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P100 A PRACTICAL FRAMEWORK FOR THE ASSESSMENT OF RISKS AND BENEFITS OF OFF-LABEL PRESCRIBING IN PAEDIATRICS (ARBOP-P)

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Background Guidelines for off-label prescribing are emerging.[1–6] However, these guidelines do not provide practical guidance to assess the risk benefit balance and select the right paediatric dose We, therefore, aimed to develop a practical framework to guide paediatric healthcare professionals to assess the risks and benefits of off-label use.

Methods We have reviewed available literature on the suggested criteria for appropriate off-label use and evaluated these criteria for relevance in paediatrics. For guidance on dose-selection we searched for regulatory guidance on paediatric drug development. Next, the literature was searched for strategies that can be applied to assess the risks and benefits of off-label use. Based on literature findings a framework was proposed to provide practical guidance to physicians for off-label prescribing. Finally, the framework was applied to a case.

Results The following conditions for appropriate off-label use were identified based on available literature: 1. *Medical need for off-label use*. 2. *Off-label use is based on 'high quality evidence'*. As 'high quality evidence' in paediatrics is often lacking-, we propose to replace the need for high quality evidence by a positive risk-benefit assessment based on available evidence. 3. *Parents and patients are informed*. This is not feasible for every single drug prescribed off-label, we propose a graded approach 4. *The outcomes of off-label use are followed up*.

The PROACT-URL framework[7] for decision-making as well as the FDA paediatric decision tree[8] seem helpful tools to guide decisions in real-life practice.

Conclusion We identified important aspects and tools to develop a framework (ARBOP-P) to guide healthcare professionals on how to systematically assess and balance the benefits and risks for off-label use, including dose selection, to ultimately optimize efficacy and safety of paediatric off-label prescribing.

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P101 EXTENDING THE DUTCH PAEDIATRIC FORMULARY ACROSS EUROPE: SUCCESSFUL DEVELOPMENT OF COUNTRY SPECIFIC, PARALLEL, PAEDIATRIC DRUG FORMULARIES

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Backgrounds As many drugs in paediatrics are used of off-label, prescribers across Europe face a lack of evidence-based dosing guidelines. The Dutch Paediatric Formulary (DPF) was developed to provide dosing guidelines based on best available evidence from registration data, investigator-initiated research, clinical experience and consensus (1). The DPF has recently joined forces with Germany, Norway and Austria aiming to develop multi-language, parallel, paediatric drug formularies based on the DPF.

Methods

The DPF database and ICT framework were extended to a duplicate database for Germany. The dosing guidelines were translated to German and reviewed for fit with German practice. Relevant drugs and dosing recommendations were selected and country-specific information was added to address country-specific needs. Work-sharing on content development was studied in a small pilot.

Results The German Pediatric Formulary (www.kinderformularium.de) was launched on 1 October 2018 within a German paediatric medication safety project (KiDSafe). At that time 119 of 769 drugs were reviewed and published in the German formulary.The dosing recommendations of the DPF show a good fit with German practice; i.e. adaptations were needed in less than 10% of the cases caused by differences in licensing status, national guidelines or availability of formulations. There were no differences in interpretation of evidence. Nine drugs - highly relevant for German practice, but not listed in the DPF, were added to the German formulary based on SmPC. The content

work sharing was piloted by the development of a new monograph and the periodic revision of a monograph complying to the Dutch standard operating procedure by Germany. This pilot has shown the feasibility of work-sharing in developing and updating drug monographs.

Conclusion The Dutch framework has successfully been extended to the German situation. Work-sharing on the development of dosing recommendations is feasible. Similar extension to Norwegian and Austrian nation-wide formularies has started.

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P102 ALTERNATIVE SPLICING OF THE SLCO1B1 TRANSPORTER IN PAEDIATRIC LIVER

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Background Alternative mRNA transcripts occur in >90% of human genes and may be triggered by developmental signals. The hepatic transporter OATP1B1 (gene name *SLCO1B1*) traffics substrates across the hepatic membrane, and shows age-related changes in protein expression. We aimed to predict novel isoforms of OATP1B1 by studying alternative splicing of *SLCO1B1* in human paediatric post-mortem liver tissue, and the relationship of their mRNA expression with age.

Methods mRNA expression of SLCO1B1 transcripts was determined using RNA sequencing (HISAT2/StringTie). Novel mRNA transcripts were considered of relevance when (1) the expression was >5% of the annotated isoform, (2) it was a *SLCO1B7* and *SCLO1B1* hybrid transcript, or (3) when the expression was associated with age. The software packages ORF-finder, TMpred and TOPO2 were used to predict the protein sequence and structure of the novel isoforms. Relationship of expression with age was studied with the Kruskal-Wallis test for age groups (fetal, 0–1.5 year, 1.5–6 year, 6–12 year and 12–18 year) and with Spearman correlation tests for age on continuous scale.

Results In 97 hepatic post-mortem tissues (gestational age median 16.4 [range 14.7–41.3] weeks, postnatal age 0.36 [0 - 17] years) 27 novel mRNA transcripts were detected. Of these, 13 were relevant: 2 isoforms are predicted to translate into amino acid sequences similar to the annotated isoform for OATP1B1, 9 isoforms may translate into truncated versions, and the expression of 8 isoforms was associated with age. None of the isoforms had an ORF that covered the SLCO1B7 region.

Conclusion We showed that novel SLCO1B1 mRNA isoforms potentially translate into OATP1B1 protein with unknown function, and that alternative splicing may well be a regulatory mechanism for *SLCO1B1* expression during development. This data provides a better understanding of age-related changes in the expression of OATP1B1, and, with that, potentially improves prediction of disposition of endogenous and exogenous substrates.

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P103 TARGET ATTAINMENT OF AMIKACIN THERAPY IN CRITICALLY ILL CHILDREN

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Background Research regarding the optimal amikacin (AMI) dosing regimen in critically ill children is scarce.[1] Optimal AMI efficacy has been observed with plasma peak over minimal inhibitory concentration of the suspected pathogen (peak/MIC) ratios of 8 to 10. Plasma trough levels (C_{min}) >5mcg/ml are related to its toxicity.

The objectives of this pilot study were to: (1) evaluate target attainment rate and occurrence of supratherapeutic concentrations in early and assumed steady-state dose conditions, and (2) investigate the correlation between AMI clearance and estimated glomerular filtration (eGFR).

Methods Children admitted to the ICU receiving intravenous AMI (20 mg/kg once daily) were included. Serial blood samples were obtained from early (1st/2nd) and assumed steady-state (SS) doses. The evaluated target peak concentration range was 54–64 mcg/ml, assuming a *Pseudomonas aeruginosa* infection with Eucast MIC breakpoint of 8 mg/L, and a C_{min} threshold of 5 mcg/L. eGFR was estimated using the modified Schwartz formula. AMI clearance was calculated using non-compartmental PK analysis. Correlation was assessed by means of a scatter plot and Pearson Correlation Coefficient (r).

Results

Twenty-one patients (median age 1,5 years; range:0,5 months-14 year, median eGFR 162 ml/min/1,73m^2 (range:107–475 ml/min/1,73m2) were included. In early dose conditions, 69% of patients had therapeutic peak concentrations (median: 60 mcg/ml; range:26–73 mcg/ml). In SS conditions, 60% of patients had therapeutic peak concentrations (median: 59 mcg/ml; range:35–83 mcg/ml). Only one supratherapeutic C_{min} was observed. AMI clearance (median 0.08L/h/kg; range: 0.05–0.91 L/h/kg) was comparable to what has been previously reported but showed no correlation with eGFR (r=0.1; p=0,66) [1].

Conclusion This pilot study suggest that the current AMI dosing regimen may lead to subtherapeutic concentrations in patients infected with less susceptible pathogens. Supratherapeutic Cmin were far less of a concern. Dose adjustments of