a promising alternative renal biomarker but needs further investigation.

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O-7 VASOPRESSIN AND TERLIPRESSIN FOR REFRACTORY SHOCK IN NEONATES AND CHILDREN: SYSTEMATIC REVIEW META-ANALYSIS AND TRIAL SEQUENTIAL ANALYSIS

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Background Vasopressin (AVP) and terlipressin (TP) have been used as last line therapy in refractory shock in children. However, the efficacy and safety of AVP and TP were not determined these populations. We aimed to assess the efficacy and safety of AVP/TP in paediatric re-fractory shock.

Methods We conducted a systematic review, meta-analysis, and trial sequential analysis (TSA). AVP and TP, were compared with conventional therapy. MEDLINE, EMBASE, Cochrane Library, and ClinicalTrials.gov were searched up to February 2016. Reports of clinical trials were pooled using random-effects models and TSA. Main outcomes were mortality and tissue ischemia.

Results Three randomised control trials and five 'be-fore-and-after clinical' trials met the inclusion criteria. Among 224 neonates and children, with refractory shock, 152 received therapy with AVP or TP. Pooled analyses, showed no association between AVP/TP treatment and mortality (relative risk (RR),1.19; 95% CI, 0.71–2.00), length of stay in the paediatric intensive care department (PICU) (mean difference (MD), −3.58 days; 95% CI, (−9.05) −1.83) and events of tissue ischemia (RR, 1.48; 95% CI, 0.47–4.62). In TSA, no significant effect on mortality and developing tissue ischemia was observed with AVP/TP therapy.

Conclusion AVP/TP therapy was not associated with a decreased risk for mortality and for length of stay in PICU. Furthermore, in TSA, a trend for an association with an increased risk for ischaemic events was observed. Our study suggests that further large studies are necessary to demonstrate and establish benefits of AVP/TP in children.

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O-8 THE PHARMACOKINETICS OF FENTANYL AND ITS DERIVATIVES IN CHILDREN – A COMPREHENSIVE REVIEW

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Background Fentanyl and its newer derivatives sufen-tanil, alfentanil and remifentanil are strong opioid anal-gesics frequently used in pediatricpatients. Despite this extensive use insufficient information on the PK of these drugs in neonates, infants, children and adolescents is available. The goal of this analysis was to perform a thor-ough review of the PK properties of fentanyl and its deriv-atives in children of all age groups.

Methods PubMed was searched using specific terms re-lated to the pharmacology of fentanyl and its derivatives in the paediatric population. Original articles and reviews regarding the PK, PD, efficacy and safety were included. A meta-analysis of PK data was conducted using a ran-dom effects model. Individual PK data was re-analysed for subgroups.

Results Of the retrieved 372 articles, clinical studies were the most frequent, followed by case series, case and short reports, and reviews. Fentanyl and its derivatives show a satisfactory safety profile in children. Forty four eligible PK studies contained data from 821 paediatric patients, including more than 46 preterm infants, 64 neonates, 115 infants and toddlers, 188 children, and 28 adolescents. Special populations comprised preterm infants, children with chronic renal or liver disease, undergoing extracor-poreal circulation, or with obesity. Pooled mean fentanyl clearance (CL) was 14.56 (95% CI 12.16, 16.74) mL/min/kg and volume of distribution (Vd) was 5.46 (2.64, 10.27) L/kg. Mean sufentanil CL was 19.43 (12.77, 26.09) mL/min/kg and Vd was 2.39 (1.63, 3.15) L/kg. Alfentanil CL was 6.23 (4.44, 8.02) mL/min/kg and Vd was 0.57 (0.42, 0.72) L/kg. There was only weak correlation between body weight (BW) and both CL and Vd of fentanyl ($r2=0.22$ and $r2=0.43$, $p=0.0054$ and $p<0.0001$) in preterm infants, neonates and young infants. Sufentanil CL correlated strongly with BW ($r2=0.67$, $p<0.0001$) and age ($r2=0.62$, $p<0.0001$). Alfen-tanil CL exhibited strong correlation with both age and BW ($r2=0.71$ and 0.72, both $p<0.0001$). There was an iden-tical correlation with both age and BW for Sufentanil Vd (both $r2=0.81$, $p<0.0001$) and Alfentanil Vd (both $r2=0.59$, both $p<0.0001$). While remifentanil CL correlated equally strong with age and BW ($r2=0.73$ vs. 0.69, both $p<0.0001$), BW had a greater impact on the Vd than age ($r2=0.73$, vs. 0.63, both $p<0.0001$).

Conclusion There are profound differences between the fentanyl derivatives and their PK correlations with BW. Fu-ture studies should be designed to assess the PK and PD of fentanyl and its derivatives in all paediatric subpopulations.

O-9 PAEDIATRIC PBPK MODELLING OF PROPOFOL USING THE MIDDLE OUT APPROACH

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Introduction The project SAFEPEDRUG aims to pro-vide guidelines for drug research in children, based on bottom-up and top-down approaches. Propofol, one of their model compounds, is extensively metabolised in liver and kidney.[1] and, being a lipophilic molecule, dis-tributed into fat tissues, from where it redistributes into the circulation.[2] In the past, both bottom-up (PBPK)[3] and top-down approaches (popPK)[4] were applied to describe the PK of this compound. In this work, a combi-nation of the two (middle-out approach) was applied to describe propofol PK in children.

Methods Data from different trials were analysed using a 3-compartment-model in NONMEM. *In vitro* metabolism data was generated using the methodology from Gill et al.[5] All data was then described using a full PBPK model in SimcypV16. *In vivo* clearances were either obtained starting from *in vitro* clearance or scaled back from the *in vivo* clearance values estimated using NONMEM. Once an accurate *in vivo* clearance was obtained, the adult mod-el was scaled to paediatrics and the resulting model was challenged with paediatric data.

Results A CL of 1.07 L/h/kg and Vd of 822L were esti-mated using the population approach. *In vitro* CLint val-ues were consistent with literature, and an IVIVE would thus result in the same underprediction of total CL as described before. Therefore, the published model[3] was examined to see which parameters could increase the predicted CLiv. It was found that estimating the B:P and fu resulted in a predicted average CLiv of 1.01 L/h/kg compared to 0.39 L/h/kg before. Using the retrograde approach based on literature data, a match between pre-dicted CLiv and NONMEM-derived CL was obtained. The model performed better than previous models and was able to describe PK for both long-and short-term infu-sions in adults. Extrapolation to children gave better results compared to bottom-up or top-down models.

Conclusion In the past, PBPK and PopPK have mostly been used side by side to describe PK. However, a better result is achieved if both are combined. When studying a complex ADME compound such as propofol, a PBPK approach is often recommended. However, current *in vitro* systems and IVIVE are not yet optimised for these complexities. Therefore, the best strategy is to integrate *in vivo* data with *in vitro* studies. Once an adult PBPK model is built, it can be scaled to children using knowledge of the ontogeny and maturation, which implies a correctly predicted contribution of each subsystem to the systemic clearance.

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0-10 AN OBSERVATIONAL STUDY ON PLASMA PROTEIN BINDING AND TARGET ATTAINMENT OF TEICOPLANIN IN CRITICALLY ILL CHILDREN

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Background The objectives of this study were (i) to document teicoplanin plasma protein binding and, (ii) to evaluate target attainment rates using commonly used PK/PD targets in critically ill children.
Methods Patients, admitted to the PICU in whom treat-ment with intravenous teicoplanin (10 mg/kg every 12 hour for 3 loading doses, followed by 6–10 mg/kg once daily) was indicated, were enrolled. Blood samples were collect-ed during first and/or assumed steady-state dose inter-vals. Noncompartmental analysis was used to estimate the (free) AUC24h for first and SS doses. Evaluated PK/PD targets included AUC/MIC $\geq$750 hour, free AUC (fAUC)/MIC

$\geq$75 hour and total trough plasma concentration (Cmin) $\geq$10 mg/L. Correlation was assessed by means of a scatter plot and Spearman's Rank Correlation Coefficient.
Results 130 plasma samples were collected from 27 pa-tients (median age: 2.2 years; IQR: 0.8–4.8 years). The free teicoplanin fraction (n=26; median: 8.6%; IQR: 7.0%–11.7%) only varied slightly between patients. The targets of AUC/MIC (median: 823 hour; IQR: 702–949 hour) and fAUC/MIC (n=26; median: 72 hour; IQR: 55–86 hour) were achieved in 63% and 42% of patients respectively. The target Cmin (median: 16.0 mg/L; IQR: 10.3–17.9 mg/L) were reached in 78% of patients. Cmin correlated well with AUC/MIC (Spearman's Rank Correlation Coefficient R=0.84; p<0.01); fAUC/MIC and AUC/MIC did not (Spearman's Rank Correlation Coef-ficient R=0.36; p>0.05).
Conclusion Currently used teicoplanin dosing regimens frequently resulted in an AUC/MIC ratio and Cmin be-low widely accepted PK/PD targets. The fAUC/MIC ratio resulted in the lowest target attainment, despite plasma protein binding was similar to adults. Overall, target at-tainment rates varied widely depending upon the type of PK/PD target used. Future study is needed to define appropriate PK/PD indices in children.

0-11 MATURATION OF HUMAN HEPATIC MEMBRANE TRANSPORTER PROTEINS IN THE FIRST FOUR MONTHS OF LIFE

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Background Hepatic membrane-embedded proteins are involved in trafficking endogenous and exogenous compounds and may influence the pharmacokinetics of drugs. Transporter-specific age-related changes in pro-tein abundance were found in a pilot study (n=24), but now we aimed to elucidate the exact developmental pat-tern of clinically relevant hepatic transporters in a larger cohort of 63 fetuses, preterm and term neonates and in-fants and compare it with adults.
Methods Protein expression of BCRP, BSEP, GLUT1, MCT1, MDR1, MRP1-3, NTCP, OCT1, OATP1B1, OATP1B3, and OATP2B1 was quantified using UPLC-MS/MS, on snap-fro-zen post mortem fetal and infant liver samples and adult surgical liver samples. Protein expression was quantified in isolated crude membrane fractions. Pairwise compar-ison Kruskal-Wallis test was used to analyse a possible age-related difference.
Results Thirty-six fetal [median GA 23.4 weeks (range 15.3–41.3), no PNA], 12 premature neonatal [GA 30.2 weeks (24.9–36.7), PNA 1.0 weeks (0.14–11.4)], 11 term neonatal [GA 40.0 weeks (39.7–41.3), PNA 4.14 weeks (0.29-18.1)], 4 paediatric [PNA 4.13 years (1.08–7.44)] and 8 adult liver samples were studied. Expressions of BCRP, MCT1, OATP1B3, and OATP2B1 were similar in all age groups. MDR1, MRP1, MRP2, MRP3 and OCT1 expressions were low in fetus and high in adults (all p<0.05). Expression of BSEP increased from fetal to term newborn and to adult age (both p<0.01) and of NCTP increased over the whole age range (all p<0.05). GLUT1 and OATP1B1 expressions were high in fetuses and decreased towards newborns age (both p<0.01). GLUT1 expression decreased further in children's and adult age (both p<0.05).
Conclusion These data further delineate transporter specific changes in protein abundance across the first months of age.

0-12 THE INFLUENCE OF PATIENT COVARIATES ON INSULIN DOSE-REQUIREMENTS IN CHILDREN NEWLY DIAGNOSED WITH TYPE 1 DIABETES MELLITUS

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Background Type 1 diabetes mellitus (T1DM) is a com-mon chronic illness of childhood. Insulin is the mainstay of therapy and in order to maintain glycaemic control, the dose is adjusted frequently based on the patient's blood glucose until a stable dose is achieved. Guideline recommendations in regard to the initial total daily dose of insulin (TDD) at new onset of disease vary two-fold (0.5 to 1.0 IU/kg/day). The aim of the study was to identify the influence of patient covariates on the dose-requirement of insulin in newly diagnosed children and adolescents with T1DM.
Methods A retrospective chart review of children admit-ted to hospital over a five-year period due to new onset T1DM was undertaken. Demographic, clinical, insulin dosing, and laboratory data were recorded. The influence of patient characteristics on insulin TDD was analysed sta-tistically by performing univariate and multivariate linear regression analyses.
Results Clinical and insulin administration records for 70 patients were available for analysis. The median age of subjects was 9 years and median duration of admis-sion was 6 days. The median insulin TDD on first day of admission was 21 units (0.7 U/kg) and that of the day be-fore discharge was 27 units (1 U/kg). In the multivariate regression analysis, body size (total body weight and fat-free mass), HbA1C, and blood

ketone concentration were found to be significant predictors for the target TDD ($p<0.05$).

Conclusion In addition to body weight, HbA1c and ke-tone concentrations may be helpful in calculating initial TDD in newly diagnosed children with T1DM. This will potentially decrease the number of days needed to reach a stable dose and result in improved early glycaemic control. These findings may be used to study a larger cohort of patients in order to quantify the influence of these co-variates on dose-requirements.

O-13 FACTORS IMPACTING UNBOUND VANCOMYCIN CONCENTRATIONS IN NEONATES AND YOUNG INFANTS

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Background Vancomycin, a glycopeptide, is often ad-ministered to treat (suspected) serious gram-positive in-fections caused by Staphylococci, including methicillin-re-sistant Staphylococcus aureus (MRSA) and coagulase-neg-ative Staphylococci (CoNS). Vancomycin pharmacokinetic (PK) and pharmacodynamic (PD) data in neonates are based on total concentrations. However, only unbound vancomycin is pharmacologically active and available for elimination. The objective was to determine vancomycin protein binding and the covariates impacting unbound vancomycin concentration in neonates and young infants.

Methods Neonates and young infants, admitted to the neonatal intensive care unit of the University Hospitals Leuven to whom vancomycin was administered inter-mittently for medical indications, were considered for inclusion after parental informed written consent. In our unit, each vancomycin dose (15 mg/kg) is intravenously administered over 60 min. The dosing interval de-pends on postmenstrual age and plasma creatinine.[1] Total and unbound vancomycin plasma concentrations were determined using a validated LC-MS/MS method.[2] Sampling occurred randomly during vancomycin ex-posure, covering a broad range of vancomycin concen-trations. Impact of covariates on unbound vancomycin concentration was determined using Spearman correla-tion, linear regression or Mann Whitney U test. Significant results of the univariate regression were entered in a mul-tiple regression.

Results Thirty-seven samples in 33 patients [median (in-terquartile range) gestational age 35 (29-39) weeks and postnatal age 14 (8-29) days] were collected. Median total and unbound vancomycin concentrations were 14.3 (7.4–20.6) and 13.6 (7.2–22.5) mg/L, respectively. Median un-bound fraction was 0.90 (0.77–0.98). Multiple regression re-vealed total vancomycin concentration ($\beta=0.88$, $p<0.001$) and albumin ($\beta=-0.32$, $p=0.007$) as most important covari-ates of unbound vancomycin concentrations, resulting in an R^2 adjusted of 0.95 ($p<0.0001$). Unbound vancomycin concentration (VAN) can hereby be predicted using the formula: Unbound VAN (mg/L) =0.88 x total VAN (mg/L) – 0.32 human albumin concentration (g/L)+10.61.

Conclusion The unbound vancomycin fraction in neo-nates is higher compared to children and adults and total vancomycin concentration and albumin were the most important covariates of unbound vancomycin concen-tration. Integration of protein binding in future PK/PD analyses is appropriate to optimise vancomycin dosing and to determine population-specific vancomycin PD targets for neonates.

O-14 NEONATAL CARDIOVASCULAR AND CEREBRAL FUNCTION AFTER ANTENATAL MATERNAL EXPOSURE TO MAGNESIUM SULFATE

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Background Low dose antenatal magnesium sulfate (MgSO4) was found to be an effective neuroprotective intervention. However there is evidence from animal and clinical studies that high dose magnesium can have detri-mental effects to the foetal brain. Optimal dose and duration of magnesium treatment are still unknown although PK models have been described. The aim of this study was to explore associations between antenatal magnesium exposure, neonatal magnesium levels, neonatal ce-rebral and echocardiographic biomarkers.

Methods This is a prospective observation study re-cruiting preterm neonates 24–28+6 weeks' gestation and postnatal age ≤72 hours. Echocardiography (PDA severity score), cranial ultrasonography [grade of intraventricular haemorrhage (IVH)], amplitude integrated electroen-cephalogram (aEEG) (Burdjalov score a composite score for the measurement of cerebral maturity) and near in-frared spectroscopy [cerebral tissue oxygenation index (cTOI)] were measured during the transitional period and associated with neonatal magnesium levels.

Results 51 infants were included with median gestation-al age of 26.6 weeks [Interquartile range (IQR) 25.7–28] and median birth weight (BW) of 900 grams (IQR 760–1,080). Thirty three mothers (65%) received antenatal magne-sium sulphate for neuroprotection (included seven who had preeclampsia) and eighteen (35%) did not receive. The median duration of magnesium sulphate infusion was 7.5 hours (IQR 3–12). Neonates exposed to antenatal magnesium had significant higher magnesium levels in the first two days after birth ($p<0.001$). Duration of an-tenatal magnesium exposure was also significantly cor-related with neonatal magnesium levels in the first three days of life (Day 1, $p<0.001$, $R2=0.774$). There was a signifi-cant negative correlation between maternal weight and body mass index (BMI) and neonatal magnesium levels on second and third day of life (Day 2: $p=0.005$ and 0.013 respectively). Higher gestation and birth weight was also associated with higher neonatal Mg levels on third day of life ($p=0.008$ and 0.012 respectively). Mg did not have any significant effect on echocardiographic biomarkers. Neonatal Mg levels on second and third after birth were correlated with cerebral tissue oxygenation and Burdjalov score. Infants with a higher serum Mg on Day 3 were more likely to have normal cranial scan result ($p=0.017$). A model was created using MgSO4 administration, BW, maternal BMI as the main background demographics parameters which may have significant effect on the cerebral and cardiovascular biomarkers and severity of cerebral injury.

Conclusion As expected, antenatal MgSO4 had signif-icant effects on neonatal magnesium levels. Maternal BMI and neonatal BW have significant impact on neona-tal Mg levels and possibly on clinical outcomes. Further dose-finding studies should be based on multicompart-mental population PK studies that include maternal and neonatal PD measures.

O-15 POPULATION PHARMACOKINETIC MODELLING OF PARACETAMOL AND ITS TWO MAJOR METABOLITES AFTER CARDIAC SURGERY IN CHILDREN WITH AND WITHOUT DOWN SYNDROME

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Background Nearly half of children with Down Syn-drome (DS) who undergo cardiac surgery, receive parac-etamol as part of their post-operative pain treatment (Fudge et al., 2010). Differences have been reported in paracetamol metabolism in children with or without DS (Griener et al., 1990). The aim of the study was to deter-mine the population pharmacokinetics of intravenous paracetamol after cardiac surgery and the elimination through the major metabolic pathways in two groups of children – those with and those without DS.
Methods The model was based on 483 plasma sam-ples from 30 children of whom 17 (median age 176 days [92-300] and bodyweight 6.1 kg [4.2–12.9]) had DS and 13 (median age 204 days [105-944] and bodyweight 5.9 kg[4.0–8.2]) did not. All received three paracetamol dos-es of 7.5 mg/kg (<10 kg) or 15 mg/kg (>10 kg) at 8 hour-ly intervals. Population pharmacokinetic modelling for paracetamol, paracetamol-sulfate and paracetamol-glu-curonide was performed using NONMEM 7.2. One, two and three compartment models were evaluated and the influence of different covariates such as age, bodyweight, cardiopulmonary bypass time and DS was investigated. Model selection criteria were statistical significant de-crease in objective function and evaluation of diagnostic plots.
Results All compounds were best described with a one-compartment model, in which clearance (Cl) in-creased linearly with bodyweight. Volume of distribution (Vd) was not statistical significantly influenced by any covariates. The population value [relative standard er-ror] for paracetamol Cl and Vd were (27.6 ml/min/6.1 kg [22%]) and (7560 ml/6.1 kg [19%]) respectively. For parac-etamol-sulfate and paracetamol-glucuronide Cl and Vd were 23 [29%] and 1590 [33%], and 68.1 [25%] and 5330 [7%] respectively. DS did not have a statistically significant influence on any model parameter for any of the com-pounds.
Conclusion Population pharmacokinetic analysis re-vealed that bodyweight influenced clearance of parac-etamol, paracetamol-sulfate and paracetamol-glucuro-nide in children from 3–36 months of age. However, no statistically significant differences in any of the pharma-cokinetic parameters of paracetamol between children with and without DS after cardiac surgery were observed. As paracetamol is also metabolised through cytochrome P450 2E1 oxidation, the following step will be to incorpo-rate these metabolites in this model to evaluate potential differences in paracetamol metabolism between children with or without DS.

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O-16 LEAN BODY WEIGHT BASED DOSING ACHIEVES COMPARABLE SYSTEMIC PANTOPRAZOLE EXPOSURES FOR NORMAL-WEIGHT AND OVERWEIGHT/OBESE CHILDREN

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Background We previously reported increased AUCtot and decreased CL/F for the commonly prescribed pro-ton pump inhibitor (PPI) and CYP2C19 substrate, pan-toprazole, in obese vs. non-obese children. In light of increasing concerns regarding adverse events associated with high systemic exposure to PPIs in children (e.g., os-teopenia, infection, micronutrient deficiencies), we aimed to identify a pantoprazole dosing strategy appropriate for overweight/obese children, who are six times more likely to suffer from gastroesophageal reflux disease and require PPI therapy than normal weight peers. Given that most physiologic metabolic processes occur in lean body tissues, lean body weight (LBW) based doing was implemented in this prospective paediatric pharmacokinetic investigation.
Methods 62 children (6–17 years of age; 39% Female), genotyped for CYP2C19 *2, *3, *4, *17 alleles (TaqMan), received a single oral dose of pantoprazole (1.2 mg/kg lean body weight). LBW was calculated via the Janmahasatian equation. Plasma pantoprazole and metabolite concen-trations were measured (HPLC-UV) at 10 time-points, over 8 hours, and pharmacokinetic parameters (PK) generat-ed via non-compartmental techniques (Kinetica 5.0). For children with at least one wild-type CYP2C19 allele (*1), select pantoprazole PK were compared in normal-weight (Body Mass Index (BMI) 10-84th% for age; n=29) and over-weight/obese (BMI ≥85th % for age; n=30) children, using independent student t-test (SPSS v23; α=0.05).
Results No statistically significant differences were observed for pantoprazole AUCtot in normal-weight (13.9±32.2 μMolar*h) vs. overweight/obese (14.68±31.03 μMolar*h) children (p=0.9). No statistically significant dif-ferences in pantoprazole CL/F (23.9±16.6 vs. 19.8±25.8 L/h; p=0.5) or Cmax (5.66±3.8 vs. 7.76±4.4 uMolar; p=0.06) were observed between normal-weight and overweight/obese children.
Conclusion LBW, rather than total body weight, based dosing is most appropriate to achieve comparable sys-temic exposures to pantoprazole for normal-weight and overweight/obese children. This dosing strategy appears to eliminate the systemic pantoprazole overexposure previously observed in obese children and will likely min-imize their risk for adverse events associated with high-dose PPI therapy. Future pharmacokinetic-pharmacody-namic studies of PPIs may be warranted for overweight and obese children.

O-17 TRANSPLACENTAL TRANSPORT OF PARACETAMOL AND ITS METABOLITES USING THE EX-VIVO HUMAN PLACENTA PERFUSION MODEL

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Background In Europe, 50%–60% of pregnant women uses paracetamol (Dafalgan). While its use in pregnan-cy was considered safe, recent studies show an associ-ation between prenatal exposure to paracetamol and increased incidences of autism, cryptorchidism, asthma and attention deficit hyperactivity disorder in a dose and duration dependent manner1-3. Data on transplacental transfer and metabolism of paracetamol are limited.

Methods In an *ex vivo* placenta perfusion model (closed circuit) (n=38), maternal-to-fetal and fetal-to-maternal transplacental transfer of paracetamol (PCM) and its me-tabolites, paracetamol sulfate (PCM-S) and paracetamol glucuronide (PCM-G), was determined at a concentration corresponding to the maximum (PCM: 30 µg/ml; PCM-S: 10 µg/ml; PCM-G: 25 µg/ml) and steady state (PCM: 10 µg/ml; PCM-S: 5 µg/ml; PCM-G: 12.5 µg/ml) plasma con-centrations in normal clinical use. Antipyrine 100 µg/mL was added as internal control. PCM, PCM-S, PCM-G and antipyrine concentrations in perfusion medium and pla-cental tissue were determined using HPLC and LC-MS.

Samples were taken at 0, 3, 6, 10, 15, 20, 30 min then ev-ery 15 min until 150 min followed by every 30 min until 210 (PCM) or 360 min (PCM-S and PCM-G). Fetal-to-ma-ternal and maternal-to-fetal ratios were normalised for antipyrine for each time point. Tissue accumulation and recovery of the compounds was calculated. Statistical dif-ferences were assessed using ANOVA.

Results The maternal-to-fetal as fetal-to-maternal trans-port of PCM was 44%–48%. For PCM-S, transplacental trans-fer was 38%–40% for maternal-to-fetal transfer and 28% for fetal-to-maternal transfer. PCM-G had a transfer of 31%–36% for maternal-to-fetal and 25% for fetal-to-maternal transfer. An equilibrium between the maternal and fetal concentrations was reached for PCM after 210 min for perfusion from maternal-to-fetal circulation. Fetal-to-ma-ternal transport of PCM-S and PCM-G was significantly slower then maternal-to-fetal transport. Extrapolation of maternal-to-fetal transport data till 360 min predict-ed equilibrium at 7.5 hour (PCM-S) and 9.5 hour (PCM-G). For fetal-to-maternal transport extrapolation of data till 210 min (PCM) and 360 min (PCM-S and PCM-G) predict-ed equilibrium for PCM after 270 min, PCM-S 36 hour and PCM-G 44 hour. PCM-S and PCM-G were converted to PCM by the placenta during the perfusions.

Conclusion This study shows that PCM rapidly crosses the placental barrier via passive diffusion for both mater-nal-to-fetal and fetal-to-maternal transplacental transfer. PCM-S and PCM-G, larger and more hydrophilic mole-cules, cross the placenta at a significantly lower rate. For PCM-S and PCM-G fetal-to-maternal transport is signifi-cantly slower than maternal-to-fetal transport.

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O-18 CLINICAL STUDIES AT-HOME: FEASIBILITY OF DATA AND SAMPLE COLLECTION IN PAEDIATRIC PAIN MANAGEMENT AFTER TONSILLECTOMY (TOMACHI)

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Background Clinical studies in children are challenging, yet they are necessary to improve current therapeutic strategies. The success of 'care-at-home' initiatives sug-gests their potential to be adapted to paediatric clinical trial settings. This pilot aims to study the feasibility of such a patient-centred, innovative model for clinical research in children.

Methods This was a single-centre, prospective pilot study in children undergoing elective tonsillectomy at the University of Basel Children's Hospital. Tonsillectomy as a model population had been chosen due to the fre-quency of this surgical procedure performed in this age group requiring standardised pain management with distinct inpatient (2–4 days) and at-home phases. Data on pain scores and concomitant medication and saliva samples were collected by caregivers on 2–4 inpatient study days with the support of study nurses and on 3 consequent study days at home. A specifically developed mobile application supported data collection. The prima-ry endpoint was the proportion of complete and correct caregiver-collected clinical data (pain score) and saliva samples in the at-home setting. Secondary endpoints included practicability, and the proportion of caregivers consenting to take part in the study (incl. reasons asso-ciated with non-consent), and the cost-effectiveness of the study.

Results A total number of 23 children were included in the study of which 16 children, median age 6.0 years (IQR 4.8, 7.5), provided evaluable data. During the at-home phase, 76.2% of the saliva samples and 91.8% of the pain score data were complete. At home, 42.5% of the saliva samples and 80.7% of the pain scores were collected cor-rectly. Overall, 56.7% of all saliva sample and pain score data were complete and correct in the at-home setting. Most parents supported the concept of conducting stud-ies at home, but the most-common reason for non-par-ticipation was lack of time. Study costs for a sample size of 100 patients were calculated 20% lower for the at-home than for a traditional in-patient study setting.

Conclusion At-home study conduction might be a feasible approach in paediatric clinical trials when certain circumstances are met. While this method seems to work well for data entry (e.g. questionnaires or diaries), it clear-ly does not for collection of samples within narrow time frames.

O-19 INCIDENCE AND RISK FACTORS OF ADVERSE EVENTS DURING IMMUNOSUPPRESSIVE THERAPY AFTER RENAL TRANSPLANTATION IN CHILDREN

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Background Transplantation has become an important treatment option in children with end-stage renal dis-ease. In the last decades progress in immunosuppressive treatment options and surgical techniques have reduced the frequency of acute rejection, graft loss and mortality. However, adverse events occur in patients treated with immunosuppressive therapy. These adverse events are well described for adults but few data are available for children. Our objective was to describe the frequency of adverse events (AEs) under different immunosuppres-sive regimen including either ciclosporin or tacrolimus in children after renal transplantation. Secondary objectives include comparison of AEs with known adverse drug re-actions (ADRs) as described in the Summary of Product Characteristics. Furthermore, risk factors for AEs will be examined.

Methods Children receiving a renal transplant at our institution between 2002 to 2015 were included in the study. Initial immunosuppression was obtained by thy-moglobulin or monoclonal antibody, calcineurin inhib-itors (tacrolimus or ciclosporin), mycophenolate mofetil, and corticoids. AEs reported after transplantation were collected from medical reports and coded using Med-DRA (version 19.1). Descriptive statistical analyses were performed using SAS 9.4. Data were stratified by tacrolim-us or ciclosporin treatment schedule at the time of the AE.

Results A total of 164 children fulfilled the inclusion cri-teria. Finally, complete medical records were available for 125 children (53 girls and 72 boys). The median age was 12 (2 – 19) years old. The indication for renal transplan-tation included congenital, familial and genetic disorders for 61% of the patients and renal and urinary disorders for 39% (including 30% of nephritis). The median time of observation until last follow up was 2.7 (0.6–4.3) years. Initially, 91 patients were treated with tacrolimus and 34 with ciclosporin. During the observation period 6 patients switched from tacrolimus to ciclosporin and 14 switched from ciclosporin to tacrolimus.

A total of 1520 AEs were reported. For patients receiving tacrolimus 1122 AEs (233.6 person-years of exposure) were reported and 372 AEs (71.4 person-years of expo-sure) for those treated with ciclosporin. Twenty-six AEs were reported in patients not receiving any calcineurin inhibitor. The most frequent medical AEs reported for pa-tients treated with tacrolimus and ciclosporin by system organ class were renal and urinary disorders (0.3 vs 0.3 AEs per person-year of exposure), infections (0.3 vs 0.4 AEs per person-year of exposure), vascular disorders (0.2 vs 0.3 AEs per person-year of exposure) and gastrointestinal disor-ders (0.2 vs 0.2 AEs per person-year of exposure). For 46 patients at least one episode of transplant rejection was reported.

Conclusion This study describes AEs up to 4 years after renal transplantation in children treated with immuno-suppressive therapy. Our findings will contribute to the understanding of the benefit-risk balance of immuno-suppressive therapy following renal transplantation in children.

O-20 PREDICTIONS OF SYSTEMIC DRUG EXPOSURE TO GABAPENTIN AND TRAMADOL FOLLOWING ADMINISTRATION TO CHILDREN

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10.1136/archdischild-2017-esdppp.20

Background Gabapentin and tramadol are drugs com-monly used in various treatment of pain in adults. Gab-apentin has been successfully given for neuropathic pain and has been used off-label to treat children with the same condition. Tramadol has been licensed for the use in children older than 1 month in some European coun-tries, but its use has been limited to children>12 years. The management of chronic pain in paediatric patients is burdened by the insufficiency of clinical information, therefore, in order to investigate appropriate dosing for this population, pharmacokinetic (PK) modelling and simulation of virtual patient groups is a most useful ap-proach. In this study we report the analyses used to characterise the population PK and corresponding hier-archical models that are required to provide an adequate description of the time course and variability of drug con-centrations in plasma.

Methods Non-linear, mixed-effect modelling was used to simulate the plasma concentrations of gabapentin and tramadol in subjects between the ages of 3 months and 18 years, under the assumption of comparable ex-posure-response relationships in adult and paediatric patients. Previously published PK models in paediatric pa-tients by Ouellet et al[1] and Garrido et al[2] were chosen and adapted for gabapentin and tramadol, respectively. Dosing regimens for both drugs were evaluated in a cohort of virtual patients, based upon off-label doses used empirically. The population for the simulations was constructed using data from the NHANES database; individu-al body weight was the primary covariate factor affecting PK disposition. The exposure (AUC) and Cmax parameters were derived from the simulated plasma concentrations, to compare with efficacious adult levels. Both drugs are titrated to a maximum dose over a period of 3 weeks, giv-en three times daily.

Results The desired exposure in children should be comparable to the median value obtained for area under the concentration vs. time curve at steady state. An adult AUC range of 25 mg/L*h to 75 mg/L*h corresponded to gabapentin dosing at 63 mg/kg/day and 45 mg/kg/day in patients weighing 5–15 kg and >15 kg, respectively (after a three week titration). Mean plasma concentrations of between 200–300 ng/mL were chosen as a target level for tramadol, and a titration scheme over a three week period up to a maximum of 8 mg/kg/day proceeded to achieve safe dosing. At the end of the titration phase, all weight groups showed drug exposure in the range shown to be safe and effective for the proposed regimens.

Conclusion Clinical trial simulations showed how the proposed dosing regimens yielded suitable drug expo-sure in paediatric populations, suggesting a solution to the issue of under-or over-dosing in this subgroup, and informing appropriate dosage information. This informa-tion contributes to avoiding unnecessary adverse events or, conversely, ineffective treatment.

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O-21 USE OF ANTIPSYCHOTICS IN CHILDREN AND ADOLESCENTS: A PICTURE FROM THE ARITMO POPULATION-BASED EUROPEAN COHORT STUDY

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Background Drug utilisation studies, essentially based on Northern American data, have consistently demon-strated that the prevalence and duration of use of anti-psychotics (APs) are increasing over time in the paediatric population. The aim of this study was to describe prev-alence and incidence of AP use in children and adoles-cents from five European countries.
Methods This was a dynamic retrospective cohort study. Data were extracted from five population-based elec-tronic healthcare databases in Europe: the THIN database in the UK; the PHARMO in the NL; the Aarhus University Hospital Database in Denmark; the GePaRD database in Germany and the Emilia Romagna Regional database in Northern Italy. Study population comprised all children and adolescents registered with the databases during the study period. All drugs under the 'N05A' pharmacologi-cal subgroup of the ATC classification system (except for lithium) were included. Prevalence and incidence of AP expressed per 1000 PYs. A Poisson regression model was applied to determine the influence of increasing calendar year on annual AP use.
Results During study period, in Denmark (2001–2008), prevalence increased from 1.44 to 3.41/1000 PYs and in the NL (2000–2009) from 2.69 to 6.22/1000 PYs. Incidence rates also increased from 0.69 to 1.52/1000 PYs in Den-mark and from 1.12 to 2.13/1000 PYs in the NL. In the UK (2000–2009), prevalence slightly increased from 2.8 to 3.24/1000 PYs and in Germany (2005–2008) from 1.53 to 1.74/1000 PYs. Similarly, incidence rates varied from 1.53 to 1.74/1000 PYs in the UK and from 0.79 to 0.8/1000 PYs in Germany. In Italy (2006–2010) both prevalence and in-cidence respectively decreased from 0.61 to 0.34/1000 PYs and from 0.32 to 0.2/1000 PYs. Overall, use of APs increased parallel to age, with a maximal use observed between 15 and 18 years, and a more prevalent and lon-ger use in boys than girls at all ages. However, maximal prevalence and incidence of use was observed in boys between 10 and 14 years of age in NL and in girls be-tween 15 and 18 years in the UK, while mean duration of prescription was longer in girls than boys at all ages in IT. Also, although use was altogether more frequent among adolescents, the use observed in younger age groups (5–9 years) was found to be comparatively high in some countries such as the NL. Risperidone was the most frequently prescribed antipsychotic in all countries with the exception of IT where chlorpromazine is generally pre-scribed at all ages. Prescriptions of second generation APs were privileged however, in some countries clinicians still favoured first generation APs especially in the youngest.
Conclusion A steady increase in AP use in children and adolescents was observed in some European countries over the calendar years although use remained un-changed in others. The high use of AP in children of less than 9 years of age clearly underlines their off-label use and should be carefully monitored as the risk/benefit ra-tio of these medications remains unclear in the youngest. Altogether, AP use was found to be lower in Europe than in North America.

O-22 SAFE EXCIPIENT EXPOSURE IN NEONATES AND SMALL CHILDREN – THE SEEN PROJECT

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Background Several medicines frequently used in neonates and infants contain potentially harmful excip-ients like ethanol, propylene glycol (PG), methyl-and propyl-parabens. Especially preterm neonates may bechronically exposed as a result of being poly-medicated for extended periods. Hence, safeties of such excipients in relation to age and developmental-status have be-come a hot topic. Adverse drug events (ADEs) due to the content of excipients may be difficult to detect. The preservative methyl-paraben has been shown to displace bilirubin-binding to albumin and may cause hyperbiliru-binemia in concentrations as low as 1.2 mg/kg. Likewise, ethanol and PG are known to be neurotoxic and may re-sult in delayed neurological development after early-life exposure. The European Medicines Agency (EMA) has proposed tolerance limits of daily exposure rates (mg/kg/day) for some of these excipients in each drug prepa-ration. Tolerance limits of parabens only exist for meth-yl-paraben (10 mg/kg/day) and is based on data obtained after oral administrations -although commonly found in parenteral solutions. However, neonates may be more susceptible to excipient–excipient and/or drug–excip-ient pharmacokinetic-interactions compared to adults because of their reduced metabolic activity in the elim-ination pathways.
Aim To quantify the cumulative daily exposure level of benzyl alcohol, ethanol, PG, methyl-paraben and pro-pyl-paraben (in mg/kg/day) administered to poly-medi-cated neonates and infants.
Methods The study was conducted at the national hospital, Rigshospitalet, Denmark. All preparations ad-ministered to neonates receiving more than two drugs and infants receiving more than three drugs per day were registered. Levels were calculated based on quantities ob-tained from manufacturers or databases. Excipient levels were compared to tolerance limits outlined by the EMA.
Results In total, 470 neonates and 160 infants were in-cluded covering 4207 prescriptions and 316 preparations. Ethanol was administrated to 38%, PG to 23%, and benzyl alcohol to 2% of the neonates and infants, respectively. Methyl-paraben was administered 31% and propyl-para-ben to 24% of the neonates and infants. In patients re-ceiving drugs containing ethanol, the cumulative level exceeded the daily tolerance limits in 53% (n=81) of neo-nates and 62% (n=53) of infants, respectively. In patients receiving PG, the cumulative level was exceeded in 40% (n=36) of the neonates and 57% (n=32) of the infants. Few infants (n=14) were exposed to benzyl alcohol. The cumulative level of methyl-paraben exceeded the tolerance limits in less than one percent of both neonates (n=5) and infants (n=5). No tolerance limit for propyl-par-aben was available for comparison.

Conclusion Tolerance limits for ethanol and PG pro-posed by the EMA are exceeded in more than 50% of poly-medicated neonates and infants due to the cumu-lative effect of these excipients. A constant awareness of potential pharmacokinetics, pharmacodynamics and, excipient–excipient-interactions, especially in NICU neo-nates taking multiple medications cannot be highlighted enough. Further, EMA might propose a tolerance limit for methyl-paraben based on safety-data obtained from in-travenous administrations.

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O-23 IBUPROFEN IN INFANTS YOUNGER THAN 6 MONTHS: WHAT IS THE EFFICACY AND SAFETY PROFILE?

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Background Ibuprofen is a non-steroidal anti-inflam-matory drug frequently administered to children of var-ious ages for relief of fever and pain and is approved as over-the-counter medication in many countries world-wide. Although there is extensive data on its efficacy and safety in children and adults, there are divergent dosing recommendations for analgesia and treatment of fever in infants, especially in the age group between 3 and 6 months of age. The purpose of this analysis was to assess the safety and efficacy profile of ibuprofen in this age group in an attempt to optimise pain and fever manage-ment.

Methods A comprehensive PubMed search was con-ducted in order to identify publications concerning the use of ibuprofen in infants younger than 6 months of age. Identified studies were reviewed so that only those pre-senting original clinical data regarding the pharmacoki-netics, safety or efficacy of ibuprofen in infants younger than 6 months would be included.

Results The literature search identified 5 pharmacoki-netic and 10 efficacy and safety studies which met the re-view inclusion criteria. Eligible PK studies presented data of 243 children, which included at least 18 infants under the age of 6 months. Eligible efficacy and safety studies contained data of 39 234 children including minimum 207 children younger than 6 months. The most common underlying pathological condition was fever. The most common clinical setting was outpatient care.

Conclusion Based on the current evidence, short-term use of ibuprofen is considered safe in infants older than 3 months of age having a body weight of more than 5–6 kg when special attention is given to the patient's hydration. Ibuprofen should be prescribed based on body weight using a dose of 5–10 mg/kg. This dose can be adminis-tered 3–4 times a day resulting in a total daily dose of max-imally 30–40 mg/kg. The rectal route has been shown to be less reliable because of erratic absorption, especially in young infants. Since most efficacy and safety data have been derived from paediatric trials in infants with fever, future studies should focus on the efficacy of ibuprofen in young infants with pain.

O-24 ADRIN 1 METHODOLOGY STUDY: ADVERSE DRUG REACTIONS IN NEONATES: WHAT ARE THE BEST WAYS TO EVALUATE SUSPECTED ADVERSE DRUG REACTIONS IN NEONATES?

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Background There are 90 000 babies admitted to neo-natal care units in the UK annually, and many of these require medications.[1] Use of unlicensed and off-label medications is common in neonatal units, with accounting for up to 90% medicines.[2] The incidence of adverse drug reactions (ADRs) in children is estimated to range between 0.6% and 16.8%, but the data specifically for neonates is limited.[3] A number of tools exist to help clinicians to assess the causality of ADRs, but few have been validated in neonatal settings. This study aims to compare three existing methods for assessing causality of ADRs in a neonatal setting and to compare the outcomes be-tween tests and raters.

Methods Following ethical approval, data were col-lected prospectively on suspected ADRs occurring in a tertiary neonatal care unit in the north of England over a five week period. Summaries of these cases were pre-sented to two investigators who undertook three sepa-rate causality assessments of each case using the Karch and Lasagna algorithm(KL), the Liverpool ADR Causality Assessment Tool (LCAT), and the New Adverse Drug Re-actions Algorithm for Infants in Neonatal Intensive Care Units(NAINICU).[4,5,6] Inter-rater and inter-test statisti-cal analyses were performed.

Results Causality assessments have been undertaken on 21 ADR cases reported from the unit to date. The KL algorithm rated 14.3% of cases as definite/likely, NAINICU 42.9% definite and LCAT 0% definite. Inter-rater reliability Kappa scores were 0.131, 0.136 and 0.294 for the 3 tools respectively. Inter-test reliability was greatest between the KL algorithm and the LCAT (Kappa 0.211) and least between NAINICU and LCAT (Kappa −0.149).

Conclusion These three tools produced varied causali-ty assessment outcomes when used on neonatal ADRs. Marked inter-test and inter-rater variability was noted. The study is continuing to collect cases to help determine the optimal way to assess causaility in this popualtion.

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O-25 REDUCTION OF CALCULATION ERRORS WITH THE DUTCH PAEDIATRIC FORMULARY'S WEB-BASED PAEDIATRIC DOSING CALCULATOR

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Background Calculating a paediatric dose is complex due to a variety of parameters influencing the dose and therefore error prone, ultimately resulting in incorrect dosing, lack of efficacy and/or adverse effects. The devel-opment and implementation of a paediatric dosing cal-culator could reduce calculating errors.

Objectives 1. To develop a clinical decision tool for cal-culating an individual paediatric dose, using the compre-hensive Dutch paediatric formulary as dosing reference.

2. To show a 50% reduction of calculation errors by establishing an individualised paediatric dose through a paedi-atric dosing module.

Methods The Paediatric Dosing Calculator consists of a calculation interface which integrates the dosing rec-ommendations of the Dutch paediatric Formulary with clinical patient variables, thus resulting in an individual recommended dose. After establishing the functional requirements and risk minimization measures the dosing calculator was developed by using a test-retest approach. The alfa version was validated by performing 2 calcula-tions for an aselect sample of 230 drugs of the formulary. Two groups of healthcare professionals were presented with 15 cases for which they were asked to calculate a dose. One group (n=37) was instructed to calculate with conventional tools i.e. a mathematical calculator and the dosing recommendations as listed in the Dutch Paediat-ric Formulary. The second group (n=36) was instructed to use the integrated paediatric dosing calculator interface. The time for the calculating tasks was limited to 2 min-utes per case as to mimic the stressful circumstances of daily practice. The% of calculating errors was compared between groups.

Results Of the 460 test calculations of the first calculator version 5% contained a calculation error. After analysing, correction and re-testing an error-free beta version was launched. Using the calculator interface resulted in a 35% reduction of calculating errors compared to manual cal-culations (18,7%/ (range 0%–83%) vs 28,4% (range 9%–61%), respectively.

Conclusion We successfully developed a web-based dose calculator. The use of this calculator appears to re-duce dosing errors by approximately one third. Health-care providers may benefit from using the calculator in-terface provided that they carefully enter and select the parameters required.

O-26 FOLIC ACID DURING PREGNANCY AND THE RISK OF AUTISM: A NESTED CASE-CONTROL STUDY

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Background During the past two decades there has been a dramatic increase in the prevalence of autistic spectrum disorders (ASD) among children worldwide, concurring with growing use of periconceptional folic acid supplements for the prevention of neural tube de-fects (NTD). This has raised the question of possible as-sociation between maternal folic acid exposure and ASD. We aimed to examine the association between the cu-mulative dose of folic acid purchased by the mother from 3 months before and throughout pregnancy, and the risk of autism.

Methods In a nested case-control study, we identi-fied 1650 children with ASD diagnosed from a cohort of 5 04 028 children born in a large health organisation in Israel from 2000 through 2013. ASD patients were in-dividually matched in a ratio of 1:5 to ASD-free children (n=7591) from the cohort on age and maternal age, sex, residential area and level of socio-economic status. Odds ratios and 95% confidence intervals by mean daily dose of supplemented folic acid during the 12 month period were calculated using unconditional multivariable logis-tic regression. The model was adjusted for potential con-founders including age of mother , place of the child in the family, having a fertility problem and being enrolled in our fertility register, suffering from epilepsy, maternal BMI, and serum concentrations of vitamin B12.

Results In univariate analysis, mean daily dose of folic acid purchases among ASD cases (177.84 μg, SD=250.7) during the 12 month study period was significantly high-er when compared to controls (145.87 μg, SD=214.2) ($p<0.001$) . However, significantly more ASD children were first born, and mothers purchased significantly more folic acid during the first pregnancy than in the second preg-nancy, and even less in the third pregnancy. Similarly, the ages of ASD mothers were significantly older, they exhibited significantly more subfertility, visited significant-ly more often at their physicians' offices. In multivariable analysis, accounting for these confounders, there were no apparent differences in the amount of folic acid pur-chased between the groups and no dose – response ef-fect of folic acid on occurrence of autism was discerned. In a sensitivity analysis we compared folic acid purchases between healthy and ASD first born children while accounting for all other variables; here too there was no association between higher folic acid purchases and ASD occurrence.

Conclusion No association was found between the amount of folic acid purchased and the occurrence of ASD. The univariate finding of higher folic acid exposure in autistic children is most probably the result of colinear-ity between the order of birth (first born) and the trend of mothers to consume significantly more folic acid in their first pregnancy.

O-27 CROSS-SECTIONAL STUDY EVALUATING PREGNANCY RELATED USE OF VITAMINS AND MEDICATION IN BELGIUM (PREVIM-STUDY)

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Background Medication use during pregnancy is ex-tremely common and has increased over the past decades.[1–3] Unfortunately, no Belgian data are available on the number and type of products used. The aim of the PREVIM-study (Pregnancy related use of vitamins and medication) is therefore to provide

a detailed overview of the prevalence of different types of health products' use among Belgian pregnant women.

Methods All pregnant women, ≥18 years, attending the obstetrics department of the University Hospitals Leuven and understanding Dutch, French or English were asked to complete an online web-survey once between No-vember 2016 and February 2017 (cross-sectional study). The questionnaire consisted of sociodemographic and pregnancy-related questions, questions about the use of health products and questions about medication beliefs and information desire. Support from a study collabo-rator was available. The questionnaire could be finished at home if necessary. The questionnaire was linked with a database consisting of more than 100 000 pictures of available health products in Belgium. A draft Dutch ver-sion was pilot tested in ten pregnant women and the final version was translated into English and French. Approv-al of the Ethics Committee was obtained; participants signed informed consent prior to the study.

Results In total, 379 pregnant women (40,4%0–13 w, 26,4% 14–27 w, 33,2%28–40 w), mean age 32 years (range 18–48), participated in the study. Most women were pro-fessionally active (88.9%), of which one-fifth was working in health care. In 14.5% of cases, the pregnancy was the result of a fertility treatment. Almost all women (98,2%) had used a health product in the preceding week; 86.0% had used folic acid or a pregnancy-specific multivitamin; 52% had used a prescription or OTC medication reg-istered in Belgium. In 53.8% of those, it concerned one medicine; 3.56% had used four or more medicines. 64.1% of pregnant women indicated to have used alcohol in the three months preceding the pregnancy; 12.4% were at that time smokers and 2.6% used drugs. Only 34.8% of women mentioned to have changed life style before pregnancy. 91.6% of smokers stopped smoking at the time they realised they were pregnant or later during pregnancy, while 89,6% of alcohol drinkers did so. 6.1% of women had still smoked cigarettes in the week preced-ing the survey; 5.5% had used alcohol and 0.53% were substance-users.

Conclusion Preliminary data from this cross-section-al study show that almost all Belgian pregnant women used one or more health products in the week preceding the survey. Only one third of women adapted life style in the months before pregnancy; most women who quitted smoking or drinking alcohol did it too late.

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O-28 PLACENTAL TRANSFER OF THE IMMUNOSUPPRESSIVE DRUG TACROLIMUS AND ITS EFFECTS ON PLACENTAL FUNCTION; RELEVANCE FOR RENAL TRANSPLANT RECIPIENTS?

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Background The number of pregnancies in the kid-ney transplant patient population is high. During gesta-tion these women continue using immunosuppressant drugs, but knowledge about their placental disposition and toxicity is scarce. We now investigated placental transfer of the immunosuppressive drug tacrolimus (TAC) as well as the potential effects on trophoblast cell viability and barrier function.

Methods Isolated dual side perfusions of human pla-cental cotyledons were performed to study disposition of TAC. Additionally, clinical data on TAC concentrations in placental tissue of kidney transplant recipients and ma-ternal whole blood concentrations were gathered. BeWo choriocarcinoma cells were used to evaluate effects on trophoblast cell viability, while interaction with placental ATP-binding cassette transporters was studied in mem-brane vesicles derived from HEK293 cells recombinantly overexpressing human Breast Cancer Resistance Protein (BCRP) or P-glycoprotein (P-gp).

Results We found that maternal perfusate levels de-creased during 180 min of perfusion, while being unde-tectable in the fetal circulation. At t=180 min a concen-tration of 220 ±50 nM was measured in placental tissue, which is almost 100-fold higher than the maternal per-fusate concentration. Analysis of placental tissue of renal transplant recipients revealed a 13-fold higher tacrolimus concentration compared to the maternal blood concen-tration (88±7 nM and 6.8 ±1.1 nM, respectively). TAC did not affect BeWo cell viability up to the maximum concen-tration of 1 μM tested. In transporter studies we did find stimulation of P-gp-mediated transport and inhibition of BCRP-mediated transport, at 1 and 10 μM, respectively.

Conclusion TAC demonstrates strong accumulation in placental tissue and distribution across the tissue was not homongenously. However, the tissue concentrations reached are unlikely to affect trophoblast cell viability or BCRP and P-gp transport function.

O-29 MAG – MÉDICAMENTS ADMINISTRÉS PENDANT LA GROSSESSE/DRUGS ADMINISTERED IN PREGNANCY

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10.1136/archdischild-2017-esdppp.29

Background Maternal drug use in pregnancy may occur in different situations: chronic maternal disease prior to pregnancy, maternal disease not linked to pregnancy or complicating pregnancy and automedication. Studies in Europe and USA/Canada have shown high numbers of drugs used by pregnant women, up to 13 with prescrip-tion rates over 90% in France. This is a major healthcare issue for clinicians as more than 80% of the drugs used are used without knowledge of their safety/efficacy for the mother, have undetermined risks and possible adverse effects on the fetuses. In France, epidemiological data are insufficient to evaluate the drug use during pregnancy and the status of the drugs prescribed (licensed/off-label).

Objectives and methods MAG is a large multicenter and prospective study conducted using an electronic questionnaire. As a collaborative project, MAG Consor-tium includes clinical research units of APHP (CIC1426, CIC0901), the Gynaecology and Obstetrics-CIC network (GO-CIC), the «Risks and Pregnancy» University-Hospital de-partment and INSERM U953 unit.

The objectives are to determine the extent of drug use during pregnancy, determine drug status, conditions of use

(prescription/automedication), and to identify per-sonal, social and economic factors conditioning their use in a representative population of 1000 randomly selected pregnant women in France.

Therefore, France was divided into 7 regions with 1 perinatal network selected per region. Using childbirths ep-idemiological data from the French National Institute of Statistics and Economic Studies, a total of 35 maternity wards will participate: 5 units per region (1 level III, 2 level II, 2 level I) with 1 private unit to ensure the best repre-sentativeness of the results with recruitments established by region and by age groups. Seven mobile CRAs are in charge of the interviews using MAG electronic question-naire facilitating the capture and real-time monitoring of the inclusions with a list of 350 most used drugs (in preg-nant women) uploaded on the platform. MAG is conduct-ed over a period of 5 days in each centre.

Results To date, the 35 maternity wards and the perina-tal networks have been identified within the 7 regions: Yvelines (MYPA), Pays de la Loire (Sécurité Naissance), Basse-Normandie, Bourgogne (Femme et Enfant), Rhône-Alpes (Aurore) and Provence Alpes Côte d'Azur (Méditer-ranée).

From June 2016 to mid-March 2017, the MAG network allowed to recruit 860 patients in 16 centres with 13 completed weeks and 10 days of study conduct, a mean of 58 women per centre (13 centres) or 12 women includ-ed per day. MAG interviews are less than 30 min per woman. A refusal rate of 15% was observed reflecting that MAG was very well received among pregnant wom-en. The MAG survey is still ongoing with inclusions sched-uled until June 2017. Inclusions will be extended up to 2000 patients.

Conclusions MAG study will deliver essential informa-tion of drug use in pregnant women identifying potential associated factors and determine drugs that would ne-cessitate complementary pharmacological studies. MAG will orientate information and communication strategies of health professionals and women to limit inappropriate drug exposures and provide the tools for future studies to be conducted through national surveillance networks.

O-30 LEVETIRACETAM THERAPEUTIC MONITORING DURING PREGNANCY: AN OBSERVATIONAL STUDY

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10.1136/archdischild-2017-esdppp.30

Introduction Levetiracetam is a relatively new anti-ep-ileptic drug (AED), indicated as an adjunctive therapy for partial-onset seizures and primary generalised tonic-clon-ic seizures in adults and children. However, information about the influence of altered pharmacokinetics during pregnancy on levetiracetam dose, serum concentration and clinical efficacy is still limited. This study aims to de-scribe the relation between certain parameters of preg-nant women and levetiracetam blood levels in different stages of pregnancy.

Methods Pregnant women treated with levetiracetam for epilepsy from neurology clinics in several medical centres were followed in this study. Trough blood sam-ples were obtained (therapeutic range: 10–37 mg/L) at dif-ferent stages of pregnancy, while sampling frequency for each woman was decided by the neurologist. Levetiracetam dose, pregnancy week, and seizure occurrence were recorded, and levetiracetam blood concentrations were quantified using HPLC-based method. These data were analysed in order to reveal the changes in levetiracetam blood concentrations before and during pregnancy, and their potential clinical implications.

Results Fifty two pregnant women treated with leveti-racetam for epilepsy participated in this study. In many of these patients, levetiracetam plasma concentrations decreased during pregnancy, and the drug dose was in-creased gradually to maintain the concentrations in the therapeutic range. Despite this, levetiracetam plasma concentrations were below and above the therapeutic range in 41% and 5.5% of the collected samples, respec-tively. Based on the dose-normalised levetiracetam plas-ma concentrations, exposure to a given dose of the drug decreases by approximately 35% during the first trimester, and stays reduced over the 2nd and 3rd trimesters. Overall, many patients were exposed to sub-therapeutic levetiracetam plasma concentrations during substantial parts of pregnancy. However, no clear correlation between the levetiracetam plasma concentrations and occurrence of seizures was identified.

Conclusion Levetiracetam blood concentrations tend to decrease during pregnancy as opposed to pre-preg-nancy state, apparently due to increased drug clearance. As a result, levetiracetam blood concentrations during pregnancy may decline below the therapeutic range, leading to a higher risk of seizures. Therefore, monitoring of levetiracetam blood concentrations during pregnan-cy is needed to maintain therapeutic concentrations via gradual increase in drug doses. More detailed analysis is needed to reveal the pregnancy-related changes in the levetiracetam pharmacokinetics (clearance) and pharma-codynamics.

O-31 ANTIEPILEPTIC DRUG (AED) EXPOSURE IN PREGNANCY AND PREGNANCY OUTCOME FROM NATIONAL DRUG USAGE DATA

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10.1136/archdischild-2017-esdppp.31

Background Antiepileptic drugs (AEDs) taken during pregnancy are known to increase the risk of fetal malfor-mations and potentially affect the neurodevelopment in children exposed. This study aimed to investigate the use of AEDs by pregnant women and women during their childbearing years in New Zealand and the association between AED use and rates of pregnancy termination, spontaneous abortion and stillbirth.

Methods Retrospective population based cohort study using administrative databases in New Zealand between 2008 and 2014. Women who had been pregnant were identified by the National Minimum Dataset and were linked to the Pharmaceutical Collection to obtain infor-mation on use of AEDs. Women aged between 15 and 45 years dispensed AEDs were identified in the Pharmaceu-tical Collection.

Results There was a significant increase in the number of women of child-bearing potential prescribed AEDs, from 9 women per 1000 women in 2008 to 11.4 wom-en per 1000 women in 2014. Use of the older generation AEDs declined over the time period while use of the newer generation AEDs increased. General practitioners provided 60% of the prescriptions of AEDs to women of child-bearing potential. Women

who had been dis-pensed an AED had an increased rate of spontaneous abortion and pregnancy termination compared to those not dispensed an AED, 13.16 spontaneous abortions per 100 pregnancies, compared with, 8.00 per 100 pregnancies (risk ratio 1.64, 95% CI 1.50 to 1.80), and 21.29 terminations per 100 pregnancies compared with 19.50 per 100 pregnancies (risk ratio 1.09, 95% CI 1.02–1.17).

Conclusion Use of newer AEDs is increasing in women of child-bearing potential in New Zealand leading to an overall increase in AED use in this group despite a fall in the use of older AEDs. AED use is this study was associat-ed with an increased risk of spontaneous abortion and increased rate of pregnancy termination.

O-32 PRENATAL EXPOSURE TO ACETAMIN-OPHEN AND RISK FOR ATTENTION DEFI-CIT DISORDER (ADHD): A SYSTEMATIC REVIEW AND META ANALYSIS

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Background Acetaminophen is the most commonly used analgesic and antipyretic medication during preg-nancy. Recent epidemiological studies have suggested a possible association between acetaminophen exposure in-utero and impaired paediatric neurological develop-ment, including hyperactive attention deficit (ADHD) and related disorders.

Methods We conducted a systematic-review and me-ta-analysis to evaluate the risk for ADHD in children of women exposed to acetaminophen during pregnancy. We searched MEDLINE and EMBASE up to January 2017. We used meta-regression analysis to evaluate factors that may moderate this association. Reports of cohorts were pooled using random-effects models.

Results Six cohort studies met our inclusion criteria. Among 76 146 mothers who reported acetaminophen use during pregnancy, acetaminophen was associated with an increased risk for ADHD (RR=1.33, 95% CI: 1.19–1.47, I2=77%), hyperactivity symptoms (RR=1.24, 95% CI: 1.02–1.46, I2=95%), and conduct disorders (RR=1.28; 95% CI, 1.05–1.52, I2=93%). Using meta-regression, we found that the association was greater and heterogeneity re-duced as child's age at diagnosis increased (β=0.045, p=0.035, heterogeneity accounted for (R2)=65.98%).

Conclusion This meta-analysis suggests that maternal acetaminophen use during pregnancy is associated with a higher risk for ADHD or related disorders. However, there is evidence of significant heterogeneity in the observed effect, and many of the studies suffer from significant lim-itations. These findings, together with additional recent evidence on teratogenicity of acetaminophen, warrants further investigation and consideration of public health actions.

PROSPERO registry-CRD42017055827

Oral presentations in order of the programme Friday, 23 June 2017

O-33 FEASIBILITY OF A PAEDIATRIC MICRO-DOSE STUDY OF [14C]MIDAZOLAM TO STUDY THE ONTOGENY OF CYP3A-MEDIATED DRUG METABOLISM

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Background Microdose studies present an interesting innovation to study age-related changes in drug metab-olism in young children. To further delineate maturation of intestinal and hepatic CYP3A activity, in this pilot study we aimed to study the feasibility of an oral [14C]midazol-am (MDZ) microdosing study in children.

Methods Children admitted to the paediatric intensive care unit were eligible to receive a single oral [14C]MDZ microdose when they received IV midazolam for thera-peutic reasons and had an arterial line in place enabling blood sampling. Blood samples were taken up to 24 hours after dose administration. Plasma concentrations of [14C] MDZ and the metabolite [14C]OH-MDZ were determined by accelator mass spectrometry (AMS). Pharmacokinetic (PK) parameters were estimated using non-compartmen-tal PK models with PKSolver software (Microsoft Excel).

Results Of 139 eligible patients, 125 were excluded and informed consent was obtained from parents of nine chil-dren [median age 3.3 months (range 12 days – 4.2 years)] who received a midazolam microdose (19.3 [18.7–21.3] ng/kg; 58 [56-64] Bq/kg). [14C]MDZ and [14C]1-OH-MDZ were detectable at expected concentrations: plasma [14C]MDZ AUC0-∞ was 49.9 (4.0–107.7) ng/L*h, Cmax was 7.5 (1.5–22.2) ng/L, Tmax was 0.5 (0.3–3.1) hour, T0.5 was 4.6 (1.1–14.0) hour, CL/F was 0.4 (0.2–5.3) L/h/kg and Vss/F was 3.1 (1.7–10.7) L/kg. Plasma [14C]1-OH-MDZ AUC0-∞ was 7.8 (1.3–28.3) ng/L*h and CL/F was 2.4 (0.7–14.6) L/h/kg. Plasma Cmax of [14C]MDZ normalised to a dose of 0.1 mg/kg was 39.9 (7.0–114.9) ng/ml.

Conclusion We demonstrate the feasibility of an oral [14C] MDZ microdose to study MDZ and 1-OHMDZ dis-position in young infants and children with AMS. This method can be used to study developmental changes in intestinal and hepatic CYP3A activity.

O-34 NEOCORD: MRNA EXPRESSION OF CYTOCHROMES AND TRANSPORTERS INVOLVED IN DRUG METABOLISM AT BIRTH, USING HUMAN UMBILICAL CORD BLOOD

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Background Growth, maturation and physiological modifications are mainly responsible for the difference in pharmacokinetics and pharmacodynamics of drugs ob-served between adults and children, especially neonates. Ontogeny of drug metabolising enzymes and transporters play an important role in drugs inter-individual phar-macokinetic variability in this population. Data on neona-tal developmental pharmacology remain very limited.

Neocord aims to characterise mRNA expression of the main cytochromes and transporters involved in the phar-macokinetics and pharmacodynamics of drugs in twin newborns, using umbilical cord blood, according to iden-tified covariates such as genetic background, pregnancy environment, gestational age, sex, maternal pathologies and treatments, etc. A population of twins will allow a precise comparison of individuals with different or identi-cal genetic background.

Methods Umbilical cord blood samples (2.5 ml) were collected from women pregnant with twins, both dizygotic and monozygotic, in the maternity ward of Robert-Debré Hospital using PaxGene Blood RNA tubes. Isolation and purification of total RNA from the blood samples was performed using the PAXgene Blood RNA kit with sub-sequent RNA reverse transcription (RT-PCR). Amplification of DNA and gene expression profiling was performed by real-time polymerase chain reaction (qPCR) using Ap-plied Biosystems TaqMan gene expression assay tech-nology. Expression of the 18S ribosomal reference gene was used as internal control for normalisation of expres-sion profiles.

A large panel of drug metabolising enzymes and trans-porters genes was quantified: cytochrome P450 system (n=12), UGT family (n=6), transporters (n=3) and TPMT.

Relative gene expression levels between the different samples were calculated using the ΔΔCt method.

Results Fifty umbilical cord blood samples (32 males and 18 females) from 25 women pregnant with twins, deliver-ing between April 2015 and March 2017, were collected.

Median age of the women was 33.2 years(23.2–49.5) and median gestational age at delivery was 37.3 weeks of amenorrhea (34.4–39.6). Nineteen women delivered at term and 6 delivered before 37 weeks. Five women had a monochorionic diamniotic pregnancy and 20 women had a dichorionic diamniotic pregnancy. Monochorionic twins were assumed to be monozygotic (n=10) and dif-ferent-sex twins as dizygotic (n=20). Zygosity of the 20 same-sex dichorionic twins could not be assessed.

Preliminary results were obtained after analysis of 30 cord blood samples. Females (n=12) and males (n=18) showed no differences of weight or gestational age at birth. From these 15 twins pairs: UGT1A6 and UGT2B7 expressions were not found in umbilical cord blood samples while others were expressed at different levels. Gene expression was different between newborn genders ($p<0.05$) for 5 genes: CYP2A6 ($p=0.035$), CYP2C9 ($p=0.032$), CYP3A4 ($p=0.005$), UGT1A3 (0.035), UGT1A9 ($p=0.039$), females having greater expressions of all of them. Further analyses are currently ongoing.

Conclusion Identification of differences in protein ex-pression profiles will allow a better understanding of the pharmacokinetics and pharmacodynamics variability of drugs in the newborn. Such factors will help improving neonatal care and define appropriate dose regimens in the neonatal population.

O-35 A NOVEL APPROACH IN PAEDIATRIC DRUG DESIGN: THE CONVENTIONAL PIG AS JUVENILE ANIMAL MODEL

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Background To date, the paediatric subpopulation is often neglected during drug development. The main reasons are limited economic profit of drugs adapted to children, ethical concerns for performing paediatric clinical trials and lack of appropriate preclinical animal models and methodologies, taking maturation and metabolic de-velopment into account. Lack of clinical trials and conse-quently the lack of paediatric formulations frequently leads to off-label use of drugs in the paediatric subpopulation, which may lead to inappropriate dosage regimens and/or increased toxicity (Kimland et al, 2012). Since children are no small adults, extrapolation from adult clinical trials is not recommended. Therefore other strategies, such as suited animal models taking growth and maturation into account, should be investigated. Traditional animal mod-els including rodents, dogs and non-human primates, have already been explored, but seem to be insufficient due to either differences in physiology and ADME pro-cesses or ethical concerns. The aim of the present study was to determine whether the conventional pig could be a feasible juvenile animal model to study the pharma-cokinetic processes of drugs, since its striking anatomi-cal and physiological resemblances with humans. More specifically, the ontogeny of the glomerular filtration rate (GFR) and cytochrome P450 (CYP450) liver enzymes was assessed and compared to human maturation data.

Methods An extensive literature search was performed based on the comparative anatomy and physiology of pigs and humans. The main focus of this meta-analysis was growth and ontogeny of the major organ systems involved in the pharmacokinetic processes of drugs, namely gastro-intestinal tract, liver and kidney. The GFR of conventional pigs was determined in four age categories using three different techniques, namely creatinine clear-ance in plasma and urine determined with Jaffe reaction and enzymatic method, and clearance of exo-iohexol. The ontogeny of the CYP450 enzymes was determined by *in vitro* activity experiments in liver microsomes of the same age categories next to the determination of the amount of CYP proteins by high definition data directed analysis (HD-DDA) mass spectrometry.

Results Literature reports demonstrated that devel-opmental variability in ADME processes was most pronounced at birth and neonatal stage of life. The piglet might be a more appropriate juvenile animal model for PK studies when reaching infancy. An easy-to-apply creatinine equation was developed to estimate the GFR in growing piglets and to provide a useful tool in preclinical porcine studies. Furthermore, the maturation profile of GFR in pig-lets was comparable to humans. The *in vitro* metabolic capacity of the CYP enzymes increased with age which is probably due to maturation of the enzymes itself as well as to an increase in absolute amount of CYP proteins.

Conclusion These data supports the use of the conven-tional pig as juvenile animal model, although additional studies are required to fully elucidate the suitability of the piglet preclinical animal model.

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O-36 A HUMAN PROXIMAL TUBULAR EPITHELIAL CELL MODEL TO EXPLORE A KNOWLEDGE GAP ON NEONATAL DRUG DISPOSITION

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Background Finding the right drug-dosage for neonates is still a medical challenge. Up to now, neonatal doses are extrapolated from adult and children doses. However, there are differences between neonatal and adult kidney physiology that should be put into consideration, especially when it comes to active drug metabolism. Studying renal drug clearances in neonates is limited by the lack of reliable human cell models. Our aim was to illustrate the feasibility to develop an *in vitro* model for neonatal proximal tubule epithelial cells (nPTECs) for studying renal drug clearances at this age.

Method nPTECs were isolated from urine samples of neonates of different gestational age (GA) and conditionally immortalised using a temperature sensitive SV40T anti-gen and human telomerase hTERT. The cell clones were characterised on gene expression level for PTECs markers such as P-glycoprotein (P-gp), aquaporin1 (AQP1), and organic cation transport protein 2 (OCT2). In addition, protein expression and functional assessment were per-formed for P-gp and OCT2.

Results We established 101 clonal cell lines of cinPTECs derived from neonatal urine. Gene expression analy-sis confirmed the expression of the PTECs (P-gp, AQP1, and OCT2), similar to the expression in the adult control ciPTECs. P-gp was expressed in cinPTECs from the differ-ent gestational ages and exhibited similar functionality as the adult derived ciPTECs. In contrast, OCT2 functionality was significantly lower in the cinPTECs cell lines com-pared to the adult ciPTECs.

Conclusion We demonstrate the feasibility of culturing cinPTECs expressing mature ciPTECs markers with high efficiency out of the urine samples of neonates. The cell model presented here can serve as a valuable tool to study proximal tubule physiology and pharmacology in new-borns. In addition, we demonstrate the physiolog-ical differences between the neonatal and adult kidney, which puts emphasise on the importance of studying drug pharmacokinetics in neonatal models instead of ex-trapolating from adult models.

O-37 PREVENTING AMINOGLYCOSIDE-INDUCED NEPHROTOXICITY USING STATINS: AN EXAMPLE OF BENCH-TO-BEDSIDE RESEARCH

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Background Megalin-mediated endocytosis is the prin-cipal pathway for the accumulation of aminoglycosides in proximal tubule epithelial cells,[1] resulting in kidney toxicity. Activation of this pathway depends on intermediates derived from mevalonate, the product of 3-hydroxy-3-meth-ylglutaryl-coenzyme A (HMG-CoA) reduction, catalysed by HMG-CoA reductase.[2] We hypothesised that inhibition of HMG-CoA reductase by statins would reduce uptake of aminoglycosides in the proximal tubule, leading to a re-duction in toxicity. This has previously been demonstrated *in vitro*.[3] We tested this in two *in vivo* models.

Methods Sprague Dawley rats, (n=4/group) received in-traperitoneal (IP) dosing with saline (control), gentamicin (200 mg/kg/day), rosuvastatin (40 mg/kg/day), or gentami-cin and rosuvastatin for 9 days. Nephrotoxicity was measured using urinary N-Acetyl-β-d-glucosaminidase (NAG) and kidney injury molecule-1 (kim-1) on urine samples collected within 24 hours after the final dose. Male Hartley guinea pigs (n=6/group) received IP dosing with saline (control), gentamicin (100 mg/kg/day), statin, or combined gentami-cin and statin (simvastatin or rosuvastatin, 0.4 to 40 mg/kg/day) for 9 days. Nephrotoxicity was measured using serum creatinine and blood urea nitrogen (BUN) on urine samples collected within 24 hours after the final dose.

Results In rats co-administered rosuvastatin and gentami-cin, urinary concentrations of NAG and kim-1 were signifi-cantly lower than for gentamicin alone ($p<0.01$). In guinea pigs, rosuvastatin reduced gentamicin-induced nephro-toxicity in a dose-dependent manner: doses of 0.4, 4 and 40mg/kg/day led to 46% ($p<0.01$), 81% ($p<0.0001$), and 83% ($p<0.0001$) reductions, respectively, in serum creati-nine compared to animals receiving gentamicin only. Simi-lar results were seen with BUN. The minimum effective dose to prevent toxicity was 0.97mg/kg/day. Using a dose scaling algorithm this equates to a dose of 10mg/day in children. Simvastatin did not protect the kidney from gentamicin-in-duced nephrotoxicity. The results from the in vitro and in vivo animal studies led to the design of a phase IIa multi-centre, randomised, controlled clinical trial (RCT) in children with cystic fibrosis receiving clinically indicated treatment with aminoglycosides, where co-treatment with rosuvasta-tin (10mg) will be compared with current standard of care.

Conclusion Rosuvastatin inhibits gentamicin-induced nephrotoxicity in both rat and guinea pig models; in the latter, at therapeutic doses used in humans. This led to an RCT in children which has just completed recruitment. This bench-to-bedside translational research showcases the exciting area of drug repurposing with potential for signifi-cant patient benefit.

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O-38 THE INFLUENCE OF BODY COMPOSI-TION ON PAEDIATRIC DRUG DOSING

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Background Body size is an important patient covariate in scaling drug doses. While total body weight has been the most commonly used size descriptor, fat free mass (FFM) has been advocated as an alternative size descrip-tor to scale drug doses in adults and children. FFM de-scribes the non-fat component of the body thus having a better correlation with the metabolic rate and drug clear-ance (CL). The aim of this work was to evaluate FFM as a covariate in a PK model of unfractionated heparin (UFH) developed in a paediatric population.
Methods Data from 64 infants and children who re-ceived 75–100 IU/kg of UFH during cardiac angiography were analysed. Four plasma samples were collected at baseline and at 15, 30, 45, and 120 min post-dose. UFH concentration (231 measurements) was quantified using a protamine titration assay. UFH effect (164 mea-surements) was quantified using activated partial throm-boplastin time (aPTT). A PKPD model was fitted to the data using the non-linear mixed effects modelling (in NONMEM v7.2). Various patient covariates such as age, weight (Wt), body surface area, and FFM were tested. The final model was evaluated using the likelihood ratio test and visual predictive checks (VPCs).
Results A one-compartment model with linear elimina-tion provided the best fit for the dose-concentration data. Wt and FFM had substantial influence on model fit; FFM was preferred statistically. A linear model provided the best fit for the concentration-effect data using the PPP and D sequential estimation method. Censored PD data (above the upper limit of quantification) were accounted for us-ing likelihood estimation. The PKPD model performed well using visual predictive checks.
Conclusion A PKPD model to describe the time-course of UFH effect was developed in a paediatric population which received a high single bolus dose. FFM was shown to describe drug disposition well and can potentially be used in dose calculation after appropriate evaluation.

O-39 TACROLIMUS INTRA-PATIENT VARIABILITY IS AN INDEPENDENT FACTOR ASSOCIATED WITH THE NEED FOR LIVER BIOPSY IN PAEDIATRIC LIVER TRANSPLANT RECIPIENTS

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Background The intra-patient variability in tacrolimus exposure (TAC-IPV) after paediatric liver transplantation and its impact on patient outcomes has been poorly studied. The present study aims to investigate whether there is a trend in TAC-IPV during the first 5 years post transplantation, which variables influence IPV and wheth-er the IPV during the first year is associated with liver transplantation outcomes in paediatric patients.
Methods We conducted a single centre retrospective study including 41 living paediatric patients transplanted between January 2003 and September 2016 at the Ghent University Hospital. The intra-patient variability in the dose-adjusted tacrolimus pre-dose concentrations was calculated yearly during the first five years following trans-plantation, expressed as coefficient of variation (CV%1–5) The difference in CV% in the years following transplanta-tion was analysed using the Friedman test. A linear uni-variate and multivariate regression analysis was applied to identify factors associated with TAC-IPV. The following parameters were tested: age, gender, origin, the number of missed clinic appointments as a surrogate marker for ther-apy adherence, the total number of medications, concom-itant medications potentially interfering with TAC metabo-lism-CYP3A4/A5 inductors or inhibitors and biochemical parameters. Logistic and linear regression models were fit-ted to test an association of TAC-IPV with patient outcomes: need for biopsy during year 1, 3 and 5; hypertension and renal function at 1, 3 and 5 years; acute rejection and CMV/EBV viremia during year 1 post-transplantation.
Results We identified a significant decrease in TAC-IPV during the first 3 years after transplantation with the me-dian CV% 1=39,4%; CV%2=30,9%; CV%3=28,5% (p=0,004), after which the CV% reaches a plateau (CV%4=23,6% en CV% 5=28,9%). Multivariate analysis showed that serum albumin in the first year (p=0,029), haematocrit in the third year (p=0,019) and the number of missed clin-ic appointments in the fifth year after transplantation (p=0,009) were associated with TAC-IPV.in the 1 st, 3rd and 5th year, respectively. Univariate analysis showed that CV%1 was significantly associated with the need for bi-opsy during the first year post-transplantation (p=0.036) and the occurrence of one or more episodes of acute al-lograft rejection during the first year post-transplantation (p=0.031). In univariate analysis a trend was observed for association with hypertension one year after transplan-tation (p=0,085). Multivariate logistic regression analysis confirmed that CV%1 was an independent factor associ-ated with the need for liver biopsy in the first year follow-ing liver transplantation. (p=0.05; Exp(B)=1.045).
Conclusion As expected, tacrolimus intra-patient vari-ability is higher during the first two years after transplantation. Our results suggest that while albumin and hae-matocrit are associated with TAC-IPV in the first 3 years, therapy adherence expressed as the number of missed clinic appointments is associated with TAC-IPV after a longer follow-up. A high TAC-IPV during the first year was an independent factor associated with the need for liver biopsy. Our results therefore highlight the importance of monitoring the variability of the tacrolimus trough levels.

O-40 NOVEL TAILORED TRAINING CONCEPT TO FACILITATE SUCCESSFUL STUDY CONDUCT AND OPTIMISE RECRUITMENT IN PAEDIATRIC CLINICAL TRIALS

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Background Poorly conceived study designs are still a main reason for clinical trials to fail in paediatric patients. Especially, recruitment of a representative population re-mains hard to be achieved. Low recruitment rates prolong study conduct and reduce data acquisition and quality. Pharmacokinetic and

pharmacodynamic investigations are mandatory in the paediatric study designs for submission to competent authorities. Therefore, non-professional tech-niques in blood sampling and patient/parent communica-tion can be main drivers for low recruitment rates. To meet these particular challenges, a novel approach for the train-ing of study teams in the EU-funded LENA project was cho-sen that goes beyond current standards. Aim of LENA (**L**a-belling **E**nalapril from **N**ewborns up to **A**dolescents) is to investigate pharmacokinetic (PK) and pharmacodynamics (PD) data of enalapril in children suffering from heart failure.

Methods A three-parted modular training was designed by addressing the most critical hurdles of the paediatric LENA trials by focusing on communication of study related information and blood sampling of time-critical and sensi-tive parameters. As first step, the entire team (principle inves-tigator, physicians, nurses) of every clinical centre involved in the project attended a hands-on simulation training at the specialised Medical Simulation Centre in Salzburg. During this training, LENA specific situations were exercised using manikins and original medical devices. Video-based de-briefing of the scenarios enriched the learning experience. In the second training step, the complex PK/PD sampling procedure was refreshed during an on-site training. Scope of this individualised training element was to evaluate the trial centres' capability for obtaining samples for all pharma-cokinetic and pharmacodynamic investigations as required in the most realistic scenario possible. This phase was de-signed to resemble a regular LENA study-visit and included performance of study related procedures from sampling to bioanalysis at the central laboratory utilising healthy volun-teers. Third, -if requested-the clinical teams were accompa-nied during the first paediatric patient visits by experts to ensure the maximum support during recruitment and study conduct in the beginning. Additionally, participants' perfor-mance and preparedness for the study as well as the useful-ness of the training were assessed using surveys based on five-point Likert scales.

Results 23 participants from five different European coun-tries were trained at the simulation centre. The performance in sampling of time-critical humoral parameters was op-timised to meet the predefined time limits, and to enable maximum reliable data extraction by reducing invalid sam-ples. Participant's abilities to communicate core elements of the studies and to successfully perform PK/PD sampling increased significantly ($p=0.0003$). The on-site training re-vealed results out of specification at one site. After repeating the on-site training, PD samples collected at all sites allowed for detection of sensitive parameters in low sample volumes. PK data were within the expected specifications.

Conclusion Simulation training and on-site training sub-stantially improved the participants' performance. This tai-lored training was assessed as a helpful teaching tool in trial preparation and lead to good recruitment rates within the LENA project so far. Further follow-up surveys will evaluate the actual impact of this training on the study success.

The research leading to these results has received funding from the EU's Seventh Framework Programme (FP7/2007-2013) under grant agreement n°6 02 295 (LENA).

O-41 PHARMACOGENOMIC STUDIES OF CORTICOSTEROID EFFECTIVENESS IN PAEDIATRIC ASTHMA: A SYSTEMATIC REVIEW

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10.1136/archdischild-2017-esdppp.41

Background Genetic variations has the potential to al-ter therapeutic efficacy. The aim of the study is to analyse polymorphisms associated with variation in response to corticosteroid treatment in paediatric asthma patients. Asthma is one of the most common chronic respiratory diseases in childhood, with about 300 million asthmatic patients worldwide and a sharp increase in their preva-lence. Despite corticosteroids being highly effective for the chronic treatment of asthma, there are variations in therapeutic responsiveness. These variations can be at-tributed to a degree of heterogeneity, which is associated in part to genetic variation. This provide the rationale for pharmacogenetic studies of corticosteroids.

Methods Relevant literature was identified through CENTRAL, CINAHL, MEDLINE and Scopus. Studies in which pharmacogenetic methods, such as genome-wide association studies, candidate gene studies and genome sequencing, were used to identify and repeatedly vali-date the effect of one or more single nucleotide polymor-phisms on the efficacy of inhaled corticosteroids.

Results The search returned 341 studies, with 23 full text articles assessed for eligibility. We excluded 14 full text articles with the remaining 9 studies included (incorpo-rating analysis of 210 SNPs and including in over 7000 children). Variants that enhanced response to cortico-steroids include CRHR1 (rs1876828), T gene (rs3127412 and rs6456042), TBX21 gene (rs2240017) in TXB21 gene, ORMDL3 (rs2872507). Genes containing polymorphisms predictive of reduced response to corticosteroids were FCER2 (rs28364072) and ST13 (rs138335 and sr138337), and GLCCI1 (rs37972). Successful replication of CRHR1 and FCER2 in additional publications has been achieved, but GLCCI1 was not successfully replicated. Various out-come measures were used across the studies.

Conclusion Numerous SNPs that alter the effectiveness of corticosteroid treatment in asthma have been identi-fied, but external replication has been limited to date, and application into clinical practice is not routine.

O-42 EPTRI – EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH INFRA-STRUCTURE TO PROMOTE TECHNOLOGY-DRIVEN PAEDIATRIC RESEARCH

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ID-EPTRI project, coordinated by CVBF-TEDDY (Consorzio per Valutazioni Biologiche e Farmacologiche European Network of Excellence for Paediatric Clinical Research), has been submitted on March 29th, 2017, with-in the INFRADEV-01–2017 single-stage call for proposals with the aim to create the framework for a new Research Infrastructure (RI) intended to enhance technology-driven paediatric research in discovery and early develop-ment phases to be translated into clinical research and paediatric use of medicines.

The project arises from the need to find answers to the serious lack of medicines for children in EU and world-wide and to propose development models for paedi-atric medicines that integrates technology-driven as-pects with clinical trials. The interest for Paediatrics was indeed mentioned in the ESFRI Road Map 2016 (http://www.esfri.eu/sites/default/files/20160309_ROADMAP_ browsable.pdf) where it was recognised that a similar RI should be included into the landscape of the research in Europe.

The main idea underpinning the project is to provide the European scientific community with a new Research
Infrastructure: EPTRI, the European Paediatric Trans-lational Research Infrastructure aimed to harnessing the research and services for the development of med-icines for children, as well as identify gaps in paediatric medicines research which prevent efficient use of re-search technologies across pertinent medicine research fields, from discovery and preclinical phase, all the way to ameliorate the therapeutic use of medicines in clini-cal practice. Sharing understanding of patients' needs and concerted efforts in critical areas of research will end in further enhancing the health of children and will also have a positive impact on European competitiveness in the pharmaceutical sector.

EPTRI will be a complementary RI in the context of the existing RIs covering the current gaps in paediatric medi-cines. The new RI will represent a 'one-stop-shop' and will act as a paediatric common service with three already es-tablished Research Infrastructures (BBMRI, EATRIS, ECRIN) strengthening collaboration within the scientific paediat-ric community.

The project is aimed to prepare 'on field' a whole **Conceptual Design Report (CDR)** of EPTRI, describing the scientific and technical requirements as well as the key components of this new RI. To prepare the CDR, the proj-ect will encompass three phases.

During the **Context Analysis phase**, that will be per-formed in 5 technical and scientific domains (1-Paediatric Medicines Discovery, 2-Biomarkers, 3-Paediatric Pharma-cology, 4-Formulation Science, 5-Underpinning Paediat-ric Studies), the perceived value and the possible gaps to be covered will be estimated, by enquiring the scientific Communities, the concerned national Authorities and many other Stakeholders.

During the **Operational phase**, the different compo-nents of the new RI will be organised, including gover-nance model, strategies for interaction with national Au-thorities and the existing RIs, the IT-architecture model, services to be provided and a business plan.

Finally, a **Feasibility phase** is proposed to develop virtu-al exercises simulating the operations of the RI.

Poster Presentations

PP-2 ETHANOL CONTENT IN REGISTERED PAEDIATRIC PREPARATIONS: ADDRESS THE EXCESS

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Background Ethanol is commonly used in many pe-diatric liquid formulations as a solvent or preservative, with concentrations varying widely between products per formulation design. Therefore, acute or chronic use of certain products in paediatric patients may expose them to excessive amounts of ethanol. Both the U.S. Food and Drug Administration (FDA) and the Europe-an Medicines Agency (EMA) recommend to exclude ethanol from medicinal products intended for use in children whenever possible. If deemed necessary, however, the FDA has set (1995) a maximum quantity of ethanol content in over-the-counter (OTC) pediat-ric formulations for different ages. Recently (2014), the EMA suggested to lower the ethanol content limit set previously (2006). The use of ethanol in paediatric for-mulations is being evaluated these days by the Israeli Drug Registration Department and new regulations regarding limitations of ethanol content in liquid pediatric formulations (both OTC and prescription drugs) are being finalised. The objective of our study was to com-pile a list of oral liquid paediatric formulations registered in Israel that contain ethanol, and identify products whose ethanol concentration may produce dangerous ethanol blood levels in infants, either by taking the recommended dosage or by accidental consumption of large amounts of the preparation.
Methods The Israeli Drug Registry was searched using the following keywords: elixir, solution, syrup, suspension, drops, tincture and ethanol, and the results were sent to the Drug Registration Department to provide the exact amounts of ethanol in each product per manufacturer's data. Thirty-nine registered products were identified, of which 29 are currently registered for paediatric use. The majority of formulations are indicated for the treatment of cold and cough symptoms (n=14). Other formulations include antihistaminic, antiemetic and sedative prepara-tions (n=6); analgesics and antipyretics (n=3); antibiotics and anti-epileptics.
Results The preparations were found to differ widely in ethanol content, ranging from <1% v/v to 66.4% v/v. The majority of products (n=28) contain 1%–20% v/v of ethanol, 2 products contain 20%–50% v/v of ethanol, and 1 product contains a very high concentration of ethanol (66.4% v/v). Most of the paediatric products are not ex-pected to produce ethanol blood levels that exceed the upper limit allowed (25 mg/dL) following administration of the recommended dose. However, for a 2-year-old child weighing 12 kg (on average), an accidental intake of an entire bottle of such medications may result in much higher ethanol blood levels, which

may reach the toxic ethanol blood level of 50 mg/dL and even higher.

Conclusion Ethanol consumption is strongly discour-aged during pregnancy and lactation, whereas children are constantly at risk for exposure to ethanol through routine use of registered medications. Many paediatricians and parents acknowledge the harmful effect of ethanol in this young population, but are unaware of the high potential for exposure. More than half (n=26) of the available products that contain alcohol do not meet the require-ments set by the new Israeli regulations and would be subject to changes accordingly (either in total volume or alcohol content of the formulation).

PP-4 DIAGNOSTIC AND THERAPEU-TIC APPROACHES IN CHILDREN WITH ASTHMA IN LOMBARDY REGION, ITALY

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Background Asthma is the most common chronic dis-ease in childhood and it represents a huge burden for children and their families. Pharmacological therapy is es-sential to control symptoms and to prevent asthma epi-sodes. Periodic monitoring of airway function is necessary in asthma management, and guidelines recommend the use of spirometry at the initial assessment and after treat-ment is initiated and symptoms have stabilised, and every 1–2 years or more frequently.

Methods Data collected in healthcare administrative databases of Lombardy region, Italy, were analysed. A co-hort of 78 184 children born in 2002 in Lombardy region was followed for the first 10 years of life. Children were identified as potential asthmatics (PA) according to the following criteria, previously validated: one or more pre-scriptions of anti-asthmatic drugs (R03 group of the Ana-tomical Therapeutic Chemical classification system), with the exclusion of nebulised formulation, and at least one prescription occurring after the 5th birthday. Children re-ceiving anti-asthmatic prescriptions for two consecutive years (chronic treatment) were subsequently selected. The first anti-asthmatic drug prescription was identified as 'index prescription (IP)', and drug prescriptions in the 24 months after the IP were analysed with the aim to eval-uate the changes in asthma therapy. Moreover, the rate of monitoring (allergologist/pneumologist visit and/or spi-rometry testing) in the 12 months before and 24 months after the IP was estimated.

Results In all, 4475 children (6% of the sample) were identified as potential asthmatics treated for at least 2 years. 60% of PA started with one active substance (monotherapy): 38% had a prescription of a short-acting beta2 agonist (SABA), 37% of an inhaled corticosteroids (ICS) and 22% of a leukotriene receptor antagonist (LTRA). Of the subjects starting with a polytherapy, 88% received SABA+ICS. In the 24 months after the IP, 22% continued with the index active substance, 45% switched to other anti-asthmatic drugs, 19% had a step-down of the initial therapy, while 14% had an add-on. Between 12 months before to 24 months after the starting date, 33% of po-tential asthmatic children had a specialist visit and/or a spirometry testing. In particular, the rate of monitoring was 11% in the year preceding the start of the asthma therapy and 28% in the following 2 years. The percentage of monitored children was greater in children who had their IP after their 5th birthday (43% versus 22%), while no differences were found between genders. Differences existed between local health units, with an incidence of asthma ranging between 4% and 9%, and a frequency of monitoring between 17% and 54%. An inverse correla-tion was found at local health unit level between asth-ma incidence and percentage of PA with a monitoring. (rS=−0.6464)

Conclusion The initial therapy appears adherent to guidelines, even if in many cases modifica-tions were necessary to obtain optimal asthma control. The finding that only 1 out of 3 children was monitored at least once before and/or after the start of the therapy is a reason for concern and underlines the need for a better compliance to guidelines recommendations.

PP-6 INTEGRATION AND VALIDATION OF THE EX VIVO HUMAN PLACENTA PERFUSION MODEL

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Background Pregnant women and their fetuses are or-phan populations with respect to knowledge on safety and efficacy of drugs. It is estimated that over 90% of pregnant women uses over-the-counter or prescription medication.[1] Albeit, data on transplacental transfer or fetal effects are still lacking for most of the medicines and food supplements. The *ex vivo* human placenta perfusion model is an effective and non-invasive method to study transplacental passage of drugs and environmental com-pounds in humans.[2] It is the only method that retains the full structure of a full term human placenta, making it possible to study transplacental passage without harming the foetus or the mother.[3] Due to many challenges and its high complexity it remains difficult to incorporate it routinely into laboratories.

Methods A step-by-step protocol for the implementa-tion and validation of a closed-closed *ex vivo* perfusion model was developed. Different quality controls were implemented to ensure the integrity, viability and func-tionality of the method: (i). Antipyrine is a small drug molecule that does not bind to proteins and that passes the placental barrier by passive diffusion; It was used here to determine 'overlap' (solute exchange) between foetal and maternal circulation; (ii) the pressure and the flow rate in the foetal circulation as a marker for leakage; (iii) pH and glucose consumption were implemented as a marker for tissueviability.

Results In total 89 placentas were collected of which 34 placentas were successfully perfused with antipyrine and fulfilled all quality control measurements. A foe-tal/maternal antipyrine concentration ratio of 0.75 was reached within 89±21 min, while 210 min were required to achieve equilibrium. The foetal pressure remained un-der 70 mmHg during the entire experiment. The end foe-tal flow was 98% of the foetal starting flow. The average glucose consumption was 0.30±0.15 µmol/min/g. Every 30 min the maternal pH declined to 7.29 ±0.06 and was adjusted to 7.4. The foetal pH stayed stable at 7.30±0.05.

Conclusion Based on the multiple quality control mea-surements, the described method of a closed human ex-vivo placenta perfusion model was validated. The success rate (38%) was more than twice the success rate reported in literature (15%).

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PP-8 TRANSITION INSTEAD OF TRANSFER FOR DRUG TREATMENT IN ADOLESCENT DIABETES TYPE 1

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10.1136/archdischild-2017-esdppp.46

Background Diabetes mellitus is one of the most com-mon diseases in childhood and the incidence increased over the past 20 years about 3%–4%. Micro-and macrovas-cular complications, due to poor metabolic control, can lead to long-term complications such as high blood pres-sure. Especially in adolescence lower medication adher-ence is a huge risk for complications. The DIADEMA study,

a randomised controlled trial, has shown that community pharmacists can have a positive impact on therapy ad-justment and glycemic control of adolescent diabetes patients The objective of this analysis was to understand how the intervention provided by the community phar-macist can help to support transition of the adolescent into adulthood regarding drug treatment.

Method A quantitative, statistical analysis of the 39 inter-vention group patients case-report-forms was conduct-ed, to evaluate the impact of community pharmacists on the different outcomes e.g. fasting blood glucose levels. A Wilcoxon-signed-rank test or fisher-extact test were used to evaluate the difference in the amount of self-moni-toring of blood glucose (SMBG), daily insulin injections, average fasting blood glucose levels, insulintherapy ad-herence, daily insulin dose and number of patients, which are following their nutrition plan or doing exercise or hav-ing hypoglycemic episodes. Inconsistent and imprecise data were excluded from the statistical analysis. Missing data was marked with n.a. and before the analysis was conducted a significance level of alpha=0.05 was set.

Results The statistical analysis revealed that pharma-ceutical care provided by community pharmacists can support transition of the adolescent regarding drug treatment becasue it resulted in more frequent SMBG, a greater amount of patients complying to their individual nutrition plan and injecting the correct insulin dose. Ad-ditionally, the insulintherapy adherence increased and resulted in lower fasting blood glucose levels. However, all these changes did not lead to an increase of hypogly-cemic episodes.

Conclusion The DIADEMA study demonstrated that ad-olescent diabetes patients benefit from the community pharmacists´approach to guide transition of drug treat-ment into a self responsible behaviour. With this empow-erment patients achieved better glycemic control mea-sured by lower HbA1c-values (1). Better glycemic control can minimise the risk of short-and long-term diabetes related complications such as retinopathy or blindness.

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PP-10 ADVERSE DRUG REACTIONS IN HOSPITALISED CHILDREN IN AN ACA-DEMIC HOSPITAL IN THE NETHERLANDS

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Background In paediatrics, 80% of the prescribed drugs are off label or unlicensed. From previous research its known that the amount of adverse drug reactions (ADR's) in off label or unlicensed drugs are higher in comparison to drugs who are registered.[1] Reporting ADR's in The Netherlands is voluntary and can be done at Lareb, the Dutch national network for collecting and investigating ADR's. We aim to determine the quantity of reported and missed ADR's in paediatric medium care wards in an aca-demic hospital in The Netherlands.

Methods Retrospective study of all patients who were hospitalised in June 2016 on the paediatric medium care ward in an academic hospital. Two researchers in-dependently looked at discrepancy in the numbers of ADR's which were reported in the medical file by medical doctors (MD's), and the number of ADR's the researchers found based on the medical file. MD's working at the ward were not informed about the study.

Results 323 patients were hospitalised in June 2016; 310 patients received one or more drugs. 57 ADR's (possible ADR's included) were reported in the medical file by MD's. The researchers found 67 'missed' ADR's by reading the medical files. In total, 67 children (21.6%) suffered from one or more ADR's (reported ADR's and missed ADR's added together). None of the ADR's reported in the medi-cal file by MD's, was reported to Lareb (the Dutch national network for collecting and investigating ADR's).

Conclusion more than 50% of (possible) ADR's are not reported in the medical file. Possible explanations are:

1) the poor training in ADR recognition, 2) MD's think expected ADR's don't need to be reported, and 3) MD's may have struggle admitting ADR's because they feel like causing them by prescribing the drug.

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PP-12 MAG – MEDICAMENTS ADMINISTRES PENDANT LA GROSSESSE/DRUGS ADMINISTERED IN PREGNANCY

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10.1136/archdischild-2017-esdppp.48

Background Maternal drug use in pregnancy may oc-cur in different situations: chronic maternal disease prior to pregnancy, maternal disease not linked to pregnancy or complicating pregnancy and automedication. Studies in Europe and USA/Canada have shown high numbers of drugs used by pregnant women, up to 13 with prescrip-tion rates over 90% in France. This is a major healthcare issue for clinicians as more than 80% of the drugs used are used without knowledge of their safety/efficacy for the mother, have undetermined risks and possible adverse effects on the fetuses. In France, epidemiological data are insufficient to evaluate the drug use during preg-nancy and the status of the drugs prescribed (licensed/off-label).

Methods MAG is a large multicenter and prospective study conducted using an electronic questionnaire. As a collaborative project, MAG Consortium includes clinical research units of APHP (CIC1426, CIC0901), the Gynecology and Obstetrics-CIC network (GO-CIC), the 'Risks and Pregnancy' University-Hospital department and INSERM U953 unit. The objectives are to determine the extent of drug use during pregnancy, determine drug status, conditions of use (prescription/automedication), and to identify per-sonal, social and economic factors conditioning their use in a representative population of 1000 randomly selected pregnant women in France. Therefore, France was divid-ed into 7 regions with 1 perinatal network selected per region. Using childbirths epidemiological data from the French National Institute of Statistics and Economic Stud-ies, a total of 35 maternity wards will participate: 5 units per region (1 level III, 2 level II, 2 level I) with 1 private unit to ensure the best representativeness of the results with recruitments established by region and by age groups. Seven mobile CRAs are in charge of the interviews using MAG electronic questionnaire facilitating the capture and real-time monitoring of the inclusions with a list of 350 most used drugs (in pregnant women) uploaded on the platform. MAG is conducted over a period of 5 days in each centre.

Results To date, the 35 maternity wards and the perina-tal networks have been identified within the 7 regions: Yvelines (MYPA), Pays de la Loire (Sécurité Naissance), Basse-Normandie, Bourgogne (Femme et Enfant), Rhône-Alpes (Aurore) and Provence Alpes Côte d'Azur (Méditer-ranée).

From June 2016 to mid-March 2017, the MAG network allowed to recruit 860 patients in 16 centres with 13 completed weeks and 10 days of study conduct, a mean of 58 women per centre (13 centres) or 12 women includ-ed per day. MAG interviews are less than 30 min per woman. A refusal rate of 15% was observed reflecting that MAG was very well received among pregnant wom-en. The MAG survey is still ongoing with inclusions sched-uled until June 2017. Inclusions will be extended up to 2000 patients.

Conclusion MAG study will deliver essential information of drug use in pregnant women identifying potential associated factors and determine drugs that would ne-cessitate complementary pharmacological studies. MAG will orientate information and communication strategies of health professionals and women to limit inappropriate drug exposures and provide the tools for future studies to be conducted through national surveillance networks.

PP-14 SUBSTANDARD PRESCRIPTION OF DRUGS IN A POPULATION OF OVERWEIGHT AND OBESE CHILDREN. AN OBSERVATIONAL RETROSPECTIVE COHORT STUDY

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Background Obesity is a major area of public health concerns, since it is associated with a wide range of se-rious health complications, including diabetes type 2, musculoskeletal disorders, sleep apnea, depression, asthma, hypertension, and cancer. Consequently, obese children are more likely to receive drug treatment than their normal weight peers. Further, obesity is known to be associated with changes in pharmacokinetics of drugs (1–5). Dosing overweight (OW) and obese (OB) children by the use of traditional paediatric dosage strategies (e.g. mg per kilogram or fixed dose by age) may therefore result in a potential risk of sub-or supra-therapeutic doses. We aimed to investigate currently applied dosage strategies in OW/OB children, in a clinical treatment facility. In par-ticular, whether dosage guidelines were used and metrics of body size applied with special attention to drugs with a narrow therapeutic interval and/or loading dose of clin-ical importance.

Methods A retrospective cohort study conducted at the Children's Obesity Clinic in Denmark, in the period 2008–2015. OW/OB children≤18 years, having at least one drug prescribed, were included. 200 patient records were reviewed. The study was approved by the Data Protection Agency (BBH-2014–045, I-suite 03045)

Drug treatments/prescriptions were registered with reference to the Anatomical Therapeutic Chemical (ATC) Classification System. Dosage strategies were registered as dosage by total body weight (TBW), fixed dose by age (years), use of adjusted weight measures (e.g. IBW, ABW) or dose estimation by other strategies.

Results A total number of 455 prescriptions were iden-tified, primarily distributed in ATC groups N, A, R and J. Guidelines for dosage of OW/OB children were not avail-able in the clinic, for any of the recorded drugs. Only one prescription of gentamicin was adjusted by weight (ABW) using metrics of body size. Otherwise, gentamicin was dosed after three different dosage regimens. In 35/455 prescriptions, dose was adjusted by an undocumented dosage strategy. Dose was primarily limited to the max-imum recommended adult dose, when dose (mg/kg) exceeded adult dose, i.e. acetaminophen.

Conclusion This study highlights the shortage of dos-age guidelines in OW/OB children. We found as suspect-ed a large inter-individual variability in dosage regimens even in drugs with narrow therapeutic intervals or drugs which has loading doses important for clinical effects. The clinicians are left with 'best practice', as evidence based dosage regimens are missing for several drugs prescribed during childhood.

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PP-16 IN SEARCH OF AN ALGORITHM FOR CALCULATION OF ANTIBIOTIC USE IN A CHILDREN´S HOSPITAL

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Background The analysis of antibacterial consumption in association with patient-specific parameters allows con-clusion on the efficiency of antibiotic treatment and may predict development of antibacterial resistance. Accurate and consistent measures of therapeutically used antibiot-ics are required for

meaningful inter-and intra-institutional comparisons. The commonly used algorithm to measure in the adult population is based on the ratio of DDD/PD.

Thus, the consumed amount of a specific antibiotic is quantified by units of defined daily dose (DDD) and relat-ed to number of inpatient days (PD) at a defined hospital setting as denominator.Calculations using DDD/PD do not take into account the individual characteristic and heterogeneity of the paediatric population in terms of weight, age and disease spectrum compared to adults. Alternative calculations, such as days of antibiotic treat-ment (DOT) independent of dose; and prescribed daily dose (PDD), are not applicable at all hospital settings due to lack of specific electronic recording, and don't allow comparisons across all age groups.This study deals with the development and evaluation of a novel algorithm, allowing intra-institutional comparison of antibiotic con-sumption across all age groups and hospital units repre-senting diverse range of pathologies.

Methods The use of antibiotics was assessed in a large paediatric clinical setting encompassing all relevant wards, such as neonatology, newborns, internal wards, surgery, paediatric oncology and intensive care units. The analysis differentiated the classes of antibiotics dependent on their antimicrobial properties, including antibiotics with activity against MRSA/MRSE, last-resort-and broad spec-trum antibiotics. Several parameters were tested as Nom-inator and Denominator and results were evaluated by relating the consumption of each ward to average age of patients, length of inpatient stay, severity of disease and proportion of parenterally administered antibiotics.

Results An algorithm was identified, able to delineate the usage of antimicrobial medication among the different hospital units in accordance with their estimated vulnerability for infectious disease. The metric is restricted to antibiotics administered by parenteral route, shows a negative correlation with age, and emphasise the antibi-otic consumption of neonatal units.

Conclusion Currently there is no single antibacterial consumption measure for the paediatric populations. Stratifying patients by age and/or weight is required. However, for intra-institutional comparisons at paediatric hospitals, a single metric comprising all the diverse popu-lations would be helpful.

PP-18 RANITIDINE-INDUCED THROMBOCYTOPENIA IN A NEONATE-A CASE REPORT AND REVIEW OF LITERATURE

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Background Thrombocytopenia is defined as a plate-let count <150×109/L.[1] It regularly occurs in newborns, but is especially observed in critically ill neonates.[2,3] Early (<72 hours of life) and late (>72 hours)-onset thrombocy-topenia are caused by different categories of underlying conditions. Chronic fetal hypoxia and sepsis or necrotiz-ing enterocolitis are by far the most frequent causes of, respectively, early-and late-onset neonatal thrombocy-topenia.[1,3]

Methods We describe the clinical case of a SGA (small for gestational age) neonate who experienced a severe ranitidine-induced thrombocytopenia. An extensive lit-erature search was performed to document other cases of ranitidine-and H2-antagonist-induced thrombocyto-penia. Furthermore, other case reports of drug-induced thrombocytopenia in newborns were explored.

Results We report on a late preterm male infant, who showed an unexpected, severe thrombocytopenia (8 × 109/L) at day 5 of life. He was born SGA and had also showed a mild early-onset thrombocytopenia with a low-est platelet count of 87 × 109/L on day 1, spontaneously normalising by day 3 (169 × 109/L). The low platelet count on day 5 only minimally responded to platelet transfu-sion. It did however recover completely within 5 days after cessation of ranitidine (4 × 0.5 mg/kg/day), which was started on day 3 of life in a context of feeding diffi-culties. Other causes of neonatal thrombocytopenia were explored and ruled out. The likelihood of an adverse drug reaction in this case was indicated as 'probable' on the Naranjo scale.[4] Besides a brief report on a cimetidine-in-duced thrombocytopenia over 25 years ago,[5] no other neonatal or paediatric cases of H2-antagonist-induced thrombocytopenia have been reported to date. Several adult cases have been published nevertheless.[6] It seems that neonatalthrombocytopenia, although one of the most frequent haematological conditions in newborns, is only rarely attributed to an adverse drug reaction.

Conclusion Neonatal thrombocytopenia is a frequent haematological abnormality and has a variety of causes. In rare cases, this low platelet count might be caused by an adverse drug reaction, supposedly immune-mediated. Although H2-antagonist are widely used in paediatric and neonatology departments, we describe the first case of a severe ranitidine-induced thrombocytopenia in a neo-nate. We believe that SGA infants are more at risk because of their inherent state of bone marrow depression at birth. Clinicians should be aware of the risks for (unexpected) adverse reactions, especially in routinely used drugs and in critically ill patients. Case reports may aid in expanding our knowledge of rare pharmacological complications.

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PP-20 THE USE OF PHYSICAL ACTIV-ITY TRACKERS IN CLINICAL RESEARCH – AN OVERVIEW

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Background The number of clinical trials using wear-able physical activity trackers is increasing. The benefits of using consumer-level wearable activity trackers in clinical research are low costs, consumer friendliness and easy at-home monitoring in contrast to medical-grade accel-erometers. Paediatric studies could benefit from using activity trackers to monitor physical activity in real-life conditions. The objective of this analysis was to provide an overview over the use of physical activity trackers in clinical research.

Methods The National Library of Medicine's PubMed database was searched for clinical trials on physical ac-tivity trackers using the following search term: 'activity tracker' [MeSH Terms] OR 'activity tracker'[tw]. All of the resulting articles were reviewed and assessed regarding year of publication, study design, population, study du-ration, type of activity tracker, and inclusion of paediatric patients. Only original articles and published study proto-cols (without any publications of results) were included in this overview.

Results The PubMed search resulted in 79 results. Thirty publications were excluded due to publication type (sys-tematic reviews, commentaries and protocols for which subsequent publications of study results were available). Forty-nine publications (including 9 research protocols) were further assessed. The years of publication were 2010 (n=1), 2014 (n=2), 2015 (n=15, including 3 protocols),

2016 (n=24, including 3 protocols), and 2017 (n=7, including 3 protocols). Of the remaining 40 publications, 27 articles had a total population of 1–50 participants (me-dian 24 range 1–48), 5 articles 50–100 (median 58 range 57–87), 7 articles 100–1000 (median 396 range 130–806) and 1 article 1000+ (19 000 participants). Nine studies had a duration of 1–7 days (median: 2 days range 1–7), 10 studies lasted 1–4 weeks (median 3 weeks range 1–4), 7 studies lasted 4–12 weeks (median: 9 weeks range 5–12), 8 studies lasted 12–26 weeks (median 19 weeks range 13–26), 4 studies lasted 24–52 weeks (median 52 weeks range 30–52), and 1 study lasted 104 weeks. The duration was not available for one study. A Fitbit© tracker was most commonly used (29 of 49 studies), followed by Jawbone© (8/49), Garmin© (4/49), Withings© (4/49) and Nike© (3/49). Median wearing adherence was 64.8% (range: 31.7%–85%) in 14 studies (including 2 paediatric trials). Only 7 of 49 studies were in the paediatric setting, of which 2 were published protocols. A total number of 157 children (median 24 range: 16–87) participated in the 5 paediatric trials. The median age of the children was 8.9 years (range 3–17). A total number of 102 boys were included in the trials (65% of participants). Median wearing adherence in 2 paediatric studies was 78.5% (range 28%–98%)

Conclusion The use of wearable physical activity track-ers is becoming more popular in clinical research. This analysis revealed promising tracker wearing times with an overall median of 64.8% and a paediatric median of 78.5%. The adherence and feasibility of the use of activ-ity trackers should be further investigated in paediatric research. Physical activity trackers are a promising tool to obtain objective data on physical activity during real-life conditions in children with chronic diseases who partici-pate in clinical or pharmacological trials.

PP-22 ADHERENCE TO LABELLING GUIDELINES, THE CASE OF FLUOROQUINOLONES. RESULTS OF A RETROSPECTIVE MULTICENTER DRUG UTILISATION STUDY

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Introduction Labeledpediatric indications for prescription of fluoroquinolones (FQ) are limited. Furthermore, the safety of systemic FQ for growing children has been debated for a long time.[1,2] Nevertheless, prescribing FQ for children can be advantageous. First, FQ cover a broad spectrum of bacteriae.[3] Second, pharmacokinetic (PK) characteristics of systemic FQ are favourable. The bioavailability of common FQ agents is usually high and FQ typically penetrate in deep compartments.[4,5] In this retrospective multicenter drug utilisation study, we aimed to investigate indications for FQ prescription in a population of children hospitalised in two Belgian university children's hospitals. Additionally, another goal was to assess the adequacy of prescribed doses, and risk factors for incorrectly dosed FQ prescriptions within our population.

Methods Using data obtained from electronic medical files, the study included all children who received a sys-temic FQ prescription in two Belgian university children's hospitals between 2010–2013. Two authors reviewed pre-scribed daily doses. Univariate and multivariate logistic regression models were used to analyse risk factors for inadequately dosing.

Results A total of 262 FQ prescriptions for unique pa-tients were identified. Most children (57.6%) had signifi-cant chronic comorbidity such as any type of cancer, a neurologic disease, or congenital anomalies of the kid-neys and urinary tract. Ciprofloxacin was by far the most frequently prescribed FQ, representing 253 prescriptions (96.6%). Overall, the number of on-label FQ prescriptions was 43 (16.4%), and prescription was guided by a micro-bial culture in 62 cases (35.1%). 79 prescriptions (30.2%), of which 78 ciprofloxacin prescriptions, were considered to be inaccurately dosed. Underdosing was the most common type, as 57.1% of all inaccurately dosed pre-scriptions were underdosed. In the univariate logistic regression analysis, children younger than 6 years of age were at particular risk of receiving an inadequately dosed prescription. In the final multivariate logistic regression model, when controlled for the sort of FQ prescribed, Odds Ratios for infants and preschool children remained statistically significant.

Conclusion FQ were often prescribed off-label and not guided by bacteriological findings in our study popula-tion. Dosing errors were common, particularly in infants and preschool children. FQ prescriptions for children should be improved by specific paediatric antimicrobial stewardship teams.

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PP-24 CONSENT IN NEONATAL RESEARCH: A DELPHI SURVEY INTERROGATING PARENTS OF PRETERM NEWBORNS AND HEALTHCARE PROFESSIONALS

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Background Adherence and obtaining parental con-sent for their children's participation are key factors in clinical neonatal research influenced by: the quality of the information delivered and the interaction between parents and investigators. This exchange of information is one of the most serious challenges as failure to disclose some important items by clinicians would lead to difficul-ties in decision making by parents,

not being an informed consent process anymore. This Delphi survey aims to es-tablish a consensus between parents of preterm infants and healthcare professionals on the information criteria deemed essential by both parties in order to improve the recruitment of newborns in clinical trials.

Methods This study has been conducted among par-ents of preterm newborns and healthcare professionals (pediatri Drug use during pregnancy: a systematic re-viewcians, neonatologists, obstetricians; experts in phar-macology, researchers, clinical research studies coordina-tors; ethicists and members of ethics committees). In this 3-phase study, the items were defined by the Scientific Committee (CS), composed of 11 clinicians (from 7 coun-tries: Belgium, Canada, France, Spain, Switzerland, United Kingdom, United States) and 1 European representative of newborn parents associations (European Foundation for the Care of Newborn Infants, EFCNI). Then, the Com-mittee of Experts (CE), composed of 16 clinicians and 16 parents, members of preterm newborns parents associa-tions (with a balanced distribution in 10 countries), evalu-ates these items on two occasions.

Results 96 items were selected by the SC, submitted and evaluated by the CE on a scale from 1 to 9 accord-ing to the importance they had for them, based on their personal experience and beliefs. In the first round, 63/96 items were retained (first level of consensus criteria: me-dian score above 7, 65% of responses in the top tertile between 7 and 9-). The second round, in progress, will refine this selection and only items meeting the second level of consensus criteria (median score above 7, 75% of responses in the top tertile -between 7 and 9-) will be conserved for the final consensus.

Conclusion This parental/professional consensus will improve parents' information and decision-making pro-cess, respecting ethical and quality criteria to include newborns in clinical trials.

PP-26 NEOCORD: MRNA EXPRESSION OF CYTOCHROMES AND TRANSPORTERS INVOLVED IN DRUG METABOLISM AT BIRTH, USING HUMAN UMBILICAL CORD BLOOD

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Background Growth, maturation and physiological modifications are mainly responsible for the difference in pharmacokinetics and pharmacodynamics of drugs ob-served between adults and children, especially neonates. Ontogeny of drug metabolising enzymes and transport-ers play an important role in drugs inter-individual phar-macokinetic variability in this population. Data on neona-tal developmental pharmacology remain very limited.

Neocord aims to characterise mRNA expression of the main cytochromes and transporters involved in the phar-macokinetics and pharmacodynamics of drugs in twin newborns, using umbilical cord blood, according to iden-tified covariates such as genetic background, pregnancy environment, gestational age, sex, maternal pathologies and treatments, etc. A population of twins will allow a precise comparison of individuals with different or identi-cal genetic background.

Methods Umbilical cord blood samples (2.5 ml) were collected from women pregnant with twins, both dizygotic and monozygotic, in the maternity ward of Robert-Debré Hospital using PaxGene Blood RNA tubes. Isolation and purification of total RNA from the blood samples was performed using the PAXgene Blood RNA kit with sub-sequent RNA reverse transcription (RT-PCR). Amplification of DNA and gene expression profiling was performed by real-time polymerase chain reaction (qPCR) using Ap-plied Biosystems TaqMan gene expression assay tech-nology. Expression of the 18S ribosomal reference gene was used as internal control for normalisation of expres-sion profiles. A large panel of drug metabolising enzymes and transporters genes was quantified: cytochrome P450 system (n=12), UGT family (n=6), transporters (n=3) and TPMT. Relative gene expression levels between the different samples were calculated using the $\Delta\Delta$Ct method.

Results Fifty umbilical cord blood samples (32 males and 18 females) from 25 women pregnant with twins, deliv-ering between April 2015 and March 2017, were collect-ed. Median age of the women was 33.2 years (23.2–49.5) and median gestational age at delivery was 37.3 weeks of amenorrhea (34.4–39.6). Nineteen women delivered at term and 6 delivered before 37 weeks. Five women had a monochorionic diamniotic pregnancy and 20 women had a dichorionic diamniotic pregnancy. Monochorionic twins were assumed to be monozygotic (n=10) and dif-ferent-sex twins as dizygotic (n=20). Zygosity of the 20 same-sex dichorionic twins could not be assessed.

Preliminary results were obtained after analysis of 30 cord blood samples. Females (n=12) and males (n=18) showed no differences of weight or gestational age at birth. From these 15 twins pairs: UGT1A6 and UGT2B7 expressions were not found in umbilical cord blood samples while others were expressed at different levels. Gene expression was different between newborn genders ($p<0.05$) for 5 genes: CYP2A6 ($p=0.035$), CYP2C9 ($p=0.032$), CYP3A4 ($p=0.005$), UGT1A3 (0.035), UGT1A9 ($p=0.039$), females having greater expressions of all of them.

Conclusion Identification of differences in protein ex-pression profiles will allow a better understanding of the pharmacokinetics and pharmacodynamics variability of drugs in the newborn. Such factors will help improving neonatal care and define appropriate dose regimens in the neonatal population.

PP-28 UNLICENSED AND OFF-LABEL MEDICATION USE IN A PAEDIATRIC AND NEONATAL INTENSIVE CARE UNITS AT A SINGLE MEDICAL CENTRE: NO CHANGE OVER A DECADE

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Background Many of the prescribed medications to hospitalised children are off-label and/or unlicensed. To determine the extent of unlicensed and off-label medi-cation use in the NICU and PICU at one medical centre and to compare it to a study performed in the same units thirteen years ago.

Methods All drugs prescribed to patients admitted to the NICU/PICU, during 2 months of observation, were prospectively recorded and classified as licensed, un-licensed or off-label, according to their license status, indication, age, prescribed dose, frequency and way of administration specified in each specific marketing au-thorization.

Results NICU: 134 patients were included. 1069 prescrip-tions for 49 medications were prescribed: 312 (29.2%)-li-censed. 63

(5.9%)-unlicensed and 693 (64.8%)-off-label. 23.9% of the patients received at least one unlicensed medication and 96.3% received at least one off-label medication. thirteen years ago, 16% of the prescription were unlicensed, 63% off-label and 93% of the patients received at least one unlicensed/off-label medication.

PICU: 56 patients were included. 388 prescriptions for 75 medications were prescribed. 205 (52%)-licensed,

13 (3.4%)-unlicensed, 170 (43.8%)-off-label. 86.8% of patients received at least one off-label medication, and 88.7% received at least one unlicensed/off-label medi-cation. 13 years ago, none of the medication prescribed were unlicensed, 41% were off-label and 90.5% of the pa-tients received at least one off-label medication.

Conclusion There is high prevalence of unlicensed and off-label drug use in a PICU and NICU. After thirteen years, despite regulatory efforts, the prevalence of unapproved medications is still high.

PP-30 CLINICAL UTILITY AND SAFETY OF GANODERMA LUCIDUM EXTRACT IN ACUTE LYMPHOBLASTIC LEUKAEMIA AS A ADJUVANT THERAPY: A CASE REPORT

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Introduction Acute Lymphoblastic Leukaemia (ALL) is the most common childhood malignancy. Optimal util-isation of chemotherapy in addition with supportive care achieves highest survival rates (about 85%) for children. The main problem is the drug toxicity (mostly myelosup-pression, mucositis, and nausea/vomiting) as well as re-current infections. Complementary and Alternative Medicines (CAM) are often used in Paediatric Oncology. The medicinal mush-room Ganoderma lucidum plays a pivotal role as im-mune-modulator. Medicinal mushrooms are boosters or restoring agents of the ability of the immune system to fight infections, cancer and other diseases. The main bio-active compounds in Ganoderma lucidum are polysac-charides, in the form of beta-d-glucans, and triterpenes, both with well-defined biological properties.

Beta-d-glucans have demonstrated antitumor and im-mune-stimulating activities. They modulate both innate and adaptive immune responses and increase opsonic and non opsonic phagocitosis, enhancing antitumor cytotoxicity. They also induce natural killer (NK) cell cy-totoxicity against various cancer. Triterpenes are able to inhibit cancer cell growth and activity as we showed in previous experients using different cancer cell lines.This mushroom also increases plasma antioxidant capacity and enhances immune response in cancer

Aim Chemotherapy is a cause for neutropenia, increas-ing therefore the susceptibility to infections. Ganoderma lucidum previously showed to increase lymphoprolifer-ative responses in immunocompromized children with cancers in a randomised, double-blind and placebo-con-trolled study. However, clinical evidence supporting the use of medicinal mushrooms in paediatric patients is still scarce. Therefore, we decided to investigate the role of this mushroom in improving the quality of life, prevent-ing recurrences and infections in patients affected by ALL. Prior to any use the product developed, based on Local strains from Ganoderma lucidum, showed no inter-ference with the hepatic cytochromes, as we showed in previous studies

Case study A 4 year old boy with confirmed diagnose of ALL type B without leucocitosis finished his chemothera-py treatment 2 years after the initial diagnose date, with a complete remission. The patient followed the protocol 58 081 of the EORTC with good response. After getting the Informed Consent from their parents, and estimate the initial dose based on BW (mg/Kg), the child received an oral dose of 445 mg of Ganoderma lucidum powder (Bioganoderma ©) daily with excellent tolerance. Six months later, we decided to double the dose with ex-cellent clinical response as well as tolerability. Two years later, daily providing the same oral dose, the patient still was free from infection (the neutropenia was corrected), no recurrence of his malignancy) or side effects referred. Blood tests are absolutely normal, as well as the myelo-gram. In fact, currently he follows a complete normal life (school, outdoors activities).

He does not have any neurological or hepatic con-sequences from this treatment. His parents referred an impressive improving in his performance status since the child has being taking this mushroom compound, Ganoderma lucidum.

Conclusions We need novel therapeutic approaches for Paediatric Cancer in order to improve the quality of life, prevent consequences and recurrences. As for adults, Ganoderma lucidum is an excellent opportunity for pae-diatric patients due to its safety, tolerability and clinical response.

PP-32 DO PLASMA AMINO ACID LEVELS REFLECT ARGININE METABOLISM IN PARENTERAL NUTRITION (PN) DEPENDENT VERY PRETERM INFANTS?

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Background Arginine plays an important role in several metabolic pathways as well as being a substrate for pro-tein synthesis. Arginine metabolism involves multi-com-partment processes that vary according to cell type/body organ. Enterocytes are a major site for arginine synthesis. The key amino acid (AA) metabolites of arginine synthesis pathways in the enterocytes of very preterm infants (VPIs) include glutamine, glutamate and proline with interme-diates ornithine and citrulline. The key arginine degrada-tion AA metabolite in the liver is ornithine. In contrast to these metabolically active AAs, histidine is presumed to be a metabolically inert AA and hence probably a useful indicator of non-metabolic factors (e.g. renal elimination). Newborn infants are dependent on enteral milk proteins for the AAs required for enterocyte arginine synthesis. However VPIs are dependent on parenteral nutrition (PN) and therefore parenteral AA for the first 2 weeks of life un-til milk feeds are established.

Methods Secondary analysis was performed on the plasma AA data collected during a previously published randomised controlled trial.[1] Plasma AA were collected in the second week of life in infants randomised to receive either 3.2 g/kg/d (standard) or 4.3 g/kg/d (high dose) par-enteral AA.[2] A Spearman's correlation analysis was run on the plasma data for the AA subgroups involved in argi-nine metabolic pathways to assess their relationship with arginine in the VPI population. The data also underwent multivariate regression analysis

(combining both groups) to test if any of these AA significantly predicted plasma arginine levels.

Results Plasma AA levels were performed on median (IQR) day 9 (8-10) in both groups. Mean (95% confidence intervals) plasma arginine levels were 41 (25-57) and 35 (22-46) micromol/litre in the high and standard AA dose groups respectively ($p=0.21$) well below the reference range minimum (57μmol/L). Data analysis showed that arginine had the strongest positive correlation with or-nithine, $r=0.602$, $n=107$, $p<0.001$, followed by gluta-mine, $r=0.564$, $n=107$, $p<0.001$. A significant regression model was found [$F(3,103)=24.318$, $p<0.001$] with an $R2=0.415$

Conclusion Plasma ornithine, glutamate and histidine are significant predictors of plasma arginine in PN depen-dent VPIs. This indicates that there are both metabolic and non-metabolic factors that play a role in determination of plasma arginine levels.

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PP-34 ADVERSE DRUG REACTIONS IN NEONATES: COMPARING RETROSPECTIVE SPONTANEOUS YELLOW CARD REPORTS TO PROSPECTIVELY COLLECTED REPORTS

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Background The UK Medicines and Healthcare prod-ucts Regulatory Agency (MHRA) encourages the report-ing of all adverse drug reactions (ADRs) in children that are 'serious or result in harm'.[1] The rate of under-report-ing of ADRs has been estimated to be approximately 94% and neonatal ADR reports are not influencing the clinical warnings issued by the MHRA.[2,3] This study aims to compare reports of neonatal ADRs actively collected by a researcher from a tertiary neonatal unit to those reported to the UK yellow card system between 2001 and 2010.

Methods An independent researcher collected data on ADRs in a tertiary neonatal care unit by daily ward round attendance, note reviewing and staff questioning. The results collected over four weeks were then compared to the yellow cards submitted to the MHRA between 2001 and 2010 by means of reviewing a recently published paper.[3]

Results Between 2001 and 2010 there were ninety seven yellow card reports of neonatal ADRs to the MHRA. Over a four week observational period thirty three neonatal ADR cases were suspected and reported by a researcher. The highest number of yellow card reports were for swine flu vaccinations (eight), whereas the researcher only collected one report relating to a vaccine, with the highest number of reports involving diuretics or antibiotics (six each). The yellow card reports most frequently reported rashes or erythema (twenty one) whereas the researcher most frequently reported electrolyte disturbances (seven), car-diac effects (five) or gastrointestinal effects (five).

Conclusion There are a number of differences between neonatal ADRs reported to the MHRA and those occur-ring commonly. It is thought the predicted under-report-ing of ADRs and lack of knowledge or attention to neona-tal ADRs may be contributing to this.

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PP-36 THERAPEUTIC INDICATIONS FOR USE OF EXTEMPORANEOUS GLUCOCORTICOID FORMULATIONS IN CHILDREN – THE GLUFIC STUDY

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Background The majority of young children with wheezing have transient symptoms typically associated with viral upper respiratory tract infections and do not have increased risks of asthma later in life. Episodes with severe respiratory symptoms are reported in these chil-dren too. How to diagnose these patients makes clear ev-idence based treatment guidelines unfeasible. Children aged 0–5 years with wheezing may be symptomatically treated with inhaled short-acting beta-2-adrenergic-ago-nist therapy. If no relief of symptoms or severe symptoms, treatment guidelines recommend oral or systemic gluco-corticoids. Since no exact therapeutic interval exists for oral glucocorticoids, there is inconsistency on the dosing recommendations. Moreover, currently the only licensed glucocorticoid preparations in Denmark are tablets or i.v. formulations. These formulations are not suitable, since young children are unable to swallow tablets, and i.v. ad-ministration is associated with unnecessary discomfort. In consequence, children younger than 5 years are treated with extemporaneous preparations, off-label, or unli-censed medications. Use of extemporaneous formula-tions prelude several drawbacks e.g. formulation diversity, differences in bioavailability, limited shelf-live, safety-pro-file, taste etc. Despite the wide therapeutic index of glu-cocorticoids, it is important that they are administrated at the lowest effective dose as a considerable number of dose dependent adverse events exist for these drugs.

Objective To describe the use of extemporaneous glu-cocorticoids in children≤5 years of age diagnosed with acute symptoms of asthmatic bronchitis, compared to existing guidelines across three regional paediatric depart-ments. Second, to examine if high or low dose glucocor-ticoid influences the length of hospitalisation.

Methods A descriptive, chart-based study including three paediatric departments in the Capital Region of Denmark. All patients 0–5 years of age diagnosed with acute symptoms of asthmatic bronchitis in 2013–2015 were eligible for inclusion at the day they received at least one extemporaneously prepared administration of pred-nisolone.

Results During the three-year period almost 560 ad-missions were included, of which 70% were boys. The average age

was 22,3 months±13,3, and the average weight 12,2 kg ±2,9. A priori, the paediatric wards used dif-ferent dosing regimens, which were reflected in the data, primarily varying from 1 mg/kg to 2 mg/kg for the first dose administrated. The patients received eight different kinds of extemporaneous formulations, with no obvious pattern of choice. For statistical analyses COX-regression were used. No coherence between dosing and length of hospitalisation were found.

Conclusion This survey shows that the paediatric depart-ments used a variety of extemporaneous liquid prednis-olone formulations interchangeably. The degree of in-consistency raises issues concerning optimal dosing and potential toxicity. Since no association between higher doses and shorter length of hospitalisation were found we hope to encourage the paediatric departments to align the choice of formulation and dosing in order to select lowest effective dose.

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PP-38 GETTING PAEDIATRIC MEDICINES ON-LABEL – SCOPING THE NEEDS FOR PAEDIATRIC FORMULATION OF OLD MEDICINES

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The Rosalind and Morris Goodman Family Paediatric Formulations Centre of the CHU Sainte-Justine is a new non-profit organisation dedicated to supporting the development of safe and efficacious medicines that have a child-friendly formulation. One way of providing these paediatric medicines is to partner with industry to promote commercialising of a suitable paediatric formulation for commonly used medicines currently only avail-able in adult formulations. Working with all stakeholders including, pharmacists, paediatricians, Health Canada and the pharmaceutical industry, the Goodman Centre has identified commonly used off-label medicines that are currently compounded in pharmacies to produce pedi-atric formulations. In many cases, paediatric formulations and indications are available in other jurisdictions yet they have not been submitted by industry to Health Canada for regulatory approval. Using this novel approach, the Centre is to partnering with pharmaceutical companies to use existing data that has been submitted in other jurisdictions for Canadian approval. We will provide an overview of the Goodman Centre and outline the novel approach developed to improve access to paediatric for-mulations that we have undertaken.

PP-40 PRENATAL ANTIBIOTIC EXPOSURE AND CHILDHOOD CHRONIC DISEASE: A POPULATION-BASED STUDY

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Importance Antibiotic use during infancy alters gut microbiota and immune development, and is associated with an increased risk of several childhood diseases. The impact of prenatal antibiotic exposure is unclear.

Objective To determine and characterise the association of prenatal antibiotic exposure and childhood IBD, diabe-tes, allergy, cholestasis and connective tissue disorders.

Design Population-based cohort study using admin-istrative healthcare data. Antibiotic use was determined from prescription records. Diseases were defined using hospitalisation records, physician billing claims, and pre-scription records. Associations were determined using Cox regression and expressed as hazard ratios (HR) and 95% confidence intervals (CI).

Setting General population in Manitoba, Canada.

Participants 2 13 661 mother-child dyads born from 1996–2012.

Exposure Maternal antibiotic use.

Outcome childhood IBD, diabetes, allergy, cholestasis and connective tissue disorders

Results In our study population, 36.8% of infants were prenatally exposed to antibiotics. Prenatal antibiotic ex-posure was associated with an increased risk of IBD (HR 1.59 (1.46–1.71), cholestasis (1.46 (1.21–1.77)) and severe allergies (1.08 (1.01–1.15)) when controlling for maternal disease (same as child), sex, location of residence, gestational age, number of siblings, and postnatal antibiotic exposure during infancy. Higher numbers of prescriptions increased the risk for most outcomes. However, maternal antibiotics use during the 9 months before pregnancy and 9 months postpartum were similarly associated with several of the outcomes.

Conclusions and Relevance Maternal antibiotic use before, during and after pregnancy was associated with a modest, dose-dependent increase in IBD, cholestasis, and allergy risk among offspring. While our study does not support a pregnancy-specific causal relationship be-tween maternal antibiotic use and these diseases, it does provide additional warning to prescribe and use antibiot-ics judiciously, both in pregnancy and infancy.

PP-42 EVALUATION OF RHIGF-1/RHIGFBP-3 TO ESTABLISH AND MAINTAIN PHYSIOLOGICAL INTRAUTERINE SERUM IGF-1 LEVELS EARLY AFTER BIRTH IN EXTREMELY PRETERM INFANTS

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Background We conducted a phase 2 trial evaluating IGF-1 supplementation with recombinant human (rh)IGF-1/rhIGFBP-3 for prevention of complications of prematu-rity in extremely preterm infants. The primary endpoint of reduction in severity of retinopathy of prematurity (ROP) was not met; however, improvements were seen in im-portant secondary endpoints, including bronchopulmo-nary dysplasia (BPD) and intraventricular haemorrhage (IVH). In order to understand the potential influence of the rhIGF-1/rhIGFBP-3 dose regimen on outcomes, and the overall appropriateness of dosing, we evaluated se-rum IGF-1 levels, target range attainment, and correlation of IGF-1 levels with outcomes, during the trial.

Methods Infants born at gestational age (GA; wk+d) 23+0 to 27+6 were randomised to rhIGF-1/rhIGFBP-3 or standard

care. rhIGF-1/rhIGFBP-3 was administered at a dose of 250 μg/kg/24 hour (selected based on prior phar-macokinetic modelling) via continuous intravenous (IV) infusion from birth up to a postmenstrual age of 29 wk +6 d. Target levels for serum IGF-1 were 28' '109 μg/L (normal physiological intrauterine levels for GA 23–28 wk based on published literature). Target drug exposure was ≥70% IGF-1 values within target range and ≥70% intended du-ration of therapy. Serum IGF-1 levels were measured us-ing a validated radioimmunoassay at a central laboratory.

Results 121 infants were enrolled; 61 (63.9% male) were randomised to rhIGF-1/rhIGFBP-3, 60 (65.0% male) to standard care. 35/61 treated infants (57.4%), and 32/60 in-fants (53.3%) in the standard care group, were born at GA<26 wk. Mean (range) average daily dose of rhIGF-1/rhIG-FBP-3 was 248.1 (131.1–250.0) μg/kg/24 hour for the treated group. Mean (range) duration of exposure was 23.8 (0.1–45.3) days. Among treated infants, 56/61 received ≥70% intended duration of treatment and 28/61 had ≥70% of IGF-1 levels within target range. Overall target expo-sure was achieved for 24/61 treated infants. For rhIGF-1/rhIGFBP-3 treated infants, 66.2% of IGF-1 measurements were within target range vs 6.3% for the standard neo-natal care group. Mean serum IGF-1 was within target range for the rhIGF-1/rhIGFBP-3 group (39.6 μg/L) during treatment and below target for the C group (17.6 μg/L) over the same period. Very few IGF-1 measurements (1.5%) in treated infants were above the upper bound of the targeted range. Onset of endogenous IGF-1 produc-tion was estimated at around week 32 (corresponding approximately with cessation of treatment), after which both groups had IGF-1 levels within target range. In treat-ed infants, trends were observed towards lower severity of ROP (despite lack of improvement overall) and lower severity of BPD with higher serum IGF-1. Numbers of IVH events were too small to evaluate correlation with IGF-1.

Conclusion Treatment with rhIGF-1/rhIGFBP-3 at 250 μg/kg/24 hour (continuous IV infusion) achieved serum IGF-1 levels within the targeted physiological intrauterine range for ~two-thirds of measurements in treated infants. Mean IGF-1 levels were within target for treated infants but were close to the lower bound of the target range. We anticipate target level attainment could be further opti-mised to potentially improve outcomes. A phase 2b/3 tri-al is planned to continue evaluation of rhIGF-1/rhIGFBP-3 for prevention of complications of prematurity, and will explore a second, higher dose.

PP-44 DEVELOPING A PAEDIATRIC DRUG FORMULARY FOR THE NETHERLANDS

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Background As many drugs in paediatrics are used of off-label, prescribers face a lack of evidence-based dosing guidelines. Current knowledge on paediatric pharmacotherapy is empirical, practice based, and seldom systematically collected and disseminated.The overall aim was to develop an openly accessible, web based formulary con-taining best evidence based, referenced and up-to-date drug-specific information, which was acceptable to paediatricians, hospital pharmacists and general practitioners.

Methods The work was done by a team of a coordinat-ing paediatrician (0.2 fulltime equivalent (fte)), project manager (0.8 fte) and pharmacist (1.0 fte) and the multidisciplanary editorial board of 35 members. The overall budget on an annual basis was € 250 000 in the first 2 years, and currently € 220 000. The formulary started as a consensus-based formulary. From this point onwards, a dedicated pharmacist searched the available scientific literature following and assessed the risks and benefits of use in the paediatric population. The evidence is de-scribed in a risk analysis document and summarised in a drug monograph and reviewed by the editorial board before publication.

Results A framework was developed to provide dosing guidelines based on best available evidence from reg-istration data, published investigator-initiated research, guidelines, clinical experience and consensus. Dissem-ination of these dosing guidelines was established by developing an open-access online database (http://www.kinderformularium.nl/). The development has resulted in the revision of many earlier consensus-based dose rec-ommendations, clarified the scientific grounds of drug use for children and ensured uniformity in prescribing habits in the Netherlands. Also, additional projects to fur-ther improve the information and usability of the formu-lary were initiated, including dosing guidelines for renal dysfunction, a dosing calculator and parent/patient drug information leaflets.

Discussion It is almost impossible to make a paediatric risk-benefit assessment based on the same standards that are mandatory when assessing adult drug use. We are aware that many of our dosing recommendations there-fore still bear a varying degree of uncertainty. 'Best-evidence' means that we do know the scientific background that supports paediatric use. This also implies that, in the face of low-quality evidence, expert opinion or a consen-sus of a group of experts is important. It is a common misconception that a recommendation supported by low-quality evidence implies a recommendation against use. The Dutch Paediatric Formulary deliberately chose to give insights in the limited amount of evidence available and create awareness rather than to reject paediatric use because of limited evidence.

Conclusion The Dutch Paediatric Formulary is a proof of concept in creating a knowledge-based paediatric formulary. The formulary has also been of great value in timely translating scientific research knowledge to daily practice. We believe that the Dutch approach in creating a knowledge-based paediatric formulary was successful and could be used as basis for similar initiatives world-wide, preferably in a concerted effort to ultimately pro-vide children with effective and safe drug therapy.

PP-46 VORICONAZOLE DOSING STRATEGIES IN YOUNG CHILDREN: CHALLENGES AND RECOMMENDATIONS

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Background Voriconazole pharmacokinetics (PK) have been studied in paediatric studies and described by popu-lation pharmacokinetic modelling.[1] Using the currently approved intravenous (IV) dosing regimen,[2,3] paediatric patients

provided 30 trough samples resulting in a ob-served median (range) of 1.2 (0.11–17.4) mg/L.[1] This illustrates the highly variable pharmacokinetic (PK) pro-file of voriconazole in children. The aim of this case series is to evaluate the effectiveness of dosing guidelines in combination with routine therapeutic drug monitoring (TDM) to achieve therapeutic serum concentrations of voriconazole in young cancer patients (age 0–6 years old).

Methods At the VUmc, paediatric patients are treated using TDM. Voriconazole plasma concentrations are monitored and dosing regimens are individualised, aiming at trough levels of 1–6 mg/L depending on the location of the Asper-gillus. A case series of 4 children (age 0–6 years) is presented.

Results Highly variable voriconazole exposure (n=4) were observed. Case 1 Boy, 13 months, acute myeloid leukaemia: Loading dose 9 mg/kg tid (IV), maintenance 8 mg/kg tid (IV) [2] resulted in supratherapeutic levels, hepatic toxicity and circulatory insufficiency. Root cause: CYP2C inhibition by previous prophylactic Itraconazole treatment. Itraconazole has a half-life time up to two days. Therapeutic voriconazole levels achieved at 6 mg/kg tid (IV); Case 2 Boy, 5 years, acute lymphatic leukaemia: Doses varying between 7 mg/kg tid IV and 11 mg/kg tid IV during 4 months of IV therapy. Highly variable trough concentrations varying from 0.10–13.3 mg/L; 65% within the target range of 2–6 mg/L for cerebral Aspergillus: Case 3 Girl, 7 months, mixed phenotype acute leukaemia: Load-ing dose 6 mg/kgbid (IV), maintenance 9 mg/kgbid (PO) resulted in subtherapeutic trough levels (0.1–0.2 mg/L), possibly due to high first pass metabolism. Case 4 Girl, 5 years, acute lymphatic leukaemia: Loading dose 10 mg/kgbid (PO), high maintenance dose of 23 mg/kgbid (PO) re-sulted in therapeutic levels. Higher doses of 30 mg/kgbid resulted in a more than dose-proportional increase of ex-posure (trough level 22 mg/L), suggesting non-linear PK.

Conclusion Voriconazole PK is highly variable in pedi-atric cancer patients, which can only partly be attributed to drug interactions and co-morbidities. A starting dose of 18 mg/kg (IV) is recommended and could be adminis-tered as 6 mg/kg tid (IV).[2] Intensive TDM (at least twice weekly) and daily in-depth status reviews are recom-mended to achieve therapeutic drug levels.

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PP-48 POPULATION PHARMACOKINETICS AND DOSING OPTIMISATION OF CEFATHIAMIDINE IN INFANTS AND CHILDREN

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Background Cefathiamidine, a first-generation cepha-losporin, was approved by the China Food and Drug Ad-ministration for the treatment of adults and children with infections due to susceptible bacteria. As the paediatric pharmacokinetic data is limited, our aim was to evaluate the population pharmacokinetics of cefathiamidine in infants and children and define the appropriate dose in order to optimise cefathiamidine treatment.

Methods Blood samples were collected from infants and children treated with cefathiamidine and concentra-tions were quantified by HPLC-MS. Population pharmaco-kinetic analysis was performed using NONMEM software.

Results Seventy-four children (age range: 0.35–11.81 years) were included. Spars pharmacokinetic samples (n=172) were available for analysis. A one-compartment model with first-order elimination showed the best fit with the data. A covariate analysis identified that body-weight had a significant impact on cefathiamidine phar-macokinetics. Monte Carlo simulation demonstrated that the current recommended dose of 100 mg/kg/dayBID resulted in only 51.5% of simulated infants with age <2 years and 61.8% of children with age ≥ 2 years achieving the target 70% fT>MIC against Streptococcus pneumonia (MIC 0.25 mg/litre).

Conclusion The population pharmacokinetics of cefa-thiamidine was evaluated in infants and children and an optimal dosing regimen was established based on sim-ulation.

PP-50 POPULATION PHARMACOKINETICS AND DOSING OPTIMISATION OF LATAMOXEF IN NEONATES

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10.1136/archdischild-2017-esdppp.67

Background Latamoxef, a new broad-spectrum oxac-ephem antibiotic, was used off-label in neonates. The present study aims to evaluate pharmacokinetics of latamoxef in neonates and establish appropriate dosing regimen.

Methods Blood samples were collected from neonates treated with latamoxef and concentrations were quan-tified by HPLC-UV. Population pharmacokinetic analysis was performed using NONMEM software.

Results A total of 42 neonates were recruited. A one-compartment model with first-order elimination showed the best fit with the data. Current weight and postmenstrual age were identified as significant covari-ates on clearance. Current weight was identified as a sig-nificant covariate on volume of distribution. The reliability and stability of the population pharmacokinetic model was evaluated by bootstrap and normalised predictive distribution error.

Conclusion The population pharmacokinetics of lata-moxef was evaluated in neonates and an optimal dosing regimen was established.

PP-52 GETTING PAEDIATRIC MEDICINES ON-LABEL – SCOPING THE NEEDS FOR PAEDIATRIC FORMULATION OF OLD MEDICINES

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10.1136/archdischild-2017-esdppp.68

The Rosalind and Morris Goodman Family Paediatric For-mulations Centre of the CHU Sainte-Justine is a new non-profit organisation dedicated to supporting the development of safe and efficacious medicines that have a child-friendly formulation. One way of providing these paediatric medicines is to partner with industry to promote commercialising of a suitable paediatric formu-lation for commonly used medicines currently only avail-able in adult formulations. Working with all stakeholders including, pharmacists, paediatricians, Health Canada and the

pharmaceutical industry, the Goodman Centre has identified commonly used off-label medicines that are currently compounded in pharmacies to produce pedi-atric formulations. In many cases, paediatric formulations and indications are available in other jurisdictions yet they have not been submitted by industry to Health Canada for regulatory approval. Using this novel approach, the Centre is to partnering with pharmaceutical companies to use existing data that has been submitted in other jurisdictions for Canadian approval. We will provide an overview of the Goodman Centre and outline the novel approach developed to improve access to paediatric for-mulations that we have undertaken.

PP-54 PRENATAL ANTIBIOTIC EXPOSURE AND CHILDHOOD ASTHMA: A POPULATION-BASED STUDY

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Importance Antibiotic use during infancy alters gut microbiota and immune development, and is associated with an increased risk of childhood asthma. The impact of prenatal antibiotic exposure is unclear.
Objective To determine and characterise the associa-tion of prenatal antibiotic exposure and childhood asth-ma.
Design Population-based cohort study using admin-istrative healthcare data. Antibiotic use was determined from prescription records. Asthma was defined using hospitalisation records, physician billing claims, and pre-scription records. Associations were determined using Cox regression and expressed as hazard ratios (HR) and 95%confidence intervals (CI).
Setting General population in Manitoba, Canada.
Participants 2 13 661 mother-child dyads born from 1996–2012.
Exposure Maternal antibiotic use.
Outcome Child asthma, defined as meeting any of the following criteria after 5 years of age: any hospitalisation for asthma; or $\geq$2 physician diagnoses of asthma, at least 3 months apart and within a 1 year period; or $\geq$2 prescrip-tions for asthma medications within a 1 year period.
Results In our study population, 10.1% of children met the case definition for asthma, and 36.8% were prena-tally exposed to antibiotics. Prenatal antibiotic exposure was associated with an increased risk of asthma (crude HR 1.29; 95% CI 1.26–1.33). This association persisted af-ter controlling for maternal asthma, sex, location of resi-dence, gestational age, number of siblings, and postna-tal antibiotic exposure during infancy (adjusted HR 1.23; 1.20–1.27). However, maternal antibiotic use during the 9 months before pregnancy (adjusted HR 1.28, 1.24–1.31) and 9 months postpartum (adjusted HR 1.32, 1.29–1.36) were similarly associated with childhood asthma.
Conclusions and Relevance Maternal antibiotic use before, during and after pregnancy was associated with a modest, dose-dependent increase in asthma risk among offspring. While our study does not support a pregnan-cy-specific causal relationship between maternal antibi-otic use and childhood asthma, it remains important to prescribe and use antibiotics judiciously.

PP-1 THE PREMATCH STUDY: AN EFFORT TO QUANTIFY THE IMPACT OF PRETERM BIRTH ON CARDIOVASCULAR AND RENAL HEALTH

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Background and objectives The PREMATurity as pre-dictor of Children's cardiovascular and renal Health (PRE-MATCH) is a case-control study in former ELBW children (2000–2005) and controls (term) at the median age of 12 years to compare the phenotype, including body compo-sition, renal function and cardiovascular assessment.
Methods Growth (height, weight, head circumference, Z-scores), body composition (Bodystat), renal function (renal length, cystatin C converted to eGFR), cardiovascu-lar assessment and retinal vascular aspects were assessed in former ELBW children and controls.
Results Former ELBW children still have difficulties to reach their target height. ELBW adolescents show lower neurocognitive performance, grip strength and high-er fat body mass. Catch–up growth for weight in ELBW children in the first two years of life was associated with lower fat body mass. Renal length and glomerular filtra-tion rate (cystatin C) were 0.28 cm (95% CI 0.09–0.47) and 11.5 mL/min/1.73 m2 (6.4–16.6) lower in cases. The odds of having systolic (pre)hypertension in former ELBW cases was 6.43 (2.52–16.4) and 10.9 (2.46–48.4) with a low renin mechanism. Microvascular retinal arteriolar narrowing is observed in former ELBW young adolescents.
Conclusions The phenotype (growth, body composi-tion, renal function, retinal microvascularisation) of former ELBWs differs significantly from controls in early adoles-cence. All these findings reflect mechanisms related to a higher risk factor for adverse health outcomes in adult-hood.
Acknowledgements Supported by the 'Agency for In-novation by Science and Technology in Flanders (IWT)' through the 'SAFE-PEDRUG' project (IWT/SBO 130033).

PP-3 STANDARD OF CARE FOR CHILDREN WITH HEART FAILURE IN EUROPE: RESULTS OF A SURVEY AND A SUBSEQUENT DELPHI QUESTIONNAIRE

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Background Paediatric heart failure (HF) has an import-ant economic and social impact in public health. Drugs acting on the renin-angiotensin system are regarded as mainstay to lower the burden of HF for patients and families. A safe and efficient use especially in young chil-dren has been debated since several years and remains a challenge for physicians. We aimed to characterise the different therapeutic strategies for the management of paediatric HF that are currently practiced across Europe with special

focus on the use of Angiotensin Converting Enzyme Inhibitors (ACE-I).

Methods A Europe-wide web-based survey and a sub-sequent DELPHI questionnaire was developed in the con-text of EU's Seventh Framework Programme under grant agreement n°6 02 295 using standard recommendations for survey design. The questionnaire consisted of 23 ques-tions addressing different aspects of drug therapy for HF in children. Use patterns of ACE-I i.e. dosage by age group, effectiveness and toxicity assessment according to HF ae-tiology where investigated. Clinicians from 204 different hospitals of 39 European countries were invited via e-mail to participate. The subsequent DELPHI process discussed controversial responses within a selected expert panel in two rounds.

Results The response rate of the survey had been 50%. The survey delivered valuable information about the current paediatric heart failure therapy, especially with regard to the pattern of ACE-I use. Enalapril seems to be already the ACE-inhibitor of choice for children and ad-olescents. A suitable formulation and knowledge about dosing as well as adverse events might offer Enalapril also for neonates and infants. Several controversial aspects which were identified within the survey and which are re-lated to paediatric heart failure therapy had been put up for discussion to the DELPHI expert panel. They showed a high degree of consensus in their professional criteria about most of the contents presented for discussion. Pos-sible starting points in the way towards a standardisation of paediatric heart failure therapy were identified. With re-gard to non-consensus statements, DELPHI experts pro-vided a better visibility to some aspects of clinical practice with greater disparity of opinio Diagnostic and therapeu-tic approachesns among physicians.

Conclusion This survey and the subsequent DELPHI questionnaire provided an overview of the clinical treat-ment routine of paediatric HF across Europe. ACE-I seem to be a crucial part of the treatment strategies. Consensus but also still controversial aspects of clinical practice rou-tines for a safe and effective use of heart failure treatment for children in Europe were identified.

The research leading to these results has received funding from the EU's Seventh Framework Programme (FP7/2007-2013) under grant agreement n°6 02 295 (LENA).

PP-5 PRESCRIPTION OF BIOSIMILAR SOMATROPIN IN THE ITALIAN PAEDIATRIC POPULATION

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Background Omnitrope (somatropin) was the first bi-osimilar approved by the European Medicine Agency in 2006. Since somatropin is one of the biological products most commonly prescribed to children and adolescents, a study was performed with the aim to evaluate the pre-scription of this drug in the Italian paediatric population. To the best of our knowledge, no drug utilisation studies evaluated the prescription profile of biosimilars in the pe-diatric population.

Methods Data collected in healthcare administrative databases of Lombardy region, Italy, in the 2004–2012 period were analysed. Children and adolescents who received prescriptions of somatropin (H01AC01code of the Anatomical Therapeutic Chemical classification sys-tem) for at least two consecutive years were identified as prevalent cases. Subjects were defined incident cases if they had no somatropin prescriptions in the previous 2 years. Prevalence and incidence of somatropin prescrip-tion were estimated by gender, age group and observation year. Moreover, each youth with the first prescrip-tion (index prescription, IP) in the 2006–2010 period was monitored for 24 months, and somatropin prescriptions were analysed to evaluate if a switch between products occurred. In switchers, the occurrence of specialist vis-its and/or hospitalizations in the 60 days preceding the change was checked.

Results During 2012, the prevalence of somatropin pre-scription in Lombardy region was 12.0 per 10,000, with an incidence of 2.8 per 10 000. Both prevalence and inci-dence increased across time (from 9.6 and 1.6 per 10 000 in 2004, respectively). The prevalence was greater in boys than in girls (14 versus 10 per 10,000), and increased with increasing age (from 2.7 in pre-schoolers to 21.1 per 10 000 in adolescents). A total of 1415 children had the somatro-pin index prescription in the 2006–2010 period. Only 98 of them (7%) started with the biosimilar Omnitrope. The percentage of children starting with the biosimilar slightly increased with increasing age, from 4.9% in the 1–5 years old to 7.5% in the adolescents. In all, 17 out of the 98 sub-jects (17.3%) with biosimilar as IP switched to another so-matropin product during the 24 months after the starting date. Of the 1317 children who started with a 'branded' somatropin, 47 (3.6%) switched to another products (no one to Omnitrope). The rate of switch was higher in pre-school aged children (3 out of 10) and decreased with in-creasing age (5 out of 45 in adolescents). On the contrary, the frequency of switch in subjects with other somatropin products did not change among age groups.

Only 4 out of 17 subjects had a specialist visit and/or an hospitalisation in the 60 days before the switch from bio-similar to 'branded' products, while in the non-biosimilar group, a specialist visit and/or hospital admission was re-corded for 26 out of 47 children.

Conclusion Only 7% of incident (naïve) cases started with the biosimilar somatropin. Subjects who started with the biosimilar switched more frequently to anoth-er product and the change was less likely preceded by a specialist visit.

PP-7 THE SAFE-PEDRUG INITIATIVE: AN OPPORTUNITY FOR ACADEMIA TO CLOSE THE GAP

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Background The Paediatric Regulation[1] was launched ten years ago. As was also identified in the ten year report[2], this regulation has had a positive impact on paediatric research in Europe. However, some specific patient pop-ulations (such as neonates, critically ill children, children with comorbidities) do not receive enough attention in paediatric drug development. Furthermore, the top-down approach (from adults to children) results in considerable delays in making medicines available to

children. For most of the drugs long term follow-up is missing.

Methods The SAFE-PEDRUG project was initiated in Belgium in 2014 and is a collaboration of experts in pae-diatrics, pharmaceutical sciences, veterinary medicine, and ethics of three Belgian universities: Ghent Universi-ty, KULeuven, and Vrije Universiteit Brussel. An advisory board and stakeholder group consisting of national and international stakeholders support this consortium in the valorisation of results.

Results The SAFE-PEDRUG project explored the value of the porcine juvenile animal model[3] and PK modelling[4] (population pharmacokinetics and physiological-ly based pharmacokinetic modelling) in providing prior paediatric PK/PD knowledge, before the actual adult trials have been completed. For the evaluation of this approach, three case compounds were selected: des-mopressin, lisinopril, and fluoroquinolones. The results of the models are plotted against human paediatric data, including data in neonates and critically ill children.

Discussion A close collaboration of experts and stake-holders can help to tailor paediatric clinical trials to the needs of children. Pharmaceutical industry and regulato-ry authorities are key players in the paediatric drug de-velopment process. However, academia can also play an important role in rendering the paediatric drug development process more efficient by development and correct use of innovative tools. Besides, academia should defend the rights of the most important stakeholders: patients and their parents. During the SAFE-PEDRUG project additional opportunities for academia have been identified: initiation of networking; centralisation in registries and networks to improve transparency and efficiency; and education of paediatric clinical pharmacologists.

Acknowledgements The SAFE-PEDRUG project re-ceived a grant for Strategic Basic Research of the Agen-cy for Innovation by Science and Technology in Flanders (IWT-SBO 130033).

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PP-9 PARTICIPATING IN PAEDIATRIC DRUG RESEARCH: IDENTIFYING THE BURDEN

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Background Nowadays, academic researchers, pharma-ceutical companies and regulatory authorities are more aware of the need for paediatric drug research. Conse-quently, more academic and industry-driven paediatric trials are conducted to evaluate the efficacy and safety of new drugs and to a lesser extent of off-patent and off-la-bel drugs. However little information is available on the burden associated with participating in clinical trials for the patients and their family/caregivers. In attempt of be-coming a Centre of Excellence in paediatric drug research it is important for us to fully understand this burden.

Methods This is a retrospective, single centre, observa-tional study. A questionnaire will be designed focusing on the overall costs and time investment for the participants and their caregivers. Topics of interest will be absenteeism at school, at work or in leisure; number of specific study related visits (out of standard of care); financial reward by the sponsor; etc. Additional questions will gauge the per-ception and experience of the patients and their parents. We will contact the parents of patients who participated in either an academic or industry driven trial between 2010 and 2017 at the departments of paediatric nephrol-ogy and gastroenterology of the Elisabeth Children's Hospital (Ghent University Hospital). We will display the results of this questionnaire by using descriptive statistics.

Discussion By evaluating the results, we will identify what brings most burden to patients and their family/caregivers in participating in clinical trials. This will enable us to better understand this burden and eventually to anticipate by more and better information and support during the participation. This may increase compliance, especially important in drug trials. The data can help us to include these aspects in discussions with both ethical committee and sponsors (industry) during the develop-ment of the study design and during negotiation of the clinical trial agreement (inclusive of some compensation) between research centres and sponsors.

Acknowledgements The survey is an initiative of the SAFE-PEDRUG project (IWT-SBO 130033), supported by the Agency for Innovation by Science and Technology in Flanders (IWT).

PP-11 COMPARING COMPLETION RATES OF PAEDIATRIC VERSUS ADULT RANDOMISED CONTROLLED TRIALS: A CROSS-SECTIONAL STUDY

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Background Clinical trial discontinuation represents a waste in research resources and raises ethical concerns. Conduct of clinical trials is perceived to be more challeng-ing in children than in adults. The aim of this study was to evaluate the impact of the age of participants on comple-tion rates of randomised controlled trials (RCTs).

Methods This is a cross-sectional study on RCTs regis-tered in the ClinicalTrials.gov database. All RCTs registered in the database from its inception date (February 29, 2000) to December 31, 2016, were extracted. RCTs with unknown recruitment status or registered more than 60 days after their start date were excluded. Remaining RCTs were classified according to their recruitment status: active, completed, and discontinued trials, and according to the age of participants: children (0–17 years), adults ($\geq$18 years), and mixed age populations. Further RCT charac-teristics were assessed using information registered in the database: study location, funding source, year of registration, study phase, study design, type of intervention evaluated, blinding procedure, study duration, and enroll-ment achieved. A logistic regression model was applied to assess the impact of participant's age category on trial completion while controlling for other potentially rele-vant trial characteristics.

Results A total of 65 095 registered RCTs matched eligi-bility criteria. Paediatric and mixed age trials represented respectively 6.6% (n=4,314) and 8.9% (n=5,806) of regis-tered RCTs, and these proportions remained unchanged over the years. Among paediatric trials, 2151 were com-pleted (49.9%) and 367 were discontinued (8.5%). In adult and mixed age RCTs respectively, 27 338 (49.7%) and 2782 (47.9%) were completed, whereas 5584 (10.2%) and 546 (9.4%) were discontinued. Overall, paediatric and mixed age RCTs were more likely to be registered as com-pleted than adult RCTs (OR: 1.16, CI95%: 1.02–1.30; OR: 1.15, CI95%: 1.04–1.27, respectively). Also, RCTs were more likely to be registered as completed when they evaluat-ed interventions other than drugs/biologicals or devices/procedures, when the primary trial purpose was to eval-uate a non-therapeutical intervention, when they were funded by industry, when they were designed as cross-over trials, and when they included a masking procedure.
Conclusion Paediatric or mixed age RCTs are more likely to be registered as completed than RCTs in adults. Con-trary to current perceptions and despite the specific chal-lenges of paediatric research, recruitment of children and adolescents is not a limiting factor to completing a RCT. Other study features, such as funding and design, impact completeness and should be carefully considered before initiating clinical research.

PP-13 AN ANALYSIS OF THE APPLICATIONS FOR A PAEDIATRIC INVESTIGATION PLAN (PIP) FOR INDICATIONS IN URO-NEPHROLOGY

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Introduction In order to assess the requirements of the European Medical Agency (EMA) for paediatric clinical trials in nephrology we assessed the decisions on Paediatric Investigation Plans (PIPs), which are required to get approval for new drugs. Paediatric nephrology comprises rare indications, but also frequent paediatric conditions. Clinical trials are needed in order to base therapy on ev-idence, but the relevant population can be very small in paediatric nephrology.
Methods All 20 decisions on PIPs published by the EMA on the EMA website under 'uro-nephrology' were includ-ed. Data are presented as proportions (categorical data) and median (range) (numerical data).
Results Full and partial waivers: 7 of the published decisions granted a full waiver (i.e., no paediatric studies required). For the remaining 13, a PIP was agreed. For 6 of those 13 PIPs, a partial waiver was granted for certain ages (0–6 months (2x), 0–5, 0–6, 0–8, 12–18 years.Agreed PIPs: The PIPs require the conduct of 0–3 (median 1) quality studies, 0–2 (median 0) non-clinical studies, and 1–6 (median 3) clinical studies. As there are ca. 9 paediatric dialysis subjects per million of all paediatric subjects, an estimate of the number of paediatric dialysis patients in EU is roughly ca. 400 patients. At least 4 PIPs require in-clusion of paediatric dialysis subjects, requiring 14 clinical studies, i.e., ca. 14 subjects are available for each of those studies. There are no concessions in powering the studies, and therefore, the required numbers will be much higher than the available number of subjects in EU.

Time for decision and time for completion of PIP: The time between start of the procedure and the decision of the PdCo/EMA was 103 days (35–468 days). The time between the date of decision of the PdCO/EMA and the date of the required completion of the PIP ranged from 0.03 years – 13.47 years (median 4.84 years).
Conclusion All partial waivers affected the lowest age groups. Although the youngest age groups need an eval-uation of new substances most urgently, the number of granted partial waivers indicates how difficult it is to con-duct clinical trials in this subpopulation. However, only 4 of the 13 agreed PIPs are concerned with frequent indi-cations, while 9 of those aim at rare indications. For those 9, a median of 3 clinical studies is required. It is unlikely that the required number of subjects can realistically be recruited. Further, the required studies make the timely conduct (median time 4.84 years) and completion at the same time as the studies in adults questionable. This could delay approval in adults. In summary, we show some im-balances: a) studies are most difficult in infants, but they need them most, b) the number of subjects required does not fit the indication epidemiology, c) timelinies for com-pleting paediatric studies are difficult to meet.

PP-15 THE CONVENTIONAL PIG AS PK/PD/TOXICITY MODEL FOR THE PEDIATRIC SUBPOPULATION: DEVELOPMENT OF URINE AND BLOOD SAMPLING STRAT-EGIES IN GROWING PIGLETS

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Background The piglet is considered as a valuable alter-native animal model to perform preclinical pharmacoki-netic (PK), pharmacodynamic (PD) and toxicity studies in the paediatric subpopulation (Gasthuys et al., 2016). To be able to perform such studies, multiple blood and urine collections are required. The aim of the present study was to develop repetitive blood and urine sampling techniques in the same piglets (n=4, 2♂/2♀) ageing eight days, four and eight weeks.
Methods Total 12h-voided urine was collected by at-taching a urine pouch to the prepuce of the male piglets. This non-invasive technique made it possible to easily collect urine at different time points. Blood was either collected by a surgically-placed jugular vein catheter (at the age of eight days (n=4) and four weeks (n=2)) or by direct venipuncture of the jugular vein (at four (n=2) and eight weeks (n=4)), both at 12 time points within a 12h-time period.
Results Surgery and anaesthesia were uneventful. One piglet showed clinical signs of a septicemia five days after the first surgery and the animal was euthanized. No com-plications were encountered during the blood sampling in the other three piglets. The piglets were euthanized after eight weeks and the jugular veins were sampled for histological analysis. Negligible damage of the veins was observed, rendering catheterization and direct venipunc-ture suitable techniques for multiple blood collections in growing piglets. Catheterization at different age catego-ries is, however, ethically more feasible.
Conclusion The presented urine and blood sampling techniques make it possible to easily perform PK/PD stud-ies in growing piglets.

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PP-17 INTRAVENOUS PARACETAMOL IN NEONATES: SAFETY, ETHANOL-DRUG INTERACTIONS AND EFFICACY – PROTOCOL OF THE PARASHUTE TRIAL

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Introduction A chart-review of 200 neonates randomly selected from the Neonatal Intensive Care Unit (NICU) of the university hospital in Copenhagen revealed that ap-proximately 10% received intravenous (i.v.) paracetamol≥4 days (unpublished data). Paracetamol (acetaminophen) is commonly used to control mild-to-moderate pain or to reduce opioid exposure either by oral, rectal or intrave-nous route. The newborn population includes a hetero-geneous group with substantial differences in their drug disposition characteristics. Hence, reflecting their degree of immaturity, organ dysfunction, as well as genetic variation in drug metabolising enzymes and potential drug interactions. Different types of pain and pain assessment tools are used in neonatology. The pharmacokinetics and metabolism of i.v. paracetamol have been extensively published but there is very limited data on the pharma-codynamics (PD) and safety of this drug. The PARASHUTE trial will explore intravenous paracetamol in neonates in relation to: Primary objective: Safety of prolonged use (>72 hours); Secondary key objectives: Analgesic effect (PD) in neonates with chest tubes. Drug-excipient interaction with ethanol containing drugs (CYP2E1)
Endpoints Primary endpoints: To described the concentration-time data of plasma paracetamol (APAP), APAP-sulphate, APAP-glucuronide, oxidative metabolites and liver bio-markers (ALAT, PP, bilirubin) in neonates treated with i.v. paracetamol every sixth hour.

Secondary endpoints: Pain scores (COMFORTneo pain scale) combined with paracetamol concentrations and cumulative rescue dosages of morphine.Levels of oxida-tive metabolites of paracetamol and levels of p-ethanol in patients receiving one or more ethanol containing drugs.
Design A multicenter phase IV safety trial on prolonged i.v paracetamol administration in neonates combined with a randomised placebo controlled trial assessing ef-fect on pain.
Participants Neonates at any gestational age at birth for the safety and excipient study. However, for the for the PD study patients with chest tube due to pneumothorax or pleural effusion without prior operation are eligible for inclusion. For the PD and drug-excipient study the patient must weigh >1 kg.
Sample size Safety and excipient trial: 60; PD trial: 48:29 (unequal allocation)
Intervention The safety trial will follow clinical practice and i. v. paracetamol (10 mg/kg) will be administered. Plasma samples will be collected through an arterial line if present for clinical reasons. In neonates without arteri-al access, two heel pricks are necessary (start and end of trial) to collect blood. Additional plasma samples will only be collected when venipuncture is performed for clinical indications i.e. opportunistically.

Patients with chest tubes are, after bolus morphine and insertion of tube, unequally allocated to i.v. paracetamol + rescue morphine or i.v. saline + res-cue morphine. In addition to COMFORTneo pain scores and p-paracetamol, safety parameters will be gathered.

Study duration September 2017 – January 2019 (PD tri-al will end in summer 2019)
Key references Allegaert et al. Paediatr Anaesth 2013: Cook et al. Clin Pharmacokinet 2016; van Ganzewinkel et al. Acta Paediatr 2014; Palmer et al. Br J Anaesth 2008
Trial registration The trial will be registered in EudraCT before the ESDPPP congress.
Funding Funded by Department of Clinical Pharmacolo-gy and non-profit grants.

PP-19 QUANTIFICATION OF GAIT IN CHILDREN WITH MITOCHONDRIAL DISEASE: A VALIDATION STUDY

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Background Validated, clinically meaningful outcome measures should be used to detect clinically relevant effects of treatments. Since the clinical heterogeneity in mitochondrial disorders is extremely wide, the selection and validation of outcome measures is challenging. Espe-cially for children, whom are developing and growing and even have a larger phenotypic heterogeneity compared to adults, this challenge has so far resulted in a lack of val-idated outcome measures. Gait analysis is an emerging method to quantify subtle changes in walking patterns of adults with neurological disorders and can provide in-sight in the effects of a therapeutic intervention. Based on the results of a validation study in m.3243A>G carriers, we included gait quantification as the primary outcome measure for the adult randomised, placebo-controlled, cross-over, phase 2 trial performed in this population in our centre (the KHENERGY trial). We hypothesise that gait analysis is also a feasible and reliable outcome measure for intervention studies in ambulatory children with mitochondrial disease.
Methods The aim of this study was to select the opti-mal protocol to quantify gait patterns with the Gaitrite in paediatric mitochondrial patients, comparing a normal walking protocol and a post-exercise protocol. Ambula-tory children with a genetically confirmed mitochondrial disease are asked to walk across the Gaitrite three times for each trial and two times for each condition to estimate test-retest variability. First, the normal walking condition is tested. Subsequently, a 3-minte walking test is performed, followed by a post-exercise protocol. After 10 min of rest, a recovery condition is tested. Secondly, the gait patterns of the mitochondrial patients are compared to 5 age-and gender matched healthy controls to gain more insight in which walking parameters were affected by mi-tochondrial disorders.
Results and conclusion The results of this validation study will be presented.

PP-21 ENANTIOMER-SPECIFIC KETOROLAC PHARMACOKINETICS IN YOUNG WOMEN, INCLUDING PREGNANCY AND POSTPARTUM

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Background Ketorolac, a potent non-steroidal anti-in-flammatory drug, is a chiral substance. Racemic ketorolac clearance is significantly higher at delivery, but S-ketorolac disposition determines the analgesic effects. We aimed to document the impact of pregnancy and postpartum on enantiomer-specific (S and R) ketorolac pharmacokinetics (PK) in young women.

Methods Observations shortly following caesarean de-livery (n=39) were pooled with data in subgroup of these women (n=8/39) four months afterwards ('postpartum') and with 8 healthy female volunteers, resulting in 47 un-paired and 8 paired PK estimates. All women received single intravenous bolus of ketorolac tromethamine (30 mg). Five (at 1, 2, 4, 6, 8 hour) plasma samples were collected and plasma concentrations were determined using HPLC method. Enantiomer-specific PKs were calculated using PKSolver.

Results Unpaired analysis documented that median distribution volume at steady state (Vss) for S-and R-ke-torolac was significantly higher in women following cae-sarean delivery (n=31) compared to postpartum (n=8) (S-ketorolac: 12.79 vs. 7.84 L, p=0.011; R-ketorolac: 8.96 vs. 5.86 L, p=0.001) or to healthy female volunteers (n=8).

(S-ketorolac: 12.79 vs. 9.14 L, p=0.002; R-ketorolac: 8.96 vs. 5.51 L, p<0.001). When corrected for BW, median Vss for both S-and R-ketorolac were significantly higher in women shortly following caesarean delivery compared to those in healthy female volunteers (S-ketorolac: 0.18 vs. 0.15 L/kg, p=0.037; R-ketorolac: 0.12 vs. 0.09 L/kg, p=0.001). The median clearance (CL) for S-and R-ketoro-lac was significantly higher in women following caesarean delivery compared to postpartum (S-ketorolac: 6.49 vs. 3.73 L/h, p<0.001; R-ketorolac: 2.14 vs. 1.43 L/h, p=0.002) or to healthy female volunteers (S-ketorolac: 6.49 vs. 3.60 L/h, p<0.001; R-ketorolac: 2.14 vs. 0.99 L/h, p=0.001). After taking the body size differences into account, CL to body weight (CL/BW) and CL to body surface area (CL/BSA) for S-and R-ketorolac were also higher following caesar-ean delivery compared to observations in postpartum (S-ketorolac:+33.3%, L/h·kg,+38.6%, L/h·m2; R-ketorolac:+33.3%, L/h·kg,+31.4%, L/h·m2) and in healthy female volunteers (S-ketorolac:+33.3%, L/h·kg,+48.4%, L/h·m2; R-ketorolac:+33.3%, L/h·kg,+56.8%, L/h·m2). In addition, S/R-ketorolac CL/BSA ratio was significantly higher at de-livery compared to postpartum (3.07 vs. 2.73, p=0.020). Paired PK analysis in 8 women following delivery or post-partum showed the same pattern. Finally, the simultane-ous increase in CL and Vss resulted in similar estimates for elimination half-life in both unpaired and paired analysis.

Conclusion Pregnancy affects S-, R-and S/R-ketorolac disposition. This is of clinical relevance since S-ketorolac (analgesia) CL is even more increased compared to R-ke-torolac CL and S/R-ketorolac CL ratio is higher following delivery compared to postpartum or to healthy female volunteers. For definitive physiological state-specific dos-ing recommendations in women, we encourage future repeated dosing pharmacokinetic studies in this specific population.

PP-23 UNDER PRESSURE: MINOCYCLINE-INDUCED PSEUDOTUMOR CEREBRI. A CASE REPORT AND LITERATURE REVIEW

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Background Drug-induced increase of intracranial pres-sure (ICP) is a rare but serious adverse effect. Antibiotic and retinoid acne treatments are among the most frequent causes with a typical latency time of 2 weeks to 2 months.[1] Pseudotumor cerebri can cause irreversible visual and/or neurologic sequelae.

Case report A 17-year-old non-obese female patient presented to the paediatric emergency department for left hemianopia, weakness, paresthesia of the left extremities, headache and vertigo. Clinical examination showed resid-ual left-sided hemisyndrome with possible involvement of ipsilateral cranial nerves VII, VIII and XI. A stroke was suspected, but MRI, blood tests and ECG were normal, a urine drug screen was negative. Upon ophthalmologic diagnosis of massive bilateral papilledema, and considering her chronic medication with minocycline for acne, a pseudotumor cerebri was suspected. Positive modified Dandy's criteria were: transient visual disturbance, head-ache, papilledema, abducens palsy, no focal deficits, alert and fully oriented patient, normal MRI, ICP of 50 cm H20 with normal liquor composition, and no other causes for increased ICP. ICP normalised after withdrawal of 20 mL of liquor. Minocycline was stopped and acetazolamide was initiated. Symptoms and papilledema subsided partially over the following weeks.

Conclusion Using standard causality criteria, minocy-cline was the probable cause for this patient's pseudo-tumour cerebri. The stroke-like symptoms remain unex-plained. This case highlights the need for stringent indi-cation for minocycline as well as continuous risk/benefit assessment and monitoring both in the individual patient as well as in public health.

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PP-25 DRUG USE DURING PREGNANCY: A SYSTEMATIC REVIEW

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Background Maternal drug use in pregnancy is a health care issue of major concern as most drugs are used with limited knowledge of safety and efficacy for the mother, have undetermined risks, and potential adverse effects on the fetus. Recent epidemiological data are insufficient to evaluate their licensed status and use during pregnancy.

The aim of the present review is to provide a recent update on the use of medications during gestational period and determine the circumstances of this consumption in terms of prescription/automedication, according to label or off-label use.

Methods MEDLINE and Embase databases were used to select peer reviewed journal articles published between 1990 and 2016. The search included the keywords: preg-nancy, drug, medication, prescription, over-the-counter and automedication. Only epidemiological studies ana-lyzing the overall use of drugs (prescribed drugs, medi-cation available over-the-counter, vitamins and other supplements) among pregnant women were included, both international and national/regional, excluding those focusing on a specific therapeutic category.
Results The screening process led to a final selection of 77 studies, conducted in 28 different countries (2 studies were from Oceania, 9 from Africa, 14 from Asia, 18 from America, and 31 studies from Europe). The investigated period was remarkably different and ranged from a one month to 33 years with information collected at differ-ent time periods from 1976 to 2014. Sample sizes were also very variable between studies from 100 to 1 106 757 included women. Overall drug consumption was highly different among countries ranging from 17.6% to 93.9% when vitamins, minerals and other supplements were excluded. Of all the studies reporting the percentage of women using drugs during pregnancy (n=58, 75.3%), 21 studies (36%) (among 2 38 731 women) reported that more than 90% of women took one or more drugs while being pregnant. Folic acid, iron supplements and vita-mins were in most countries the most frequently used therapeutic category. Analgesics, antibiotics and other anti-infectives were also used extensively. Nineteen stud-ies reported data on automedication with an important variability in prescription/over-the-counter medicines ratio among studies. Information about off-label prescrip-tion was rarely reported.
Conclusion The use of drugs is frequent during preg-nancy. Comparisons of medication exposure rates and characteristics of drug consumption were difficult due to the observed heterogeneity of methodology, type of drugs reported or data sources. Standardised reports and analyses of drug consumption during pregnancy are needed to contribute to this issue of major public health importance. Recommendations have been made on the main criteria that should be taken into consideration when carrying out an epidemiology study on drug use during pregnancy.

PP-27 SURVEY OF CHILDREN AND YOUNG PEOPLE'S PERCEPTIONS OF CLINICAL RESEARCH

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Background Both international declarations and some national legislation required that children and young people need to consent to participating a clinical re-search when they have the capacity to make their own decisions. However, the children and young people's perceptions of paediatric clinical research is unknown. Fur-thermore, it is difficult to conduct a paediatric clinical trial because of enrollment difficulties. This study was con-ducted to investigate the children and young people's perceptions of clinical trial.
Methods The survey was conducted through We-Chat investigation network aged from 8–18 years.
Results The effective questionnaires are 800 copies. Children and young people's overall awareness rate of the clinical study is 40.13%. It revealed that 21% people believed that clinical research was to treat people as ex-perimental rats. When asked 'who have the final decision on research participation'. Chose oneself, parents/guard-ian and doctor are 46.88%,74.88% and 37% respectively. When asked 'If you want to participate a study, but your parents/guardian do not agree, what would you do?', chose give up, persuade parents agree and unknown were 35.75%,41.00%,19.63% respectively. When asked 'If you do not want to participate a study, but your parents/guardian thinks you should , what would you do? 'chose listen to parents, refuse the suggestions of parents/guard-ian, unknown were 56.75% , 24.13% and 15.5.0% respec-tively. When asked'If the trial is similar to the ordinary clini-cal treatment, would you agree to participate?', chose very willing, willing, neutral and unwilling was 10.88%, 40.88%, 27.75%, and 18.25% respectively. When asked 'If the clin-ical research is helpful to you, but it need to draw a little more blood, do you like to participate', chose very willing, willing, neutral and unwilling was 12.88%, 42.63%, 15.63% and 24.50%. When asked 'If the clinical research is helpful for you, but it need to add some unpainful tests, would you like to participate?',chose very willing, willing, neutral and unwilling were 10.13%, 39.63%, 24.25% and 23.50%. As to 'what are your most concerns of participate an in-vestigation?', chose 'worry about added pain or discom-fort' was 68.63%, chose'people treat me differently when they know me participate the research'was 11.13%. As to 'How can reduce your concerns or make you feel better to participate the research?', chose 'doctors and nurses take good care of me' was 64.00%, chose 'get to know more about research'-was 41.88%. As to'how can encour-age you to participate an research?', chose 'know that other people also participate the research' was 58.75%, chose 'know the information after research'was 48.38%, chose 'get economy compensation' was 31.13%. When asked 'If the research is not helpful for you, but it will help others , will you participate?', chose willing and unwilling was 78.75% and 21.25% respectively.
Conclusion It is very necessary to education and cor-rect guide children and young people's understanding of clinical research. It is very necessary to concern about the children and your people who involved in the research. The situation of the paediatric clinical trial recruitment dif-ficulties could be improved by efforts.

PP-29 GROWTH HORMONE DOSING IN OBESE CHILDREN

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Background Obesity has direct effects on dosing any drug by increasing the proportion of the total body weight (TBW) composed of lipid. Validated algorithms exist to convert a child's actual weight to either an ideal (IBW) or lean body weight (LBW), but these are not widely used within paediatric practice. Pharmacokinetic data in obese patients do not exist for the majority of drugs and there is little direct evidence as to how obesity affects the overall risk-benefit of medications. Recombinant human growth hormone (rhGH) offers a unique opportunity to examine this, as the population receiving it routinely has height and weight measured, and the positive outcome (height gain) and adverse effect (increase in IGF-1)

are both routinely measured. rhGH dosing derived by TBW may result in inappropriately high doses in obese children.

Methods Retrospective audit of all paediatric patients treated with rhGH at a tertiary paediatric hospital in the UK with a catchment population of 2.7 million. Change in height SDS and IGF-I SDS during the first year of treat-ment was stratified by initial BMI SDS in a mixed cohort, and a subgroup of GH deficient (GHD) patients. Alterna-tive doses for those BMI SDS ≥2.0 (obese) were calculated using body surface area (BSA), IBW and LBW.

All patients who commenced treatment with rhGH between 2010 and 2014 were identified. The following data were extracted from the appointment prior to starting rhGH treatment: clinical indication, gender, BMI-SDS, height-SDS, and IGF-1 SDS. IGF-1 SDS 1 year (+/-3 months) and height SDS 1 year (+/-2 months) following the start of treatment was also recorded. Patients were studied in two cohorts:[1] an unselected cohort of patients with multiple diagnoses, and[2] only those with GHD. IGF-1 was measured using a validated solid-phase, enzyme-la-beled chemiluminescent immunometric assay.

Results 354 patients (133 female) received rhGH, includ-ing 213 (60.2%) with GHD. Obesity was present in 40 pa-tients (11.3%) of the unselected cohort, and 32 (15.0%) of the GHD cohort. For GHD patients, gain in height SDS was directly related to BMI SDS, except in obese patients ($p<0.05$). For both the entire cohort, and GHD patients only, IGF-1 SDS was significantly higher in obese patients ($p<0.0001$ for both groups). Cross sectional data identi-fied 265 children receiving rhGH, 81 (30.5%) with a BMI-SDS ≥1.75. For patients whose BMI-SDS ≥2.0, as expected the median daily dose of rhGH is reduced when the dose is calculated using IBW or LBW instead of TBW for both males and females. The dose reduction is largest when the dose is calculated using IBW. Alternate prescribing strategies for rhGH prescribing in obese patients suggest a saving of 27%–38% annually.

Conclusion Gain in IGF-I SDS is greater in obese chil-dren, and is likely to be related to relatively higher doses of rhGH. Additional gain in height was not achieved at the higher doses administered to obese children. Alternative dosing strategies in the obese patient population should be examined in rigorous clinical trials.

PP-31 KINETICALLY GUIDED DOSING OF VANCOMYCIN IN CRITICAL ILL NEONATES AND YOUNG INFANTS TREATED FOR SEPSIS

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Background Vancomycin (Van) is frequently used in ne-onates and young infants treated for sepsis while a need for prospective dosage validation has been documented in the literature[1]. Open-label, prospective study includ-ing preterm and term neonates (n=40) and young infants (n=16) treated with Van. A median (IQR) age distribution was 34.1 (24–42) gestational weeks in neonates, 5.5 (1.5 -10) months in infants. The primary goal of the study was to perform a pharmacokinetic (PK) study of Van while the secondary aim was to analyse the influence of covariates on PK (body weight-BW, gestational age-GA, postnatal age-PNA, postmenstrual age-PMA, and glomerular filtration rate estimation (eGFR) according to Schwartz formula)).

Methods Individual PK parameters – volume of distribu-tion (Vd), clearance (CL) were calculated in a one-com-partmental PK model based on individual demographic data and observed Van-plasma levels using MWPharm++ software (MediWare, Prague, Czech Republic). Vancomy-cin population PK one-compartmental model was indi-vidualized to maximise fitting of the simulated PK profile curve with observed concentration points in each patient. AUC24 were computed using individualised PK models in MWPharm++ software. Optimal maintenance doses (MD) were calculated for each patient based on vancomycin clearance values using following formula (MD (mg/day)=24× vancomycin CL (L/hod)×25 mg/L, the value of 25 mg/L was chosen as the midpoint of target therapeutic range for intermittent vancomycin (10–40 mg/L). Descrip-tive parameters median, interquartile range (IQR), mean and standard deviation (SD) were calculated using MS Excel 2010 (Microsoft Corporation, Redmond, USA). Lin-ear regression models were used to evaluate the relation-ships of PK parameters with PK covariates using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA).

Results The mean (SD) Vd (L/kg) in neonates was 0.73 (0.31), in young infants 0.74 (0.54). The mean (SD) CL (L/h/kg) was 0.052 (0.02) in neonates, 0.0132 (0.058) in young infants. Linear regression models showed a de-crease in normalised Vd ($r2=0.3274$, $p=0.0001$) and in-crease in normalised CL with increasing (GA $r2=0.6542$, $p<0.0001$) in neonates, while PMA was a PK covariate for Vd ($r2=0.3509$,$p<0.0001$) and CL $r2=0.6537$, $p<0.0001$) in neonates and for CL ($r2=0.5930$, $p=0.0005$) in young infants. BW was the most predictive for vancomycin CL and consequently MD based on linear regression models. The daily MD calculations using the following formulas have resulted in optimal average vancomycin steady-state concentrations: MD (mg/day)=45.46× BW (kg) –24.64 for neonates, and MD (mg/day)=87.43× BW (kg)– 34.30 for young infants.

Conclusion However, since the practical utility of such an equation is very limited, we propose MD nomograms based on these formulas that can be easily used in clinical settings.

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PP-33 CODEINE AND TRAMADOL USE IN A PAEDIATRIC POPULATION IN NEW ZEALAND

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Background There are concerns regarding codeine in the <2 years age group, particularly in the context of post-tonsillectomy analgesia. Tramadol, although ap-proved for children in New Zealand (NZ), is not approved. <2 years age. From 2014, practice guidelines in NZ dis-couraged the use of codeine and tramadol in children. The WHO analgesic ladder for children advocates a two-step approach: simple analgesia

(paracetamol or ibupro-fen) as the first step with the second step for moderate or severe pain being morphine. The aim of the present study was to examine the dispensing of codeine, tramadol and morphine for children in NZ in order to identify trends in usage.

Methods All NZ community dispensing data for codeine phosphate, tramadol and morphine were extracted from national administrative databases (National Pharmaceu-tical Collection and National Minimum Dataset) for the period 01 January 2010 to 31 December 2015. The data were summarised for each calendar year by age group:<2 years, 2 to <6 years, 6 to <12 years and 12 to <17 years.

Results In the <2 year age group there was little use of either codeine or tramadol, but usage of both increased to 2014, with an abrupt drop in usage of codeine in 2015. In the 2 to <6 year age group there was greater use of codeine, also increasing to 2014 with an abrupt drop in usage in 2015; tramadol usage increased in both 2014 and 2015. In the older age group there was greater usage of both codeine and tramadol with progressively increas-ing use of tramadol. Morphine use in all the age groups appeared stable.

Conclusion These data suggest that prescribers have adopted recommendations with regard to codeine but there may be substitution of codeine with tramadol.

PP-35 CLINICAL FEATURES AND THERAPEUTIC OPTIONS IN CHILDREN WITH NEUROFIBROMATOSIS 1: A SINGLE CENTRE EXPERIENCE

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Background Neurofibromatosis type 1 (NF1) is a genet-ic disorder that affects the growth and development of nerve cell tissue, with subsequent development of mul-tiple benign tumours of the nervous system and the skin, as well as the areas of abnormal skin colour and other clin-ical manifestations. Our study aimed to examine the in-cidence of clinical features and diagnostic parameters of NF1, as well as to identify the current therapeutic options.

Methods We analysed retrospectively the medical doc-umentation of the patients of the Clinic of Neurology and Psychiatry for Children and Youth in Belgrade, in the peri-od from 2003–2016, fulfilling clinical diagnostic criteria for NF1. In addition to demographic data, the clinical mani-festations were obtained based on diagnostic criteria, ad-ditional clinical manifestations and supplementary diag-nostic tests. In statistical analysis, we used the methods of descriptive statistics, χ^2 and Mann-Whitney test. In order to identify the current treatment for the NF1, we analysed the recent pharmacological data, as well as the clinical tri-als registered in the ClinicalTrials.gov registry.

Results The study group consisted of 65 patients (35 males/30 females) up to 18 years old at the first exam-ination. Multiple café au lait spots (patches of tan or light brown skin) were present in all patients (65, 100%). The frequency of axillary and inguinal freckles and Lisch nodules were 70.8% and 61.5%, respectively, while neu-rofibromas (cutaneous, subcutaneous and plexiform) were present in 66.2% of patients. Glioma optic pathway (GOP) was present in 13.2%, pathological findings of visu-al evoked potentials (VEP) were recorded in one third of patients, epilepsy with 10.8% and pathological electroen-cephalographic (EEG) patterns were described at 27.7% patients. Unidentified bright objects (UBO) on the MRI were described in 50.0% of patients, with no statistical dif-ferences regarding to the age of patients (p=0.635). Char-acteristic bone lesions were diagnosed in 27.7% patients, and positive family history was in 63.1%. Mental disorders and learning disabilities were diagnosed in 26.2% of patients. Furthermore, there was no correlation between the appearance of axillary/inguinal spots and Lisch nod-ules regarding to the age of patients (p=0.419; p=0.521, respectively); however, there was a statistically significant correlation between GOP and VEP (p=0.003). The current NF1 treatment includes the symptomatic therapy, includ-ing surgery and chemotherapy, while the specific treat-ment is not available yet. A total of 122 clinical trials were identified in the ClinicalTrials.gov registry; however, there are only few, phase 2, interventional studies in children: with mTOR inhibitors (sirolimus and everolimus) and RAS kinase inhibitor (tapifarnib).

Conclusion NF1 is a multi-system disease that requires multidisciplinary approach and monitoring. The wide range of clinical features, inability to predict the severity of features/complications and limited therapeutic options make NF1 management a real clinical challenge. Future directions: to find therapeutic strategies or specific mol-ecule(s) to prevent/treat the harmful NF1 complications.

PP-37 DEVELOPING PAEDIATRIC ANTIMICROBIAL DOSES FOR THE NEW ZEALAND FORMULARY FOR CHILDREN

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Background Many antimicrobial medications for chil-dren are used outside of the product license and prescrib-ers encounter a lack of evidence-based dosing guidance. The New Zealand Formulary for Children (NZFC) devel-oped a process to provide antimicrobial guidance based on the best available evidence from regulatory data, pro-fessional guidelines, clinical experience and clinical con-sensus.

Methods Indications and doses for antimicrobial med-ications in the NZFC were originally derived from the British National Formulary for Children (BNFC). A clinical advisory group (CAG) from New Zealand's national paedi-atric hospital was recruited to provide guidance relating to NZFC antimicrobial monographs. The CAG consisted of two paediatric infectious disease physicians and an antimicrobial stewardship pharmacist. The CAG identified monographs requiring review, and proposed changes to make theses more suited to New Zealand practice. NZFC clinical editors then compared the proposed alterations against the New Zealand approved medicine datasheet (NZAMD). If these did not agree, comparison with rep-utable resources such as New Zealand guidelines, international guidelines, and recognised references used in the clinical field. When supporting evidence was not available, the clinical editors sought further input from the CAG. Any indications and/or doses differing from the NZAMD were identified in the NZFC monographs.

Results A total of 119 antimicrobial medications in the NZFC were identified as requiring review. Following re-view, 77 (65%) medications had indication and/or dosing information as unlicensed/unapproved. Of these 35 had no corresponding

NZAMD information, 20 recommend-ed doses outside the NZAMD age ranges, 15 included indications not stated in the NZMAD, 5 with dosing dif-ferent to that in the NZAMD and 5 with an unapproved administration route

Conclusion For a national formulary to be able to pro-vide suitable antimicrobial dosing in children, collabora-tion with national experts is essential. Validating dosing against reputable resources is an important step when providing unlicensed dosing to a recognised standard.

PP-39 PRENATAL ANTIBIOTIC EXPOSURE AND CHILDHOOD ASTHMA: A POPULATION-BASED STUDY

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Importance Antibiotic use during infancy alters gut microbiota and immune development, and is associated with an increased risk of childhood asthma. The impact of prenatal antibiotic exposure is unclear.

Objective To determine and characterise the associa-tion of prenatal antibiotic exposure and childhood asth-ma.

Design Population-based cohort study using admin-istrative healthcare data. Antibiotic use was determined from prescription records. Asthma was defined using hospitalisation records, physician billing claims, and pre-scription records. Associations were determined using Cox regression and expressed as hazard ratios (HR) and 95% confidence intervals (CI).

Setting General population in Manitoba, Canada.

Participants 2 13 661 mother-child dyads born from 1996–2012.

Exposure Maternal antibiotic use.

Outcome Child asthma, defined as meeting any of the following criteria after 5 years of age: any hospitalisation for asthma; or $\geq$2 physician diagnoses of asthma, at least 3 months apart and within a 1 year period; or $\geq$2 prescrip-tions for asthma medications within a 1 year period.

Results In our study population, 10.1% of children met the case definition for asthma, and 36.8% were prena-tally exposed to antibiotics. Prenatal antibiotic exposure was associated with an increased risk of asthma (crude HR 1.29; 95% CI 1.26–1.33). This association persisted af-ter controlling for maternal asthma, sex, location of resi-dence, gestational age, number of siblings, and postna-tal antibiotic exposure during infancy (adjusted HR 1.23; 1.20–1.27). However, maternal antibiotic use during the 9 months before pregnancy (adjusted HR 1.28, 1.24–1.31) and 9 months postpartum (adjusted HR 1.32, 1.29–1.36) were similarly associated with childhood asthma.

Conclusions and Relevance Maternal antibiotic use before, during and after pregnancy was associated with a modest, dose-dependent increase in asthma risk among offspring. While our study does not support a pregnan-cy-specific causal relationship between maternal antibi-otic use and childhood asthma, it remains important to prescribe and use antibiotics judiciously.

PP-41 RISK ASSESSMENT FOR COMPATIBILITY OF RHIGF-1/RHIGFBP-3 WITH COMMONLY ADMINISTERED NEONATAL INTRAVENOUS MEDICATIONS BASED ON AN EXPERIMENTAL MODEL

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Background Despite extensive co-administration of drugs to neonates, drug-drug compatibility has not gen-erally been tested before medicines are introduced to this population. Recombinant human (rh)IGF-1/IGFBP-3 (a protein complex) is being studied for the prevention of complications of prematurity, administered as a continuous intravenous (IV) infusion in preterm infants. Due to limited line access in neonates, coadministration with other medications via a terminal injection site would be desirable for use in clinical practice. A comprehensive risk assessment based on *in vitro* testing is evaluating the physical/chemical compatibility of rhIGF-1/IGFBP-3 with medications routinely administered intravenously in the neonatal intensive care unit (NICU). We report initial re-sults from the panel of medications assessed to date.

Methods Medications most likely to be co-infused with rhIGF-1/IGFBP-3 were identified at the start of the risk as-sessment by consulting sites for a clinical trial. *In vitro* mix-ing of rhIGF-1/IGFBP-3 with each test medication (pre-dominantly small molecules) was performed based on different volumes and/or mass ratios to mimic different dose ranges. Duration of mixing was based on average infusion rates of rhIGF-1/IGFBP-3 with each test medica-tion at the highest dose, and an estimated volume for an umbilical catheter. Physical compatibility was assessed by visual observation, optical density at 320 nm, pH, and os-molality for each mixed solution and compared with the corresponding controls. Where there was no observed colour change, precipitation, turbidity, gas evolution or clinically relevant change in pH or osmolality, the mixtures were considered compatible. The concentration of each test medication post-mixing was assessed using re-versed phase high performance liquid chromatography. A comprehensive risk evaluation was conducted for each medication based on the *in vitro* physical/chemical com-patibility data, theoretical potential for chemical modifi-cation, and clinical co-infusion history/experiences.

Results *In vitro* studies and risk evaluations have been completed for rhIGF-1/IGFBP-3 with 13 medications: do-pamine, parenteral nutrition (PN), PN+Intralipid 20%, Intr-alipid 20%, dobutamine, vancomycin, morphine, fentanyl, midazolam, fluconazole, caffeine citrate, amikacin and in-sulin. *In vitro* physical compatibility was established with 10/13 medications: parenteral nutrition (PN), PN+Intralip-id 20%, Intralipid 20%, dobutamine, vancomycin, mor-phine, fentanyl, midazolam, fluconazole and insulin. Phys-ical compatibility was not established with 3/13 medica-tions: dopamine, caffeine citrate and amikacin, owing to changes in pH post-mixing. Small molecule content was not affected post-mixing for the medications tested. A comprehensive risk evaluation confirmed a low

risk for the probability/severity of a 'risk event' (defined as incompatibility with the co-infused drug over the duration and condition of the simulated mixing studies) for those medications showing *in vitro* compatibility.

Conclusion Case-by-case, *in vitro* compatibility data for rhIGF-1/rhIGFBP-3 to date have been encouraging and indicate the likelihood of being able to co-infuse rhIGF-1/rhIGFBP-3 with the tested medicines. Further work is on-going to systematically evaluate compatibility with other IV drugs used in the NICU and develop protein-specific assays to test chemical compatibility of rhIGF-1/IGFBP-3. We believe this work will establish a new benchmark for compatibility testing of drugs utilised in neonates; con-tributions from clinicians and cross-functional disciplines will be key to the process.

PP-43 PHARMACOGENOMICS FACTORS RELATING TO IBUPROFEN AND ACUTE KIDNEY INJURY IN PAEDIATRIC PATIENTS: A SYSTEMATIC REVIEW

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Background Ibuprofen is associated with acute kidney injury (AKI), but there is marked inter-individual variation, with the majority unaffected but some with severe dam-age. The primary objective of this study was to establish if any previous studies have examined the potential phar-macogenomic associations between ibuprofen exposure and development of AKI in children using ibuprofen

Methods The search was initiated using search engines such as PubMed, Cinahl Plus and Cochrane, the key words and phrases were used, 'Ibuprofen', 'Nephrotoxicity' and 'Pharmacogenomics.' Advanced search, which allowed me to search multiple alternative key words, to ensure any available papers, were identified.

Results The PubMed search produced seven papers, which were all excluded as five were not ibuprofen and three were not relating to nephrotoxicity. Cochrane identified three papers, which were all excluded, as they were not specific to ibuprofen. The search terms had no results on Cinahl plus. This meant there was no sufficient evidence to evaluate the pharmacogenomic factors re-lating to Ibuprofen and Acute Kidney Injury in Paediatric patients.

Conclusion The search terms used were wide and in-clusive, so we believe it unlikely any studies were missed. This is a promising area for future research, although care will be needed in study design to exclude the influence of factors such as pyrexia and dehydration in the children affected.

PP-45 GENTAMICIN EXPOSURE IN NEONATES ACCORDING TO SWISS NEO-NATAL INTENSIVE CARE DOSING REGIMENS AND INTERNATIONAL GUIDELINES

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Background To assess the achievement of adequate gentamicin exposure for dosing regimens used across Swiss neonatal intensive care units (NICUs) and interna-tional guidelines.

Methods Gentamicin dosing regimens were collected from 7 Swiss level III NICUs and 8 international guidelines (Frank Shann`s, BNF for children, Nelson Textbook of Pedi-atrics, Neonatal Formulary 7th edition, The Blue Book, Lex-icomp Paediatric and Neonatal Dosage Handbook, The Red Book and Neofax). Variables used for selection of individ-ualized dosing regimen (single dose, dosing interval, total daily dose and demographic characteristics) from each guideline were assessed. Model-based simulations were performed to compare the various dosing regimens with respect to their ability to achieve effective peak drug con-centrations according to predefined minimum inhibitory concentrations (MICs), peak concentrations (Cmax/MIC >10) and safe trough concentration (Cmin <2 mg/L). Model-based simulations were based on demographic data from the ARPEC database.

Results Gentamicin dosing regimens based on Swiss NICUs and international guidelines showed consider-able variability with respect to dose, dosing interval and demographic variables (weight, gestational age, post-menstrual age and postnatal age) to determine a priori individual dosing regimens. Doss and dosing intervals ranged from 4 mg/kg to 6 mg/kg and from 24 hours to 48 hours, respectively. Overall, this resulted in seven possible dosing regimens for gentamicin in neonates, which can vary between neonatal subgroups when neonates were categorised based on demographic variables. Based on demographic variables, six different alternatives could be distinguished for the determination of individualised dos-ing regimens of gentamicin; either based on one patient characteristic (GA: n=1; PNA: n=1), a combination of characteristics (WT and PNA: n=3; GA and PNA: n=5; PMA and PNA: n=2) or no characteristics at all (n=2). Model-based simulations suggested that for a MIC breakpoint of 0.5 mg/L (i.e. target Cmax >5 mg/L), a high proportion of neonates [range: 26%–36%] did not reach the target af-ter the first dose according to current dosing approaches. Assuming a target MIC breakpoint of 2 mg/L, an effective.

Cmax is not achieved with any evaluated dosing recommendation. On the safety side, potential toxic trough con-centrations (≥2 mg/L) were observed in less than 5% of neonates.

Conclusion Current neonatal dosing approaches for gentamicin are associated with subtherapeutic drug ex-posures in a considerable portion of neonates. These sub-therapeutic exposures are associated with increasing MIC breakpoint. Therefore, there is a clear need for harmoniza-tion and simplification of dosing regimen for gentamicin in the neonatal patient population, based on quantitative rationale to achieve the effective and safe exposure.

PP-47 OFF-LABEL USE OF TACROLIMUS IN CHILDREN WITH HENOCH-SCHONLEIN PURPURA NEPHRITIS: EFFICACY AND SAFETY

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Background Tacrolimus was used off-label in the treat-ment of Henoch-Schönlein purpura nephritis (HSPN) in children. The objective of this pilot study was to assess its efficacy and safety.

Methods Children with HSPN receiving tacrolimus and steroids as empirical treatment was included. Urine protein was

assessed every 2 weeks during treatment. Pharmacogenetic analysis was performed on the CYP3A5 gene.
Results A total of 25 patients with a mean age of 7.2 (range 3–12) years was included in this study. Pro-teinuria returned to negative in 21 patients with a mean treatment duration of 101 (SD 75) days. Patients with CYP3A5*1/*3 had longer duration of treatment achiev-ing negative proteinuria as compared with patients with CYP3A5*3/*3 (131±97 versus 80 ±39 days). No patients discontinued the tacrolimus treatment due to adverse events, and no drug-related adverse events were shown to have a causal association with tacrolimus therapy.
Conclusion This preliminary study shows that tacrolim-us might be an effective, and well-tolerated drug for the treatment of HSPN in children.

PP-49 POPULATION PHARMACOKINETICS AND DOSING OPTIMISATION OF CEFOPERAZONE IN CHILDREN

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10.1136/archdischild-2017-esdppp.94

Background Cefoperazone is used in children with sus-pected or documented Gram-negative serious infections. Currently, its use is off-label partly because of lack of phar-macokinetic studies. Our aim was to evaluate the pop-ulation pharmacokinetics of Cefoperazone in children between 2–12 years of age and define the appropriate dose in order to optimise cefoperazone treatment in this vulnerable population.
Methods Blood samples were collected from children treated with Cefoperazone and concentrations were quantified by HPLC-MS. Population pharmacokinetic analysis was performed using NONMEM software.
Results The data from 83 children (age range: 2.2–10.8 years) were available for population pharmacokinet-ic analysis. A two-compartment model with first-order elimination showed the best fit with the data. A covariate analysis identified that current weight had a significant impact on cefoperazone pharmacokinetics.
Conclusion The population pharmacokinetics of Cefop-erazone was evaluated in children between 2–12 years old and an evidence-based optimal dosing regimen was established based on simulation.

PP-51 METAMIZOLE-INDUCED AGRANULOCYTOSIS IN AN ADOLESCENT TREATED FOR CHRONIC HEADACHE

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Background Metamizole (dipyrone) is used in several European countries to treat pain. Its use has been asso-ciated with agranulocytosis and the incidence of this se-vere adverse drug reaction in adults varies between 1.1 in 1 million patients and 1 out of 1439 prescriptions. In adults the moment at which agranulocytosis is detected is quite variable and ranges from appearing after a sin-gle dose or several months after exposure. So far, these serious adverse drug reactions have been rarely seen in children. Two postauthorisation safety studies in about 1500 children did not report any case of paediatric met-amizole-induced agranulocytosis. However, two cases have been published in children who used metamizole for more than 21 days and 4 weeks, respectively.
Case A 14 year old girl was treated with metamizole 2 g/d (26.8 mg/kg/d) for chronic headache which had been prescribed by her general practitioner (GP). Pre-existing atopic dermatitis deteriorated on day 7 of treat-ment, and a sore throat occurred on day 10. On day 12, she consulted her GP who initiated antibiotic treatment with penicillin due to infected and putrid skin lesions. Metamizole was discontinued, but no blood count was ordered. The patient was seen for follow-up two days lat-er since her condition had not improved. A blood count was performed revealing agranulocytosis (neutrophils $0.05 \times 10\hat{}9$/L), and the patient was admitted to hospital.
Results Upon admission, treatment with meropenem and teicoplanin was initiated due to septic appearance and shortness of breath. In addition, acyclovir was started due to suspected eczema herpeticum which was later ruled out. Further diagnostic work-up revealed skin le-sions infected with Staphyloccus aureus and multifocal pneumonia. Bronchoalveolar lavage on day 19 to rule out fungal infection was negative for any microorganisms. The patient was treated with granulocyte-colony stimu-lating factor (G-CSF) 30 Million IU for 4 days, during which the neutrophil count recovered. The patient improved clinically and was discharged on day 23 after the initial exposure to metamizole.
Conclusion To our knowledge, this is the first report of metamizole-induced agranulocytosis in a paediatric pa-tient who used metamizole for only 12 days. In patients with atopic dermatitis, drug-induced agranulocytosis might show an atypical clinical course by causing skin in-fections as the first presenting symptom. Despite a lower incidence in children than in adults, this serious adverse drug reaction should be kept in mind when prescribing metamizole, and treatment duration should be kept as short (5–7 days) as possible.