

Significant changes in pharmacokinetics of sufentanil during target controlled infusion of sufentanil for cardiac anaesthesia

T. Saari, J. Fechner, H. Ihmsen, J. Schüttler, C. Jeleazcov

Department of Anaesthesiology, University Hospital Erlangen, Erlangen, Germany

Objective: Target controlled infusion (TCI) with sufentanil is usually performed with Gepts model [1], which was derived from patients undergoing general surgery. We studied the performance of TCI during coronary artery bypass surgery with cardiopulmonary bypass (CPB) with a special emphasis on the effect of CPB on the protein binding.

Methodology:

After IRB approval, written informed consent was obtained from 13 male patients (53-71 yr, 70-96 kg) undergoing coronary artery bypass surgery. Anaesthesia was managed with propofol and TCI of sufentanil, using the Gepts model. Six timed arterial samples were drawn from each patient. Free fraction of sufentanil (f_{ub}) calculated from total and unbound sufentanil plasma concentrations as measured by HPLC with tandem mass spectrometry [2]. The accuracy of the TCI model was assessed by the prediction error (PE) and a pharmacokinetic model was determined by population analysis (NONMEM 7.2) using linear multicompartment models. The influence of demographic and clinical characteristics on the clearances and volumes of distribution were examined.

Results:

- The median prediction error of the TCI with Gepts model before, during and after CPB was 108%, 23 % and 29 %, respectively.
- The free fraction of sufentanil increased significantly during CPB.
- PK of the sufentanil were adequately described by a two-compartment model with influence of f_{ub} and hepatic blood flow (Fig. 2 Table 1 and 2).
- The elimination clearance CL_1 was significantly higher during and after CPB when compared to the pre-bypass phase (Fig. 4).
- Volumes of distribution increased slightly during and after CPB.
- CL_1 could be modelled as a function of Q and f_{ub} ("well-stirred" model) (Table 1).
- V_1 and V_2 could be modelled as a function of free fraction (Table 1).
- Statistics: $C_{p_{total}}/C_{p_{target}}$, RM-ANOVA
- Visual predictive check did not indicate any apparent deviations between the model and original data.
- Median and 95% confidence intervals of the bootstrap revealed an acceptable agreement between the population and the bootstrap estimates.

$$CL_1 = \frac{Q_H \cdot f_{ub} \cdot \theta_1}{Q_H + f_{ub} \cdot \theta_1}$$

$$V_1 = \theta_2 + f_{ub} \cdot \theta_3$$

$$V_2 = \theta_4 + f_{ub} \cdot \theta_5$$

$$CL_2 = \begin{cases} \theta_6 & \text{pre-CPB} \\ \theta_7 & \text{CPB} \\ \theta_7 & \text{post-CPB} \end{cases}$$

$$Q_H = \begin{cases} \theta_8 & \text{pre-CPB} \\ 1.5 & \text{CPB} \\ \theta_9 & \text{post-CPB} \end{cases}$$

θ_1	91.1 ± 63.3	L/min
θ_2	7.4 ± 0.8	L
θ_3	13.9 ± 11.2	L
θ_4	48.4 ± 19.9	L
θ_5	40.6 ± 6.2	L
θ_6	0.47 ± 0.12	L/min
θ_7	36.4 ± 5.8	L/min
θ_8	0.60 ± 0.08	L/min
θ_9	1.03 ± 0.06	L/min

Tab. 1: Final population model

Tab. 2: Results, population analysis

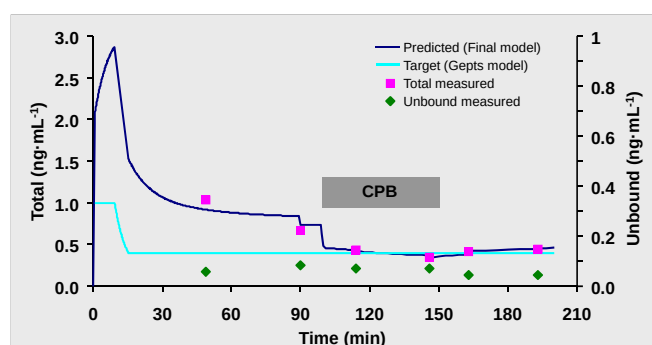


Fig. 1: Sufentanil plasma concentrations in a typical case

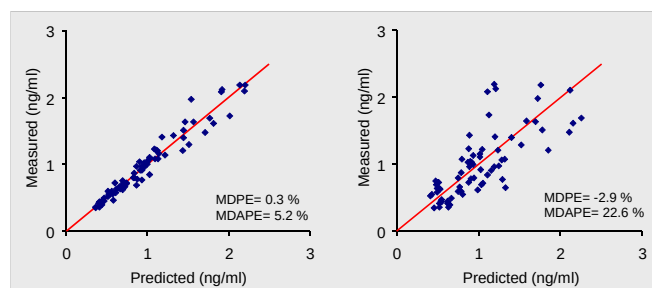


Fig. 2: Measured vs. predicted sufentanil concentrations with individual (left) and population (right) PK-parameters. Prediction error (PE) = $(C_{p_{total}} - C_{p_{pred}}) / C_{p_{pred}}$, MDPE = Median{PE}, MDAPE = Median{|PE|}

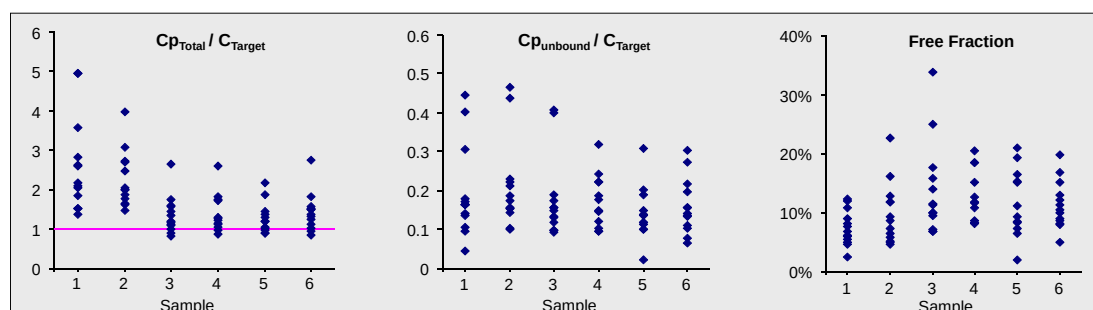


Fig. 3.: Normalised concentrations and free fraction of sufentanil. The data are normalized because of two different target concentrations. Blood sample 1: Incision, 2: 5 min before CPB, 3: CPB 15 min, 4: CPB 45 min, 5: 5 min after CPB, 6: Skin closure.

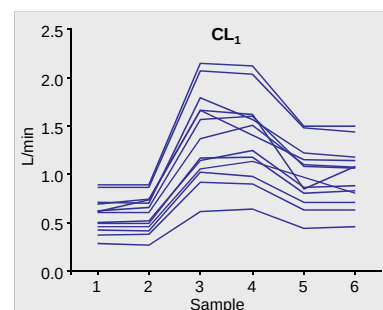


Fig. 4: Sufentanil clearance. Each line depicts a single patient

Conclusions: Dosing based on Gepts model led to an overshoot of total sufentanil concentrations at the beginning of cardiac anaesthesia. Significant changes of sufentanil pharmacokinetics during CPB could be attributed to changes in protein binding and hepatic blood flow.

Literature: [1] Gepts et al. Anesthesiology 1995; 83:1194-204; [2] Saari et al. J. Pharm. Biomed. Anal. 2012; 66:306–313

Correspondence:

Dr. Teijo Saari,
Universitätsklinikum Erlangen, Anästhesiologische Klinik, Krankenhausstr. 12, 91054 Erlangen
teijo.saari@kfa.imed.uni-erlangen.de

Presented at PAGE 2012, Venice

This study was partly supported by a grant from the German Federal Ministry of Education and Research (BMBF, FKZ 01EX1015B)