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TITLE: PROPOFOL CONCENTRATION - EFFECT RELATIONSHIPS FOR HYPNOSIS AND EYELID REFLEX
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Introduction: Propofol has been given by computer controlled infusion (CCI) for intravenous anesthesia¹. For the optimal use of this technique, information is needed about the concentration of propofol necessary for specific pharmacodynamic effects. We have investigated the propofol concentration-response relationship for two pharmacodynamic end points.
Methods: With Ethics committee approval and informed consent, 18 female patients, ASA I, 20-50 yr, were studied. Propofol was given by CCI to achieve predicted concentrations between 0.5 and 4 µg/ml, in steps of 0.5-1 µg/ml every 12 min. Every 3 min patients were tested for loss of eyelid reflex and hypnosis (unresponsiveness to verbal and tactile stimuli). At the same times arterial blood samples were taken for analysis of whole blood concentrations of propofol by HPLC. Patients breathed spontaneously 30% oxygen in air throughout the study, which was completed before the start of surgery. A sigmoid Emax model was fitted to the percentage of patients with loss of eyelid reflex and who were hypnotic as a function of propofol concentration.
Results: P_{ET}CO₂ remained < 5.5 vol % in all patients throughout the study. The EC₅₀ and EC₉₀ for loss of eyelid reflex were 2.7 and 3.5 µg/ml. For hypnosis, the corresponding values were 3.9 and 4.9 µg/ml (fig 1).
Discussion: We have defined the concentration-effect relationships of propofol for two clinically relevant end points. A noteworthy finding is that the loss of eyelid reflex occurred at lower concentrations than those causing hypnosis.

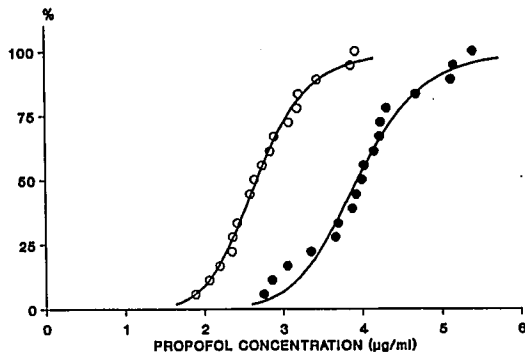


Figure 1. The concentration-effect relationships for hypnosis (●) and loss of eyelid reflex (○).

Reference
 1. Tackley RM et al. Br J Anaesth 62: 46-53; 1990.

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TITLE: NEGATIVE INOTROPIC EFFECT OF THIOPIENTAL GREATER THAN PROPOFOL AT EQUIPOTENT CONCENTRATIONS
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Introduction: Myocardial depression has been shown with thiopental and propofol, but the magnitude of this effects in relation to anesthetic potency is more relevant to clinical usage. The purpose of this study was to construct concentration-response curves for thiopental and propofol, each indexed to their respective EC₅₀ for anesthetic effect.
Methods: After approval by the Institutional Animal Care and Use Committee, 14 Hartley guinea pigs were studied. Isolated strips of left atrial tissue were tested as per Kobata, et al.¹ Concentration-response curves for propofol and thiopental were then obtained. Propofol concentrations ranged from 10 µg/ml to 500 µg/ml; thiopental concentrations ranged from 1 µg/ml to 66 µg/ml. Data were fitted to

$$R = E_0 * (1 - \frac{[AGENT]^N}{IC_{50}^N + [AGENT]^N})$$

where R=measured response (peak twitch tension, dT/dt or -dT/dt), [AGENT]=concentration of thiopental or propofol (µg/ml), IC₅₀=[AGENT] resulting in 50% myocardial depression from baseline, and E₀ is response in absence of thiopental or propofol. EC₅₀ for thiopental is 17.9 µg/ml,² and EC₅₀ for propofol is 5.0 µg/ml.³ Therapeutic index (TI) is defined as TI=IC₅₀/EC₅₀. Data were analyzed with nonlinear regression and Student's t-test for grouped data, with significance at p<0.05.
Results: Figure 1 shows the concentration-response curves for peak twitch tension indexed by EC₅₀ for thiopental (STP) and propofol. Table 1 lists IC₅₀ and TI for peak twitch, dT/dt, and -dT/dt.
Conclusions: Myocardial depression with propofol occurs at higher concentrations compared with EC₅₀ than it does with thiopental, resulting in a higher therapeutic index for propofol than thiopental.

TABLE 1. IC₅₀ & TI FOR PROPOFOL AND THIOPIENTAL

		AGENT	
		THIOPIENTAL	PROPOFOL
Peak Twitch	IC ₅₀ (µg/ml)	20.9±6.3	96.6±10.1*
	TI	1.6±.35	19.4±2.0*
dT/dt	IC ₅₀ (µg/ml)	21.1±5.9	86.9±8.3*
	TI	1.2±.33	17.4±1.7*
-dT/dt	IC ₅₀ (µg/ml)	21.0±6.1	84.3±9.2*
	TI	1.2±.34	16.9±1.8*

*MEAN±SEM, p<0.05 compared to thiopental

References:
¹J Clin Monit 5:26, 1988
²Anesthesiology 72:412-422, 1990
³Br J Anaesth 58:1080, 1986

FIGURE 1

