#6_Pharmacodynamic Interaction between Remimazolam and Remifentanil for Loss of Consciousness*

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Background/Introduction: An anesthetic/sedative and an opioid generally exhibit a synergistic pharmacodynamic interaction. This study examined the pharmacodynamic interaction between remimazolam and remifentanil for loss of consciousness.

Methods: After receiving approval from the institutional review board, written informed consent was obtained from forty adult patients. The crisscross design was used to develop a robust pharmacodynamic interaction model. In the first 20 patients, remifentanil was infused using an effect-site-targeted target-controlled infusion at 1.4-5.6 or 2-8 ng/mL for patients aged ≥65 or <65 years (n=10 in each age group), respectively. Three minutes later, a continuous infusion of remimazolam besylate was initiated at 1.0 or 1.5 mg/kg/h for patients aged ≥65 or <65 years, respectively, followed by an increment of 0.5 mg/kg/h every 5 minutes. In the second 20 patients, remimazolam was infused using a target-controlled infusion at 0.3-1.25 or 0.4-1.8 μg/mL for patients aged ≥65 or <65 years (n=10 in each age group), respectively. Three minutes later, a continuous infusion of remimazolam besylate was initiated at 0.10 or 0.15 μg/kg/min for patients aged ≥65 or <65 years, respectively, followed by an increment of 0.05 μg/kg/min every 5 minutes. Loss of consciousness was assessed as the Modified Observer's Assessment of Alertness Sedation scale <2. To determine the basic pharmacodynamic model structure, we developed both a basic logistic regression pharmacodynamic model for remimazolam and the reduced Greco pharmacodynamic interaction model between remimazolam and remifentanil using NONMEM 7 (ICON Clinical Research LLC, North Wales, PA). The model equations were as follows: logistic model; $P = RemimCe^{\gamma} / (RemimCe_{50}^{\gamma} + RemimCe^{\gamma})$, and reduced Greco model $P = \{RemimCe/RemimCe_{50} \times (1+(RemifCe/RemifCe_{50})\}^{\gamma} / [1+\{RemimCe/RemimCe_{50} \times (1+(RemifCe/RemifCe_{50})\}^{\gamma}]$, where P: probability of unconsciousness, RemimCe: remimazolam effect-site concentration (Ce), $RemimCe_{50}$: remimazolam Ce for 50% maximal effect, RemifCe: remifentanil Ce, $RemifCe_{50}$: remifentanil Ce for 50% maximal effect, and γ: steepness of the Ce *vs* response relationship. When the latter model

decreased NONMEM objective function value (OFV) by 6.63 ($P<0.01$, chi-square test with 1 degree of freedom) compared with the former model, we selected the latter as the basic model structure. Then, age and sex were examined as potential covariates of the remimazolam Ce and remifentanil Ce. A log-normal distribution was applied as interindividual variability of Ce. The Ces of remimazolam and remifentanil were calculated using the Masui and Minto pharmacokinetic models, respectively. When a covariate decreased the OFV by 6.63, the covariate was considered significant.

Results: The patient characteristics (mean±SD [range]) were as follows: 65±14 [34-89] years old, 20 males and 20 females, 59±10 [40-85] kg total body weight, and 162±9 [144-184] cm height. The reduced Greco model was better than the logistic model ($P<0.001$). The final reduced Greco model included $RemimCe_{50}$ of 0.22 μg/mL, $RemifCe_{50}$ of 17.2 ng/mL with 31% and 33% interindividual variability, respectively, and γ of 153. The model included age (27.5 decrease in OFV, $P<0.001$) as a covariate for $RemimCe_{50}$.

Conclusions: We found a pharmacodynamic interaction between remimazolam and remifentanil for loss of consciousness similar to other anesthetics. Additionally, age influenced the remimazolam effect for loss of consciousness.

*This abstract has been accepted for an oral presentation at the ASA Annual Meeting 2025.