Estimation of Pediatric Dosages Considering Rapid Development of Physiological Functions after Birth with Approximated Simple Formulae: Implementation and Comparison with Dosages Described in the Labeling

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Background and Objectives: Previously, we reported an estimation method for pediatric dosages which is applicable to premature and mature infants considering rapid development of hepatic and renal functions after birth (Fujino et al, World Conference on Pharmacometrics 2012). In this study, simple linear formulae were derivatized by approximating the previous nonlinear function, and they were applied to 45 oral and 28 intravenous drugs of which pediatric dosages have been described in Japanese labeling for comparison.

Methods: In the previous study, the pediatric hepatic clearance was estimated considering changes of CYP expression and development of the hepatic weight. Similarly, the renal clearance was estimated from development of GFR. In this study, changes of the hepatic and the renal clearances were approximated with segmented linear equations. The pediatric dosage for an arbitrary age can be calculated using Excel as a ratio versus adult from the urinary excretion ratio (Xu) in adults. The equations were applied to drugs of which pediatric dosages have been described in Japanese labeling for comparison between the theory and the current situation.

Figure: Linearized PB-PK based pediatric dosage calculation formulae (A) and ratio of estimated dosage versus described dosage in Japanese labeling for 45 oral and 28 intravenous drugs (B)

Results and Discussion: Segmented linear equations successfully approximated the previous model within 20% error. We compared the calculated dosages with those in the Japanese product labeling for ages from 0.25 to 6 years old. For 45 oral drugs, the median of the ratio (estimated versus described) was 1.15 and the interquartile range was 0.93-1.36. For 28 intravenous drugs, the median was 0.93, and the interquartile range was 0.64-1.48. Overall, the estimated dosages were agreed excellently with those described in the product labeling. On the other hand, for drugs whose discrepancies between the estimated and described dosages are significant, it seems necessary to check their efficacy, safety and pharmacokinetics in pediatric population in the future.

The results in this abstract have been previously presented in part at 19th North American ISSX Meeting and 29th JSSX Annual Meeting (San Francisco, USA) and published in the conference proceedings.