Population pharmacodynamic modelling of the sedative effect of propofol infusion and effect site concentration in children

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Introduction : Continuous infusion of propofol has been used to achieve sedation in children.(1) Although target-controlled infusion (TCI) has been widely used in anaesthesia, its in children lags because of hardware limitations, lack of integrated pharmacokinetic/pharmacodynamic studies, and target monitoring issues. (2) We investigated the effect site concentration (C_e) of propofol in children using the University of Michigan Sedation Scale (UMSS) score and population pharmacodynamic modelling.

Methods: Thirty paediatric patients underwent general anaesthesia with target-controlled infusion of propofol using Kim's paediatric propofol model (3) and remifentanil continuous infusion. Sedation levels were evaluated using the UMSS score every 20 seconds during 1 μg·mL^{-1} stepwise increases in C_e of propofol during induction and 1 μg·mL^{-1} decreases in propofol during recovery from anaesthesia. The pharmacodynamic relationship between the C_e of propofol and the UMSS score was analysed by logistic regression with nonlinear mixed-effect modelling.

Results: Increasing the C_e of propofol produced incremental increases in UMSS score and vice versa. The estimated $C_{e_{50}}$ of propofol to yield UMSS scores from 1 to 4 were 0.52, 1.87, 3.25, and 4.97 μg·mL^{-1}, respectively. The slope steepness for the relationship of the C_e versus sedative response to propofol was 2.68.

Conclusions: This study was the first investigation to estimate the sedation probability in children according to the UMSS score at the C_e of Propofol. It is commonly observed that the depth of sedation is not predictable following administration of sedative based on body weight in children. Interestingly, the C_e values for propofol varied at the same UMSS level of children in this study. We quantified the pharmacodynamic relationship between the C_e of propofol and the UMSS score, and this finding may be used to determine the likely sedation score at the target C_e of propofol in children.

Table 1. Demographic and characteristics of the patients

Clinical variables	Values
Sex (M/F)	16/14
Age (years)	4.8 (0.95)
Height (cm)	109.6 (9.4)
Weight (kg)	19.2 (4.8)
Surgery	
Otolaryngeal surgery	19
Orthopedic surgery	3
Plastic surgery	2
Urologic surgery	3

Table 2. Findings of the population pharmacodynamics models for sedative effect of propofol.

Parameter	Estimate, RSE (%)	Median (2.5%-97.5%)
$C_{e_{50_{UMSS(1)}}}$	0.52 (25.91)	0.54 (0.35-0.76)
$C_{e_{50_{UMSS(2)}}}$	1.87 (7.70)	1.91 (1.73-2.10)
$C_{e_{50_{UMSS(3)}}}$	3.25 (3.85)	3.28 (3.12-3.43)
$C_{e_{50_{UMSS(4)}}}$	4.97 (4.17)	5.00(4.73-5.26)
γ	2.68 (11.64)	2.78 (2.39-3.27)

Figure 1. Scattered plot of observation of the University of Michigan Sedation Scale (UMSS) versus effect site concentration of propofol.

Figure 2. Probability of the University of Michigan Sedation Scale (UMSS) as a function of effect site concentration of Propofol for developed population pharmacodynamic model in children. The probability of UMSS=1, UMSS=2, and UMSS=3 shows a single peak and the probability of UMSS=4 shows gradual increase as the effect site concentration of Propofol increases.

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