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Room Room 230A

## The Influence of the Administration Rate on the Front-End Kinetics of Propofol

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**Background:** Conventional compartmental pharmacokinetic (PK) models wrongly assume instantaneous drug mixing in the central compartment resulting in a flawed prediction of drug disposition for the first minutes after bolus injection.[1] Also, induction dose of propofol is dependent on dose rate.[2] We examined the influence of the administration rate and other covariates on front-end kinetics of propofol.

**Methods and Material:** Fifty patients were randomly assigned to one of five groups to receive 1.2 mg/kg propofol given as continuous infusion with the rate of 160, 80, 40, 20, or 10 mg/kg/hr. Arterial blood samples were taken at every 5 seconds until 1 minute in all groups. Thereafter, every 10 sec until 120, 150, or 200 sec in group 1, 2, and 3, respectively. In group 4, samples were taken at 70, 80, 90, 120, 150, 180, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, and 310 sec, and in group 5 at 70, 80, 90, 120, 150, 180, 210, 240, 300, 360, 420, 430, 440, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520 and 530 sec. NONMEM VI was used to determine the best structural model. We compared a conventional compartmental PK model, compartmental+transit compartments model, compartmental+lag time model, compartmental+transit compartments+lag time PK model. The best basic model was implemented to assess the influence of covariates such as weight, height, lean body mass (LBM), age and dose rate of propofol on the model performance. The lag time shifts the time of dosing to the compartment given propofol. The transit compartments consist of the chain of compartments ($K_{tr}$ is the transit rate constant for all transit compartments). The optimal number of transit compartments was assessed by stepwise addition or deletion of one compartment

**Results:** Figure 1 shows the best structural model. The final model (Figure 1) has two disposition compartment with the lag time and five transit compartments and includes following covariates; dose rate for the lag time, age for $K_{tr}$ and distribution volume of peripheral compartment, and weight for elimination clearance. Figure 2 shows the influence of administration rate and age on front-end time course of plasma concentration.**Conclusion:** More accurate prediction of early propofol disposition is found when using a 2-compartmental model enlarged with lag time and transit function. Infusion rate has an influence on the lag time. Other important covariates were age and weight.

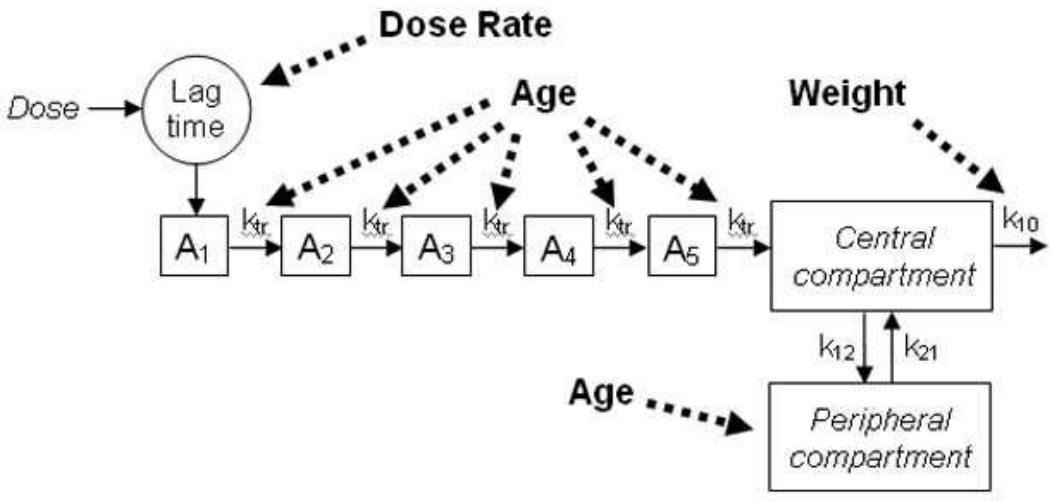
1. Struys MM *et al*, Anesthesiology 2007; 107: 386-96

2. Kazama T *et al*, Anesthesiology 2000; 92: 1017-28.[figure1][figure2]

Anesthesiology 2008; 109 A814

### Figure 1

Figure 1. Schema of the final pharmacokinetic model




### Figure 2

Figure 2. Time course of plasma concentration; A. for 50 yr, 60 kg subject with continuous infusion, B. for 60kg subject with 2 min-60mg/kg/hr infusion (dose is 2 mg/kg)