

Potential for Reduction in Interpatient Variability of Propofol Target Concentrations During Protocol Based Anesthesia

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Background/Introduction: Pharmacokinetic (PK) model based administration of anesthetics takes into account dosing history and patient characteristics. With target controlled infusion (TCI) using an “ideal” PK model, we expect the target concentration to be unbiased with regard to the patient characteristics, except for those affecting the pharmacodynamic (PD) sensitivity to the drug. We therefore assessed the potential to develop a “more accurate” PK model in a real world setting by relating the observed interpatient variability in required propofol target concentrations to patient characteristics using linear regression.

Methods: Setting: Tertiary care hospital with all surgical specialties except for cardiac surgery. Anesthesia: BIS (Covidien, Inc., Mansfield, MA, USA) guided intravenous (i.v.) anesthesia with propofol TCI, remifentanil TCI and fentanyl. TCI target concentrations and BIS values were all recorded automatically from the Fresenius Kabi Orchestra TCI system (Fresenius Vial, Brezins, France) which was programmed with the PK model published by Schnider et al. and from the BIS Monitor (Covidien) respectively.

Protocol: Fentanyl prior to induction (100–200 µg) and at the commencement of surgery. Propofol effect site concentration^{1,2} (CeT) titrated to achieve a BIS between 40 and 60. During surgery remifentanil added to compensate for offset of fentanyl effect. Towards end of surgery, propofol administration ceased according to the 70–80% decrement time and remifentanil concentration increased to prevent motor response. After the last suture, remifentanil ceased. Analysis: Surgical cases lasting less than one hour were excluded. In order to reduce variability due to differences in the anesthetic goal (e.g. sedation), only patients who were intubated were included. The CeT 30 min. after skin incision (which was also at least 30 min. before end of surgery) were considered to be the stable maintenance phase and were used for the analysis.

Statistics: Correlation between CeT and patient characteristics was sought with linear regression. Covariates included; weight, age, gender, height, ASA classification and Charlson co-morbidity index. If a covariate improved the fit by less than 1% it was removed from the model. The confidence interval (CI) of the coefficient of determination was estimated with boot strapping. The statistical software used was R version 3.5 (<https://www.R-project.org/>). The analysis of these data was approved by the local ethics committee.

Results: 4584 TCI anesthesia cases were used for the analysis. Fig 1. shows the time course of the CeT and BIS values. At 30 min. after skin incision, 99% of all CeT were between 1 mg/l and 4 mg/l. Higher CeT were associated with higher BIS values (fig. 2). The overall variability of CeT was substantial compared to the association with the covariates (fig. 2). The final linear model included weight,

age and gender (CeT~weight+bs(age)+gender, bs(): b-spline). The coefficient of determination was 11% (99% CI: 9% - 14%). That is, of the overall variability only 11% could be explained with these covariates (fig. 3), of which age contributed approximately 7%.

Conclusions: We conclude that a “more accurate” model for effect site TCI than the one used for this study, only has the potential to reduce the interpatient variability of the CeT by at most 11%. During protocol based, BIS guided, propofol TCI anesthesia in 4584 patients, the propofol concentrations required to maintain the BIS between 40 and 60 varied between 1 mg/l and 4 mg/l in 99% of the patients during the stable maintenance phase. Only 11% of this variability could be explained by or is associated with patient characteristics. We note that this includes both PK and PD variability. Age has been shown to affect the sensitivity to propofol.² It is not possible to differentiate whether the age-related interpatient variability that we observed is due to the suboptimal inclusion of age in the PK model or whether it is due to the known increasing age-related PD sensitivity to propofol. However, we believe it is likely that a substantial fraction of this age-related 7% is attributable to interpatient PD variability. Therefore, based on this “real world data”³, it is questionable whether new models based on more data will have appreciable clinical benefit.

References:

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3. Khosla S, White R, Medina J, Ouwens M, Emmas C, Koder T, et al.: Real world evidence (RWE) - a disruptive innovation or the quiet evolution of medical evidence generation? *F1000 Research* 2018; 7:

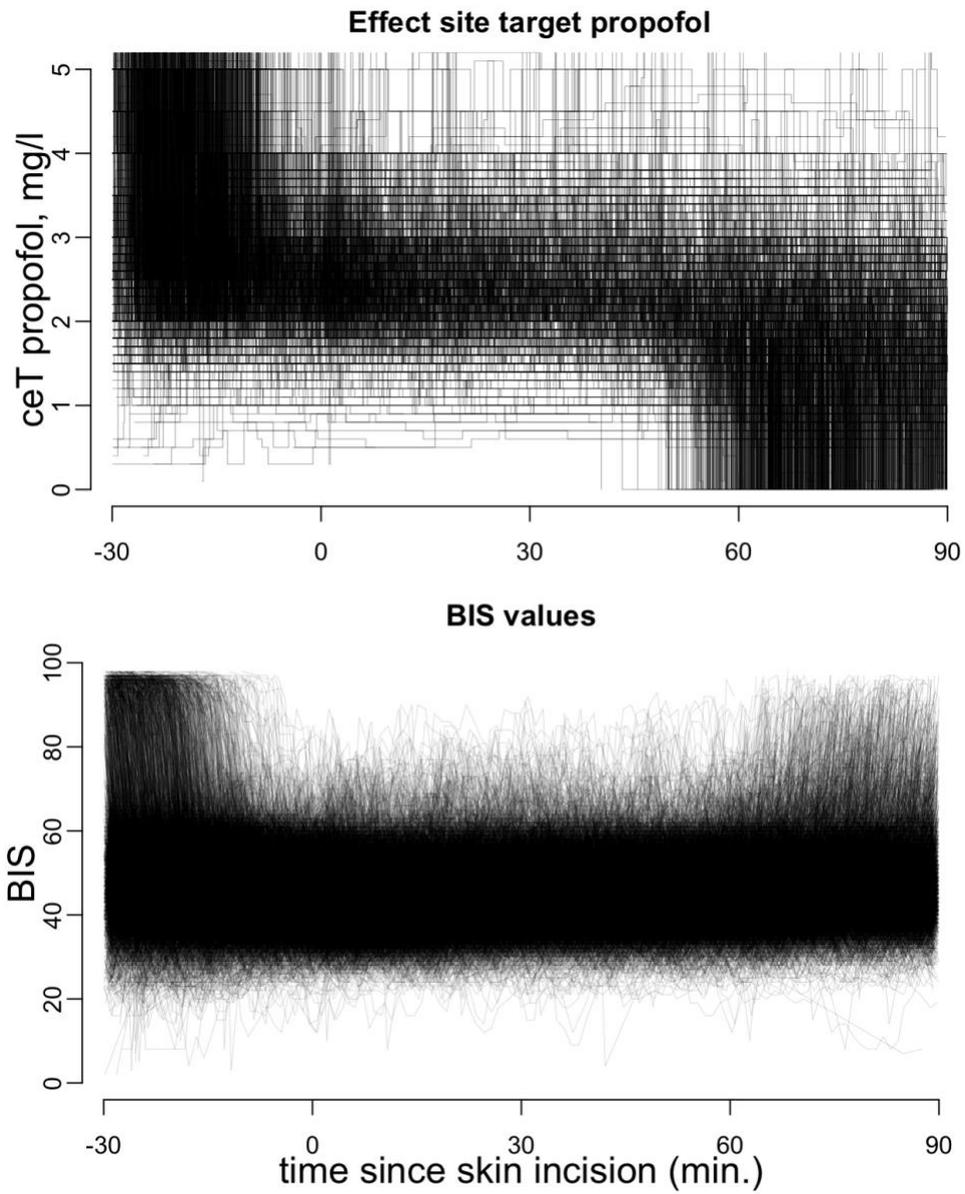


Fig 1:
The raw data of the 4584 patients.

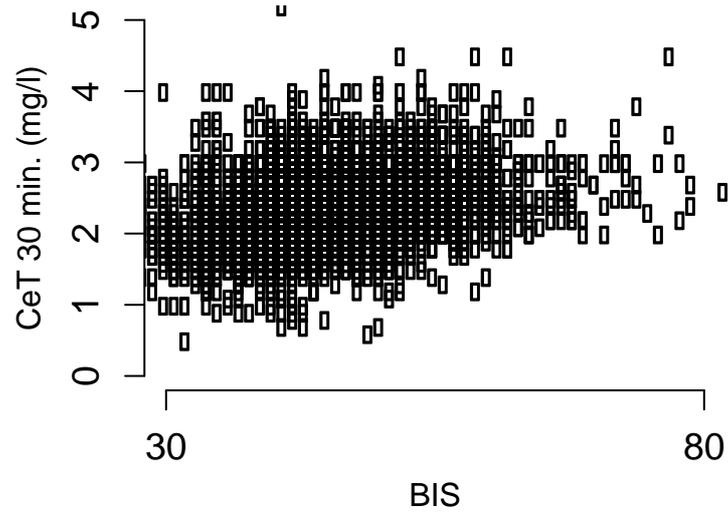


Fig 2. Higher BIS values were associated with higher CeT. That is, when the PK model is used clinically the CeT is dependent on the BIS unlike during studies where BIS is dependent on CeT.

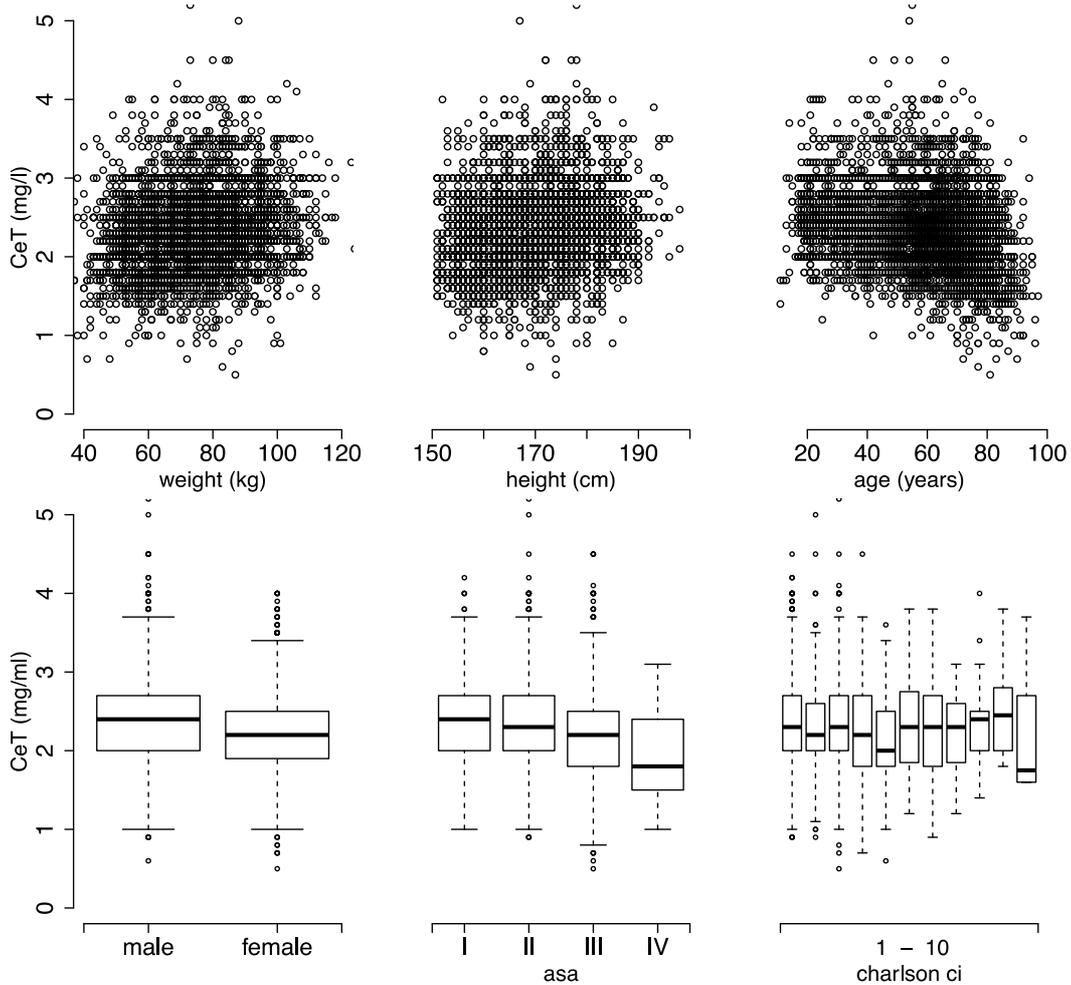


Figure 3.

Plots of the patient characteristics to CeT relationship. Only 11% of the overall interpatient variability was accounted for by covariates. Coefficient of determination from simple linear regression of covariates of the final model: Weight 3.1 %, age 7.7% and gender 2.3%.