Performance of Pharmacokinetic Models for Propofol in Early Phase of Target-Controlled Infusion

Background: Pharmacokinetic models applied to target-controlled infusion (TCI) may have a limitation in the early phase of TCI because the compartmental model assumes that an administered drug is instantaneously mixed in the central compartment. The aim of the study was to investigate the performance of pharmacokinetic models for propofol, developed by Marsh[1] or Schnider[2], in the early phase of TCI.

Patients and Methods: Before the start of the TCI, acetate Ringer's solution 10 ml/kg was infused. All patients were receiving TCI of propofol using either of the Marsh or Schnider pharmacokinetic model. Rugloop II® (Demed Medical BVBA, Belgium) and Pump 22 (Harvard Apparatus, MA) was applied for TCI. Propofol was administered for 30 minutes using TCI at fixed targeted plasma concentration determined using the equation, 1.67•(2.9 – 0.022•age).[3] Then, the infusion of propofol was terminated. Acetate Ringer's solution was infused simultaneously at 300 ml/h through the same intravenous catheter during the study period.

Arterial blood sample was taken from the radial artery every 10 s for 2 minutes, 140, 160, 180, 210 s, 4, 5, 7, 10, 15, 20, 25, 30, 30.5, 31, 31.5, 32, 33, 35, 37, 40, 45, 50, 60 minutes after the start of TCI. Predictive performance was assessed using prediction error (PE) derivatives: median prediction error (MDPE) and divergence PE. The MDPE was calculated for the first 5 minutes ($MDPE_{0–5}$), from 5 to 30 minutes ($MDPE_{5–30}$), from 30 to 35 minutes ($MDPE_{30–35}$), and from 35 to 60 minutes ($MDPE_{35–60}$). The divergence PE during 5 to 30 minutes was calculated as the slope of the linear regression of PE against time. Data was expressed as median [interquartile range]. The MDPEs between the groups were compared using the Mann-Whitney test. The median of divergence PE was compared to zero using the Wilcoxon signed-rank test. $P < 0.05$ was regarded as significant.

Results: The $MDPE_{0–5}$, $MDPE_{5–30}$, $MDPE_{30–35}$, and $MDPE_{35–60}$ were −6.9% [−17.5 to 3.6], −22.9% [−31.4 to −13.1], −46.4% [−52.7 to -42.7] and −57.2% [−60.4 to −51.7] for the Marsh model *vs.* −40.5% [−47.9 to −32.1] ($P < 0.001$), −26.4% [−33.1 to −21.6] ($P = 0.325$), −19.2% [−27.8 to −4.3] ($P < 0.001$), −21.4% [−35.3 to −15.4] ($P < 0.001$) for the Schnider model. The divergence PE was −18.8%/h [−26.1 to −3.6] for the Marsh

model (P <0.001) or 8.5%/h [3.7 to 21.7] for the Schnider model (P =0.003).

Conclusions: Examined pharmacokinetic models overestimated the propofol Cp in 30-min TCI and subsequent 30-min after the stop of infusion except the first 5-min of plasma TCI using the Marsh model. In the Marsh model, the PE decreased from 5 to 30 minutes after the start of TCI.

References

1. BJA 1991;67:41-8, 2. Anesthesiology 1998;88:1170-82, 3. Anesthesiology 1999;90:1502-16.