P77 PEDIATRIC DRUG DATA IN CANADIAN DRUG MONOGRAPHS

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Background Optimal drug therapy in children relies on availability of pediatric-specific information. European and American legislative initiatives have resulted in advancement of pediatric pharmacotherapy data. We aim to describe the quality and quantity of pediatric information in drug monographs of New Active Substances (NASs) approved by Health Canada.

Design/Methods Canadian drug monographs of NASs approved by Health Canada, from January 2007 until December 2016, were systematically reviewed for pediatric-specific information. Pediatric-specific information defined as: pediatric indication, dosing, pediatric-friendly dosage forms, and pediatric safety data.

Results Over the period of the study, Health Canada approved 281 NASs. Of all the non-biologic NASs (205, 74%), 39 (19%) were approved for use in pediatric patients. The number of drugs with pediatric approval was lowest in 2008 (1, 8%) and highest in 2016 (8, 32%), following no specific pattern. Neonates had the lowest rate of drug approvals through all pediatric age groups (4, 2%). All drugs with pediatric approval had pediatric-specific dosing information with the majority of them presenting pediatric safety data (79%). Pediatric friendly formulation was only available in 20%(8) of drugs with pediatric approval. Studies in pediatric populations were the source of pediatric information in 59%(23) of drugs with pediatric approval.

Conclusion(s) Less than 20% of the NASs approved by Health Canada for use in adults contain pediatric approval. Neonatal populations remain a therapeutic orphan, with severe lack of dosing and safety information. Safe and effective pediatric pharmacotherapy requires well-conducted pediatric research to enhance pediatric drug data. Canadian children are in need for legislative initiatives to promote pediatric drug development.

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P78 PHARMACOKINETICS OF INTRAVENOUS AND INTRANASAL NALBUPHINE IN INFANTS

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Background Nalbuphine is a mixed agonist-antagonist opioid analgesic agent frequently used in paediatrics, and licensed for parenteral use only. Intranasal delivery could be a safe, effective and non-invasive alternative, especially in infants in the acute setting. However, pharmacokinetic (PK) data for this route of administration is completely lacking. The aim of this study was to assess PK of nalbuphine in infants 1–3 months after single intravenous (0.05 mg/kg) and intranasal (0.1 mg/kg) application, respectively.

Methods We conducted a prospective, single centre, open-label pharmacokinetic study in infants 1–3 months undergoing sepsis workup in the emergency unit. Included infants received alternating nalbuphine as 0.05 mg/kg intravenous bolus or as 0.1 mg/kg intranasal spray. PK samples were taken at 3 pre-defined time points (15, 30 and max. 240 min post-dose before discharge). Area under the concentration-time curve ($AUC_{0-T_{last}}$ and $AUC_{0-infinity}$ for i.v.) was calculated using non-compartmental analysis and was compared between groups using Wilcoxon test. Further parameters derived included maximum concentration (C_{max}), time of maximum concentration (T_{max} for i.n.) and terminal half-life ($t_{1/2}$).

Results A total of 31 patients were included in the analysis. Median age was 55 days [interquartile range 38–63] in the intranasal (N=20) and 42 [37–76] days in the iv group (N=11). Median $AUC_{0-T_{last}}$ was 7.6 (5.4–10.4) mcg*h/L following intranasal versus 7.9 (6.0–14.7) mcg*h/L for iv administration ($p=0.46$). $AUC_{0-T_{last}}$ (i.v.) covered 80 [68–83]% of $AUC_{0-infinity}$. Median C_{max} was 4.5 [3.5–5.6] mcg/L (i.n.) versus 6.5 [5.3–15.9] mcg/L (i.v.) ($p=0.014$), $t_{1/2}$ 2.4 [1.3–2.8] h (i.n.) versus 1.3 [1.1–1.5] h (i.v.) ($p=0.021$). T_{max} occurred 37 [32–65] min after intranasal administration.

Conclusion This first PK study of intranasal nalbuphine in infants suggests that 0.1 mg/kg i.n. dosing provides similar exposure as 0.05 mg/kg i.v. in infants in terms of AUC, and hence intranasal bioavailability close to 50%.

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P79 PHARMACOKINETICS OF SUFENTANIL IN CRITICALLY ILL NEONATES

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Background Sufentanil is a potent synthetic opioid increasingly used as an analgesic drug for pain treatment in critically ill neonates. Clinical studies concerning the pharmacokinetics (PK) of sufentanil administered as a bolus or continuous infusion in neonates are sparse and a population model has been developed for critically ill children beyond the newborn period. The aim of our study was to determine the PK of sufentanil in critically ill neonates treated with continuous sufentanil infusion for pain management (prophylactic and therapeutic use).

Methods Eight term neonates (birth weight 2.60–4.30 kg; postnatal age 2–96 h) were treated with sufentanil (initial bolus 0.1–0.5 µg/kg i.v. administered for 5 minutes followed by continuous infusion 0.1–0.5 µg/kg per hour i.v.). Sufentanil plasma concentrations were determined using a UPLC-MS/MS assay. Totally 159 sufentanil concentrations were measured (8–27 measurements per patient). Individual sufentanil PK parameters were calculated in a two-compartmental PK model with first-order elimination kinetics based on individual demographic and clinical data and observed sufentanil plasma levels using MWPharm++ software (MediWare, Prague, Czech Republic). The sufentanil population PK model was individualized to maximize fitting of the simulated PK profile curve with observed concentration points. The fitting was performed using Bayesian method.

Results Median (IQR) sufentanil central and total volume of distribution, clearance, and distribution and elimination half-life were 4.7 (4.2–5.2) L/kg and 11.8 (9.9–14.2) L/kg, 0.552 (0.415–0.671) L/h/kg, and 0.0264 (0.0260–0.0264) h and 15.7 (13.4–19.2) h, respectively.

Conclusion We observed similar sufentanil PK parameters (preliminary results) as described previously in literature. However, further studies with more patients are needed.

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P80 OBJECTIVE PHARMACODYNAMIC EVALUATION OF DOXAPRAM IN PRETERM INFANTS

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Background Pharmacodynamic evaluation is challenging in neonatal clinical care, and often based on subjective human interpretation of clinical signs and the available 'snapshot' of physiological parameters. High frequency data (≥ 1 Hz) of bedside patient monitors provide the opportunity of continuous and objective drug evaluation.¹ This study investigates the predictive value of continuously available vital and ventilatory parameters to evaluate doxapram therapy. Doxapram is a respiratory stimulant to avoid mechanical ventilation and adverse outcomes of hypoxemia in preterm infants.²

Methods Preterm infants admitted to a level III NICU centre who received doxapram therapy were eligible for inclusion. Stored vital and ventilatory parameters were retrospectively analysed. Multivariate analysis was performed to identify variables that influenced therapy failure (intubation or death) or success. Variables with a p value < 0.1 in univariate analysis were included in the multivariate analysis. Additionally, the $\Delta\text{SpO}_2/\text{FiO}_2$ -ratio was calculated by subtracting the median $\text{SpO}_2/\text{FiO}_2$ -ratio 1 day after therapy from the median $\text{SpO}_2/\text{FiO}_2$ -ratio 1 day before therapy.

Results The first episode of doxapram treatment was analysed in a total of 61 preterm infants with a median postnatal age at therapy start (PNA) of 3.0 weeks (IQR; 2.0–3.6). The success rate of doxapram therapy was 57%. Out of all parameters, the $\text{SpO}_2/\text{FiO}_2$ -ratio showed to be the most indicative for therapy outcome. The predictive model included the $\Delta\text{SpO}_2/\text{FiO}_2$ -ratio, the PNA, the administration of a loading dose at start, and intubation within 24 hours before the start of doxapram (area under the curve of 0.828). The $\Delta\text{SpO}_2/\text{FiO}_2$ -ratio was inversely associated with therapy outcome (OR 0.26, CI 95% 0.07–0.83; $p = 0.03$).

Conclusion The $\Delta\text{SpO}_2/\text{FiO}_2$ -ratio between 1 day before and 1 day after start of the therapy is predictive of failure or success of doxapram therapy. The use of physiological data shows potential in the pharmacodynamic evaluation of doxapram therapy.

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P81 USE OF SYSTEMIC ANTIBIOTICS IN AUSTRIAN CHILDREN AND ADOLESCENTS: A SURVEY

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Background Several surveys that have assessed the use of antibiotic medicines for children and adolescents demonstrate significant heterogeneity in prescription patterns between different countries. The liberal use of antibacterial treatment, particularly unjustified use of broad spectrum antibiotics, is one of the main reasons for increasing rates of antibiotic resistance. We have studied antibiotics prescription frequencies in children and adolescents in Austria covering both primary and hospital care settings, in order to obtain a representative survey for our country.

Methods Prescription data for systemic antibiotics were assessed for the year 2014. For primary care, reimbursement data were obtained from Austrian health insurances. For hospital care, information on medicines dispensed to paediatric wards was obtained from hospital pharmacies. Frequencies of systemic antibiotic use were analyzed by Anatomical Therapeutic Chemical classification system, age groups, care setting, and in relation to all other medicines used. Systemic antibiotics were divided into subgroups, like broad and narrow spectrum penicillins, cephalosporins, tetracyclins, and others.

Results Systemic antibiotics comprised 24% and 21% of all medicines prescribed to children and adolescents in primary care and hospital care, respectively. The most frequent were broad spectrum antibiotics (32% and 35% of systemic antibiotics prescribed) in both primary and hospital care settings. Macrolides and 2nd generation cephalosporins were more frequently prescribed in primary care setting, whereas β -lactam antibiotics other than cephalosporins and antibiotics, such as fluorochinolones, aminoglycosides, or linezolid were more frequently used in hospital.

Conclusions This is the first representative survey investigating the use of systemic antibiotics in children and adolescents in Austria. The study allows comparison of prescription patterns to other European countries: it reveals rather big differences to systemic antibiotics prescription in Italy, the Netherlands and Denmark, whereas prescription patterns are similar in Germany and Austria. Furthermore, this survey provides the basis to assess temporal trends in the future.

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