Interaction of Sevoflurane, Propofol and Remifentanil Revisited

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Background and Goal of Study: The probability to tolerate laryngoscopy (P_{TOL}) was used to quantify the potency of different combinations of sevoflurane, propofol and/or remifentanil in three different studies.[1-3] In the current study the data of all three studies were pooled and the parameters of the hierarchical interaction model were re-estimated in order to form a basis to convert a given combination of propofol and remifentanil in an approximately equipotent combination of sevoflurane and remifentanil.

Materials and Methods: We extracted the measured end-tidal sevoflurane concentrations (ET_{SEVO}) and the predicted effect-site propofol (Ce_{PROP}) and remifentanil (Ce_{REMI}) concentrations before laryngoscopy and used the related response from the previous studies as independent endpoint. In the selected structural model, P_{TOL} is a function of the total potency of the drug combination (U) and a slope factor (γ) (Eq. 1).

$$P_{TOL} = \frac{U^{\gamma}}{1 + U^{\gamma}} \qquad \text{Eq 1,}$$

where U is calculated according to Equation 2 from the effect-site concentrations normalized to the Ce50ies and the slope factor of the opioid γ_O

$$U = \left(\frac{Ce_{SEVO}}{Ce50_{SEVO}} + \frac{Ce_{PROP}}{Ce50_{PROP}} \right) \cdot \left(1 + \left(\frac{Ce_{REMI}}{Ce50_{REMI}} \right)^{\gamma_O} \right) \qquad \text{Eq 2.}$$

The slope factors and the $Ce50_{REMI}$ were allowed to vary between sevoflurane and propofol. The parameters were estimated using NONMEM 7.2.0.

Results and Discussion: The new parameter estimates are presented in comparison with those from the previous studies in table 1. Whereas the slope factors γ and γ_O and the $Ce50_{REMI}$ were substantially different between sevoflurane and propofol in the previous studies, the differences were not statistically significant in the pooled analysis. This implies a similar slope of the response surface for all drug combinations. The remifentanil concentration reducing the Ce50 of sevoflurane and propofol by 50% is similar.

Conclusions: Based on P_{TOL}, a given combination of propofol and remifentanil can be converted to an equipotent combination of sevoflurane and remifentanil, and *vice versa*. The predictive potential of the calculated P_{TOL} or any related depth-of-anesthesia indicators, such as the Noxious Stimulation Response Index, needs to be validated prospectively.

Table 1: Parameter estimates (standard error in %).

	Ce50 SEVO (vol%)	Ce50 PROP (μg/ml)	Ce50 REMI (ng/ml)	γ	γ_0	N patients	N observations
Prop&Remi[1]	-	8.48 (23)	1.16 (41)	3.46 (24)	1	20	95
Sevo&Prop[2]	2.83 (7)	6.55 (8)	-	17.4 (14)	-	60	274
Sevo&Remi[3]	2.00 (8)	-	1.69 (21)	7.41 (12)	0.718 (12)	40	152
Pooled	**2.59 (5)**	**7.58 (6)**	**1.36 (11)**	**5.22 (10)**	**1**	**120**	**521**

References:

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3. Heyse B, Proost JH, Schumacher PM, et al. Anesthesiology 2012; 116: 311-23