

## **Population Pharmacodynamics of Propofol and Sevoflurane in Healthy Volunteers Using a Clinical Score and the Patient State Index: A Crossover Study.**

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**Background:** The population pharmacodynamics of propofol and sevoflurane with or without opioids were compared using the endpoints no response to calling the person by name, tolerance to shake and shout, tolerance to tetanic stimulus, and two versions of a processed electroencephalographic measure, the Patient State Index (Patient State Index-1 and Patient State Index-2).

**Methods:** This is a reanalysis of previously published data. Volunteers received four anesthesia sessions, each with different drug combinations of propofol or sevoflurane, with or without remifentanyl. Nonlinear mixed effects modeling was used to study the relationship between drug concentrations, clinical endpoints, and Patient State Index-1 and Patient State Index-2.

**Results:** The C50 values for no response to calling the person by name, tolerance to shake and shout, and tolerance to tetanic stimulation for propofol ( $\mu\text{g} \cdot \text{ml}^{-1}$ ) and sevoflurane (vol %; relative standard error [%]) were 1.62 (7.00)/0.64 (4.20), 1.85 (6.20)/0.90 (5.00), and 2.82 (15.5)/0.91 (10.0), respectively. The C50 values for Patient State Index-1 and Patient State Index-2 were 1.63  $\mu\text{g} \cdot \text{ml}^{-1}$  (3.7) and 1.22 vol % (3.1) for propofol and sevoflurane. Only for sevoflurane was a significant difference found in the pharmacodynamic model for Patient State Index-2 compared with Patient State Index-1. The pharmacodynamic models for Patient State Index-1 and Patient State Index-2 as a predictor for no response to calling the person by name, tolerance to shake and shout, and tetanic stimulation were indistinguishable, with Patient State Index50 values for propofol and sevoflurane of 46.7 (5.1)/68 (3.0), 41.5 (4.1)/59.2 (3.6), and 29.5 (12.9)/61.1 (8.1), respectively. Post hoc C50 values for propofol and sevoflurane were perfectly correlated (correlation coefficient = 1) for no response to calling the person by name and tolerance to shake and shout. Post hoc C50 and Patient State Index50 values for propofol and sevoflurane for tolerance to tetanic stimulation were independent within an individual (correlation coefficient = 0).

**Conclusions:** The pharmacodynamics of propofol and sevoflurane were described on both population and individual levels using a clinical score and the Patient State Index. Patient State Index-2 has an improved performance at higher sevoflurane concentrations, and the relationship to probability of responsiveness depends on the drug used but is unaffected for Patient State Index-1 and Patient State Index-2.