Pediat Therapeut 2016, 6:3(Suppl)
http://dx.doi.org/10.4172/2161-0665.C1.028

Drug safety in pediatric anesthesia and intensive care: The influence of physiological distinctiveness on Pharmacokinetic (PK) and Pharmacodynamic (PD) profile in pediatric pharmacotherapy

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Drug safety during pediatric anesthesia as well as intensive care has become key issue in last decade. Implementation of pharmacotherapeutic guidelines directly from adults seems impossible due to great pediatric population diversity and individual patient variability. Allometric analysis of PK and PD parameters of drugs in different age-groups constitutes crucial author's research aspect. In three studies pharmacokinetic models were used: propofol -three-compartment, sufentanil and midazolam - two-compartment and 1-OH-midazolam one-compartment model. Propofol PK values were analyzed alongside PD (PK/PD modeling) indicating its concentration influence on Bi-spectral Index values (BIS). PD properties (E_{max}-BIS), similarly to PK, were characterized by large intra-individual variability. Propofol EC50 was higher than in adults (2.77 vs. 1.98 mg/l) suggesting necessity of higher doses in younger patients for desired clinical effect. Innovative aspect of this study consists in author's proposal of pediatric PK/PD model for propofol, based on data obtained in actual clinical conditions. The aim of second research was population-based pharmacokinetic model for midazolam and 1-OH-midazolam in children (0.17-18 yrs) undergoing long-term sedation in PICU. This modeling included allometric scaling and described as the first in medical literature chronopharmacokinetic profile in critically ill infants and children, considering inter-individual variations. Clearance and distribution volume presented high variability (V_C-51%, Cl_C-13%, Cl_M-31%) in patients (5.8-90kg), with characteristic increase in ClC in children weighing 10-20kg as 0.2-1.2 l/kg/hour. It was three times lower in mechanically ventilated patients. Analysis of sufentanil during long term infusions (25-600h) in 41 children (0.17-17yrs) was conducted according to allometric principles and Non-linear Mixed-Effect Modeling (NONMEM). Clearance correlated to body mass as (BW/70) 0.75 not to age, except infants. CSHT equaled 25 minutes, while CS_{75}DT - 10 hours. These clinical trials have shed new light on drug administration in PICU based on PKPD modeling.

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