EPTRI
European Paediatric Translational Research Infrastructure

EPTRI SCIENTIFIC MEETING

BOOK OF ABSTRACTS

BOLOGNA, ITALY

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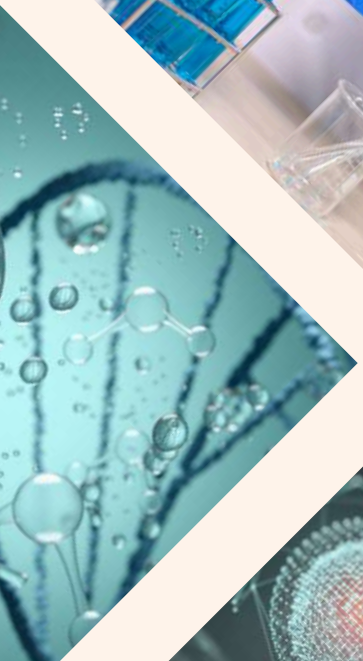

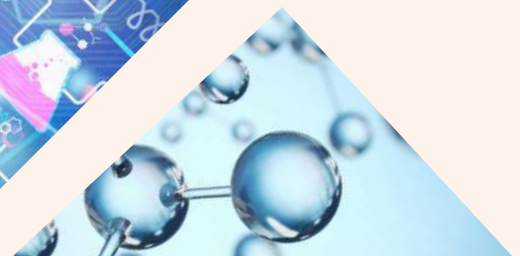

“EPTRI Developmental Pharmacology TRP”

SPEAKER SECTION

SPEAKER: KAREL ALLEGAERT

EPTRI Developmental Pharmacology TRP

Karel Allegaert[1]

1 – European Paediatric Translational Research Infrastructure (EPTRI), Leuven, Belgium

Developmental pharmacology plays a vital role in addressing the unique pharmacological needs of paediatric patients, incorporating growth, maturation, and disease-specific considerations. Collaboration across disciplines is crucial for advancing this field, ensuring that pharmacology services and clinical methods are interconnected and foster innovative solutions.

A significant challenge in paediatric pharmacology is the development of age-appropriate formulations and addressing the specific needs of children, including taste preferences and rare diseases. In recent years, regulatory frameworks have started evolving, with the ongoing revision of the European paediatric drug regulation. The focus is shifting from traditional indication-based approaches to molecular target-based drug development, a strategy successfully employed in paediatric oncology. This evolution promises greater precision but introduces challenges, particularly the feasibility of conducting multiple clinical trials and the risk of generating insufficient data to guide treatment decisions effectively. Likely relevant for paediatrics is the revision of the European Regulation, considering the mode of action concept for paediatric drug development.

Furthermore, the acceptance of extrapolation methodologies (latest ICH decision) is a positive development, enabling the application of data from adults or related diseases to paediatric populations. Advances in pharmacokinetic modelling, particularly physiologically based pharmacokinetic (PBPK) models, allow for predictions of drug behaviour in children, even in the absence of specific clinical data. These models, integrating in vitro data, animal models, and physiological data, help address scenarios where limited data exist, such as in very young or critically ill children.

In summary, developmental pharmacology is an interdisciplinary field that balances innovation with practical feasibility. It requires careful integration of regulatory, clinical, and pharmacological knowledge to ensure drugs are safe and effective for paediatric patients. By leveraging data-driven approaches, collaboration, and advanced modelling techniques, the field can overcome existing challenges and optimize drug development for children, ultimately improving therapeutic outcomes.

SPEAKER: PIER GIORGIO COJUTTI

Pharmacometrics for better dosing in children

Traditionally, dosing in children has been based on allometric scaling, which consists of predicting pharmacokinetic parameters such as clearance or distribution volume for pediatrics from normal-weight adult values. However, a single, universal allometric exponent is unlikely to exist and is instead expected to vary based on many factors such as drug properties and physiological

characteristics such as age and weight. Pharmacometrics is a new pharmacological science that, by using pharmaco-statistical models of drug pharmacokinetics and/or pharmacodynamics based on real-world observed data, enables to estimate the entity of pharmacological parameters and the clinical factors that may affect them, thuis allowing a more personalized therapy. In children, such models have been successfully applied to optimize dosing of the antimicrobials linezolid and meropenem in hospitalized patients with multi-drug resistance infections, as well as to predict the adequate dosage of FXIII in patients with FXIII congenital deficiency.

SPEAKER: CATERINA DERUVO

DOACs in pediatric thromboembolic disorders: Translating science from the lab to the clinic.

Caterina Deruvo[1], Francesco Samarelli[1], Rosa Purgatorio[1], Marco Catto[1], Modesto de Candia[1], Cosimo D. Altomare[1]

1 – Department of Pharmacy – Pharmaceutical Sciences, University of Bari Aldo Moro

Approximately 95% of venous thromboembolic events (VTE) in the pediatric population are associated with severe conditions, including cancer, nephrotic syndrome, congenital heart disease, systemic lupus erythematosus, and the use of central venous catheters (CVC) for intensive or long-term therapies. In this context, Direct Oral Anticoagulants (DOACs) such as rivaroxaban, dabigatran, apixaban, and edoxaban, already used in adults, represent promising alternatives to traditional anticoagulant therapy, based on heparins and vitamin K antagonists (VKAs). DOACs are characterized by more predictable pharmacokinetics, which reduce the need for frequent monitoring and improving treatment adherence.

Rivaroxaban and dabigatran have been approved for pediatric VTE, but concerns remain regarding their safety and efficacy. A large meta-analysis of seven randomized clinical trials (RCTs) published up to 2021 on DOACs in children with VTE suggests that they may represent a valid alternative to standard therapy. The results oof a study on 1,139 cases indicate that DOACs reduce the risk of VTE recurrence, with mortality and major bleeding rates similar to those of standard therapy, but with a higher incidence of non-major bleeding. Dabigatran and rivaroxaban showed similar effects, although rivaroxaban was associated with a higher risk of non-major bleeding. Recent studies, such as EINSTEIN Junior and DIVERSITY, confirm the efficacy of DOACs in children with VTE, with outcomes comparable to standard therapy.

One of the key aspects in the development of pediatric drugs is related to age-dependent pharmacokinetics and pharmacodynamics. Hepatic metabolism and renal function in children are not fully developed, affecting the absorption, distribution, metabolism, and excretion of drugs (ADMET). Renal clearance in neonates and infants is immature, thereby significantly affecting the elimination of drugs such as dabigatran, which is 85% dependent on renal function. Moreover, cytochrome P450 enzymes and efflux transporters, such as P-glycoprotein (P-gp), progressively mature with age, altering the bioavailability and metabolism of DOACs like apixaban and rivaroxaban, which are strong inhibitors of CYP3A4 and substrates of P-gp. Dabigatran etexilate prodrug requires metabolic activation before exerting its anticoagulant effect. Rivaroxaban and edoxaban, administered once daily (OD), may improve adherence compared to apixaban and dabigatran, which require a twice-daily (BID) administration. However, rivaroxaban's bioavailability depends on food intake, a factor that could impact its effectiveness in children, particularly in

younger patients with feeding difficulties. To develop effective and safe pediatric anticoagulant therapies, it is crucial to combine clinical studies with advanced predictive models, supported by chemoinformatic tools and in-vitro evaluations of ADMET parameters. These approaches allow for dose optimization and reduce the risk of side effects, ensuring that DOACs can be used in pediatrics with adequate safety profile. Our contribution in this field deals with in-vitro permeability assays, assessment of the potential interaction with P-gp and affinity to plasma proteins, in order to assess possible interactions with other drugs or foods and how they can affect the drug bioavailability.

POSTER SECTION

Dexmedetomidine as a Promising Neuroprotective Sedoanalgesic in Neonatal Therapeutic Hypothermia: A Systematic Review and Meta-Analysis.

Enrico Cocchi[1], Juleda Shabani[2], Arianna Aceti[1], Gina Ancora[3], Luigi Corvaglia[1], Federico Marchetti[1]

1 – Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum - University of Bologna, Bologna, Italy; 2 – Department of Medicine and Surgery, Alma Mater Studiorum - University of Bologna, Bologna, Italy; 3 – Neonatal Intensive Care Unit, AUSL Romagna, Infermi Hospital, Rimini, Italy

Background: Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal mortality and neurodevelopmental disabilities. Therapeutic hypothermia (TH) is the standard of care, but optimized sedoanalgesic strategies remain critical. Dexmedetomidine shows promise as an alternative to traditional sedatives, but its role in this context remains systematically underexplored.

Objective: This meta-analysis evaluates the safety and efficacy of dexmedetomidine in neonates undergoing TH for HIE.

Methods: A systematic search of Medline, Scopus, EMBASE, WOS, ClinicalTrials, and Cochrane Library identified studies published from January 2014 to October 2024. Studies focusing on dexmedetomidine in neonatal TH with relevant outcomes were included. Selection followed PRISMA guidelines, with independent quality assessments. The protocol was registered in PROSPERO (CRD42024605817). Results are presented as meta-analyses or evidence-based discussions when pooling was unfeasible.

Results: Seven studies involving 609 neonates were included: four cohort studies (n = 486) and three case series (n = 123). Dexmedetomidine provided comparable sedation to traditional agents (MD = -0.01 [-0.68 - 0.66], p = 0.99) and significantly reduced seizure risk (OR 0.31 [0.10 - 0.98], $p < 0.05$) with a non-inferior safety profile. Trends suggested shorter duration of mechanical ventilation and time to full enteral feeding. Substantial heterogeneity in dosing protocols highlights the need for standardization.

Conclusions: Dexmedetomidine appears to be a safe and promising sedative in neonatal TH for HIE, with potential neuroprotective, respiratory, and gastrointestinal benefits. Despite limited evidence and the absence of randomized clinical trials, its non-inferior efficacy and safety warrant further exploration and urges the development of standardized dosing protocols.

Alterations of the microbiota in lactating Göttingen Minipig sows treated with metformin.

Federica D'Amico[1] Silvia Bencivenni[1], Augusta Zannoni[1], Domenico Ventrella[1], Alberto Elmi[2], Maria Laura Bacci[1], Mikael Niku[3], Patrizia Brigidi[1], Monica Forni[1], Silvia Turroni[1]

1 – University of Bologna; 2 – University of Pisa; 3 – University of Helsinki

Background: Early gut microbiota dysbiosis can affect child's health and has been linked to the onset and progression of several diseases later in life (e.g., asthma, allergies, obesity, type 2 diabetes). Breast milk is recognized as a major driver of the structure and dynamics of the gut microbial community from the earliest moments of infant life. In addition to nutritious and prebiotic compounds, milk is associated with a specific microbiota that is shaped by several maternal factors, including gut microorganisms and medications (e.g., metformin, an antidiabetic drug). However, the impact of the latter on the milk microbiota is still largely unknown. In this context, the Göttingen Minipig has been proposed as the most appropriate animal model to study the safety of drug use during pregnancy and lactation due to its physiological and metabolic similarities to humans, milk volume and ethical factors. Furthermore, this animal model seems promising for microbiota studies due to its genetic stability and microbiological control, and has been used to study gut microbiota modifications in other contexts. In this study, we investigated the gut and milk microbiota composition of Göttingen Minipig sows receiving prolonged metformin administration, and followed the dynamics of the gut microbiota of the corresponding piglets.

Methods: One week after farrowing, four sows received oral metformin (500 mg/day) for 2 weeks, followed by 850 mg/day during the third week. Stool and milk samples were collected from each sow 5-6 days after farrowing and at the end of each weekly metformin treatment. In addition, rectal swabs were collected from piglets before treatment and weekly during the metformin administration. Characterization of all microbial ecosystems was performed by Illumina 16S rRNA amplicon sequencing.

Results: The milk microbiota of Göttingen Minipig sows after metformin administration showed an increase of biodiversity that correlated with higher drug doses. Increased levels of Prevotella and Ruminococcus, and reduced relative abundance of Fusobacterium and Porphyromonas were observed after the last week of treatment. As expected, the gut microbiota of sows was strongly affected by metformin use, with a significant reduction in health-associated Oscillospiraceae members over time. Analysis of piglet gut microbial communities is ongoing.

Preliminary conclusions: In addition to demonstrating the relevance of the Göttingen Minipig as a valid model for studying the impact of medications on maternal microbiota, our results suggest that both milk and gut microbiota of sows may be affected by metformin intake and thus have an impact on piglet gut microbial development in a critical timeframe.