

Population Pharmacokinetic Modelling of Norepinephrine in Healthy Volunteers Prior to and During General Anesthesia



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Background and Objectives

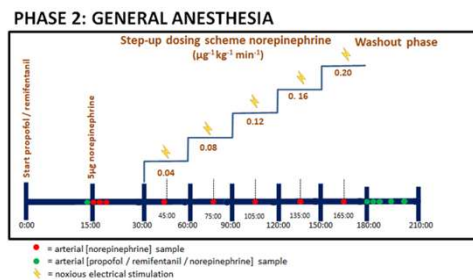
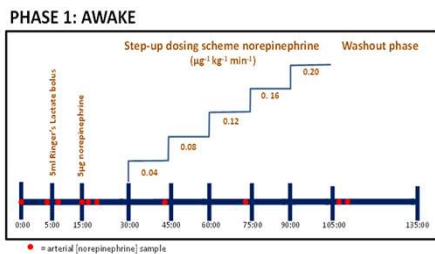
Intraoperation hypotension (IOH) is commonly observed in patients undergoing surgery under general anesthesia, and even a brief episodes of IOH can lead to unfavorable outcomes. To reduce the risk, blood pressure is closely measured during general anesthesia, and norepinephrine (NE) is frequently administered upon detecting hypotension. Despite its routine application, information on the dose-exposure-response relationship of NE remains limited. Additionally, quantification of the influence of general anesthesia on the pharmacokinetics (PK) of NE is lacking.

Using a modelling approach and data from a healthy volunteer study we aimed to:

- Describe NE pharmacokinetics in healthy volunteers in both awake phase and general anesthesia phase
- Study the effect of general anesthesia on NE PK
- Explore the possible explanation of the effect of general anesthesia on NE PK if there is any

Method

A single center, cross-over study was conducted in 36 healthy volunteers. The volunteers received a step-up NE dosing scheme in firstly awake state and then under general anesthesia.



General anesthesia was administered using propofol/remifentanyl Eleveld target-controlled infusion^{1,2}. During general anesthesia, a 30 second electrical stimulus was given as surrogate for surgical incision to the volunteers at each dosage step.

A population PK model was developed using FOCE-1 estimation algorithm in NONMEM (v 7.5).

Population PK modeling

- The two-compartmental model showed the lowest objective function value (OFV) compared to the one-compartmental model ($\Delta\text{OFV} = 243.34$ points) and the three-compartmental model ($\Delta\text{OFV} = 252.64$ points)
- Addition of a lag time to circulation time to compensate for the time of NE travels from the drug administration site to the sampling site. The search space for lag time parameter was restricted to 10-16 seconds³ to improve the model stability.
- A correlation between age with IIV CL was observed. However, the estimated age effect is rather weak, indicating patients 10 years older have about 3% lower CL.

Influence of general anesthesia

➤ Influence of general anesthesia was evaluated by the following equation:

$$P = P_{\text{TPP}} \cdot e^{\eta_P} \cdot F_{\text{SESS}}$$

➤ Influence was observed on NE CL with CL under general anesthesia being 90% (95% CI : 87.3%-92.0%) of that in the absence of general anesthesia

➤ Relevant hemodynamic and anesthetic variables (e.g. cardio output, heart rate, mean arterial pressure, the anesthetics concentration) on the NE CL were investigated for the cause of the effect by introducing them as a time-varying covariates in the model with the equation described below:

$$F_{\text{COV}} = e^{((\theta_{\text{COV} \sim \text{CL}} + \eta_{\text{COV} \sim \text{CL}}) \cdot (\text{COV} - \text{COV}_{\text{baseline median}}))}$$

➤ The addition of measured propofol concentrations as a covariate to CL lowered the OFV by 60.97 points and F_{SESS} increased from 0.90 to 1.05. Therefore, measured propofol concentrations was included as a covariate to CL

Final PK model & pvcVPC

$$CL (L \cdot \text{min}^{-1}) = 2.1 \cdot F_{\text{size}}^{0.75} \cdot F_{\text{CPRP}} \cdot F_{\text{AGE}} \cdot e^{\eta_1}$$

$$V_c (L) = 2.4 \cdot F_{\text{size}} \cdot e^{\eta_2}$$

$$V_p (L) = 3.6 \cdot F_{\text{size}} \cdot e^{\eta_3}$$

$$Q (L \cdot \text{min}^{-1}) = 0.6 \cdot F_{\text{size}}^{0.75}$$

$$\text{Prod} (ng \cdot \text{min}^{-1}) = 497.7 \cdot F_{\text{size}}^{0.75} \cdot e^{\eta}$$

$$\text{Lag time (sec)} = 13.7 \cdot F_{\text{size}}^{0.25}$$

$$\text{Baseline} = \frac{\text{Prod}}{CL/V_c}$$

$$F_{\text{size}} = \frac{\text{WGT}(kg)}{70}$$

$$F_{\text{AGE}} = e^{(-0.344/100 \times (\text{AGE} - 35))}$$

$$F_{\text{CPRP}} = e^{(-3.57 \times \frac{\text{CPRP}}{100})}$$

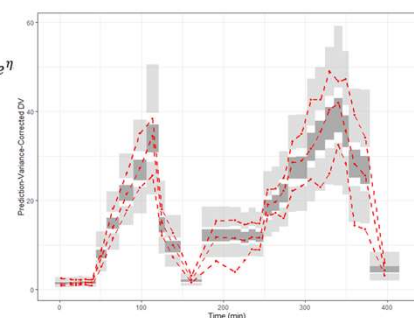


Fig. 1 Prediction-variance-corrected visual predictive check (pvcVPC) of NE concentrations vs. time.

Conclusions

1. NE PK is well described with a two-compartment model with a first-order elimination.
2. NE CL exhibited a 10% decrease under general anesthesia, with this difference being attributed to the measured concentration of propofol.

1 Eleveld DJ, Colin P, Absalom AR, Struys MMRF. Pharmacokinetic-pharmacodynamic model for propofol for broad application in anaesthesia and sedation. *Br J Anaesth*. 2018;120:942–59
2 Eleveld DJ, Proost JH, Vereecke H, Absalom AR, Olofson E, Vuyk J, et al. An allometric model of remifentanyl pharmacokinetics and pharmacodynamics. *Anesthesiology*. 2017;126:1005–18.
3 Tarr L, Oppenheimer BS, Sager R V. The circulation time in various clinical conditions determined by the use of sodium dehydrocholate. *Am Heart J*. 1933;8:766–86.