PHARMACOKINETICS OF PROPOFOL IN ARTERIAL BLOOD AND EXHALED BREATH AND REAL-TIME BREATH ANALYSIS

Cyrill Hornuss, MD; Nancy Sambol, PharmD; Kenji Tabata, PharmD; Gustav Schelling, MD,PhD; Christian Apfel, MD,PhD

Ludwig-Maximilians-University, Munich, Germany

Background: Propofol can be detected in exhaled breath and its real-time monitoring could be extremely useful to titrate intravenous anesthesia.[1] Furthermore, there is a reasonably good correlation between exhaled propofol and propofol plasma concentrations under steady-state conditions. However, measuring exhaled propofol would be clinically useful only if exhaled concentrations reflect plasma concentrations without significant delay, or if exhaled breath reflects drug response at least as well as plasma does. Thus, we developed a pharmacokinetic model for both arterial plasma and exhaled propofol in healthy volunteers.

Method: After IRB approval and informed consent, twenty volunteers (ASA status I, age 29.3 ± 8.0 yrs, 11 female) were administered propofol as an intravenous infusion (0.4 $mg.kg^{-1}.min^{-1}$) for 10 min followed by a 20 min recovery period. Propofol intravenous administration was then resumed at four escalating infusion rates (for 15 min each) to achieve targeted plasma concentrations of 2, 3, 4 and 5 $\mu g.ml^{-1}$, followed by termination of the infusion and continued data collection for 3 hours. Exhaled propofol was measured continuously using an ion molecule reaction mass spectrometry system (V&F, Absam, Austria) connected by a T-piece to the volunteer's LMA. Twenty-one arterial blood samples per volunteer were collected at time points chosen by optimal design (WinPopT program); extracted plasma samples were assayed by liquid chromatography tandem mass spectrometry. Plasma and exhaled breath concentration data were analyzed using a nonlinear mixed effects model (NONMEM® program) to develop a comprehensive PK model. Diagnostic plots and the likelihood ratio test were used to assess the goodness of fit of various structural models and covariate effects.

Results: Propofol plasma concentrations were described by a mammillary three-compartment model. Exhaled propofol concentrations were described by two additional transit compartments and a distribution compartment for the lung, with the assumption that the lung does not contribute significantly to propofol elimination. Only body weight, but not age, height, nor sex, was identified as having a significant effect on arterial plasma clearance; no covariate was detected as affecting central volume of distribution in this rather homogeneous group.

Conclusion: Propofol pharmacokinetics can be described by a semi-physiologic-based model that allows prediction of arterial plasma and exhaled propofol concentrations during non-steadystate conditions. Ongoing work will compare the time course of exhaled propofol to "effect-site" concentration and assess the clinical utility of real-time monitoring of exhaled propofol.

Reference: [1]Anesthesiology 2007; 106:665-74.