DRUG DISPOSITION II — DEXMEDETOMIDINE AND PROPOFOL

A316

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 anesthesia[1]. 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: $P_{ET}CO_2$ remained < 5.5 vol % in all patients throughout the study. The EC_{50} and EC_{90} 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.

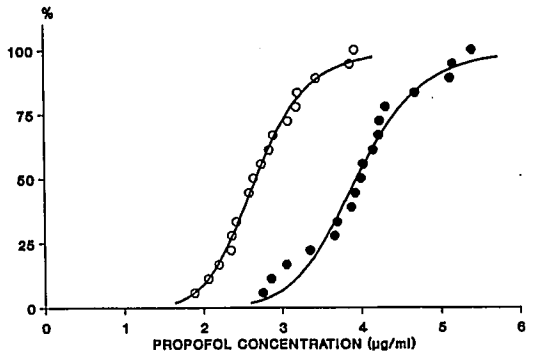

Figure 1. The concentration-effect relationships for hypnosis (●) and loss of eyelid reflex (o).

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

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TITLE: NEGATIVE INOTROPIC EFFECT OF THIOPENTAL 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 EC_{50} 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

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

where R=measured response (peak twitch tension, dT/dt or -dT/dt), [AGENT]=concentration of thiopental or propofol (μg/ml), IC_{50}=[AGENT] resulting in 50% myocardial depression from baseline, and E_0 is response in absence of thiopental or propofol. EC_{50} for thiopental is 17.9 μg/ml,[2] and EC_{50} for propofol is 5.0 μg/ml.[3] Therapeutic index (TI) is defined as $TI = IC_{50}/EC_{50}$. 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 EC_{50} for thiopental (STP) and propofol. Table 1 lists IC_{50} and TI for peak twitch, dT/dt, and -dT/dt.

Conclusions: Myocardial depression with propofol occurs at higher concentrations compared with EC_{50} than it does with thiopental, resulting in a higher therapeutic index for propofol than thiopental.

TABLE 1. IC_{50} & TI FOR PROPOFOL AND THIOPENTAL

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

FIGURE 1