Title: COMPARISON OF SODIUM THIOPENTAL/ISOFLURANE TO PROPOFOL (DELIVERED BY MEANS OF A PHARMACOKINETIC MODEL-DRIVEN DEVICE) FOR THE INDUCTION, MAINTENANCE, AND RECOVERY FROM ANESTHESIA

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INTRODUCTION. Propofol is a new intravenous anesthetic agent that can be administered by continuous infusion.[1] Comparisons between inhalational and intravenous anesthetics are difficult to interpret because intravenous anesthesia is administered according to dose ($mg \cdot kg^{-1}$) whereas inhalational anesthesia is administered to a plasma partial pressure (cf. plasma concentration). The development of pharmacokinetic model-driven infusion devices[2] allows intravenous anesthetics to be delivered to a predicted plasma concentration, thus allowing a more equitable comparison with inhalational agents.

METHODS. Following IRB approval and written informed consent, 40 patients undergoing major orthopedic (O) or gynecological (G) surgery were randomly assigned to receive either sodium thiopental for induction and isoflurane for maintenance (group I) or propofol for both induction and maintenance (group P) of general anesthesia. Propofol was administered using a pharmacokinetic model-driven drug delivery device programmed with mean kinetic parameters for propofol. This instrument uses a real-time pharmacokinetic simulation to continuously infuse the agent at rates optimized to theoretically maintain the drug plasma concentrations (setpoints) specified by the anesthesiologist. In both groups, 70% N_2O in O_2 was administered 2 min prior to induction of anesthesia and until after skin closure. In group I, thiopental (2.5%) was infused at 17 $ml \cdot min^{-1}$ until loss of eyelash reflex. In group P, the setpoint propofol plasma concentration was set at 4.5 $\mu g \cdot ml^{-1}$, and was increased if necessary, to obtain loss of eyelash reflex. Heart rate (HR) and blood pressure were monitored by an automatic cuff every minute for 10 min following induction and every 3 min thereafter until discontinuation of N_2O. Following induction in both groups, succinylcholine 1.5 $mg \cdot kg^{-1}$ was given and endotracheal intubation achieved. In group I, inspired isoflurane was set at 1.5% for the first 15 min and then decreased to 0.2% below the measured end-tidal isoflurane concentration (Puritan-Bennett Agent Monitor). Thereafter, the inspired isoflurane concentration was decreased by 0.2% every 15 min until the patient indicated inadequate anesthesia, as defined by an increase in HR or systolic blood pressure (SBP) to >15% above baseline (calculated as the mean of 3 readings taken the day prior to and morning of surgery and just prior to induction), movement, or signs of autonomic discharge. When anesthesia was inadequate, the inspired isoflurane was increased by 0.2-0.5%. Following intubation in group P, the setpoint was decreased by 0.25 $\mu g \cdot ml^{-1}$ every 15 min until the level of anesthesia was inadequate, at which time the propofol setpoint was increased by 0.25-0.5 $\mu g \cdot ml^{-1}$. Both groups received vecuronium for neuromuscular relaxation, but at least 2 twitches of a train-of-four were always maintained. Propofol or isoflurane were discontinued at or after skin closure, dependent again on signs of inadequate anesthesia, after which neuromuscular blockade was antagonized and N_2O discontinued. The times from discontinuation of N_2O until spontaneous ventilation, response to simple command, and orientation were noted. The incidence of nausea and vomiting and analgesic requirements for the first postoperative hour were recorded. Hemodynamic data were compared to baseline and a frequency histogram was constructed for each patient. These were combined to yield group means. The lowest HR and SBP following induction and the highest values following intubation were compared between the groups. As an additional index of hemodynamic stability, the absolute values of the magnitude by which SBP and HR fell outside of the range baseline±15% were integrated and normalized for case duration in each patient. Groups were compared by unpaired t tests. Data are given as mean±SD.

RESULTS. Demographics are listed in table 1 and were similar between groups. Induction and recovery parameters are given in table 2. HR and mean arterial blood pressure (MAP) are presented in figure 1. Except for HR after induction (*$p<.05$), hemodynamic changes following induction and intubation (table 2) were similar in both groups. Recovery was not different between groups. Hemodynamic stability (HR and SBP) following intubation was similar between the groups ($p>0.1$).

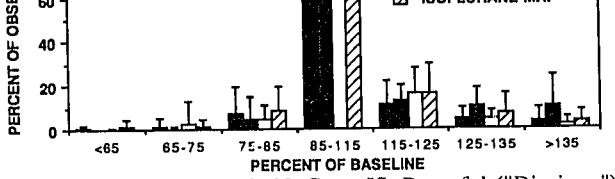
DISCUSSION. For the first time, this study attempts to make a valid comparison between propofol and isoflurane by delivering both agents to set concentrations and by ensuring that both groups were maintained just within the required therapeutic level throughout the procedure. Under these conditions, propofol provided induction, maintenance, and recovery characteristics similar to thiopental/isoflurane for general surgical procedures of 1-6 hours.

Table 1. Demographics

	GROUP P	GROUP I
Age (yr)	33±13	31±9
Weight (kg)	72±14	68±14
Gender (M:F)	8:10	11:11
Procedure (G:O)	4:14	3:19
Case Duration (hr)	2.8±1.5	3.2±1.7

Table 2. Induction and Recovery

Induction Dose ($mg \cdot kg^{-1}$)	1.2±0.3	5.7±1.5
Induction Time (min)	2.3±1.1	1.2±0.4
Induction HR change (%)	5±8	20±19*
Induction SBP change (%)	-3±9	-5±12
Intubation HR change (%)	30±16	37±24
Intubation SBP change (%)	29±11	29±15
N_2O Off to Respond Command (min)	5.5±5.5	8.1±7.1
N_2O Off to Orientation (min)	11.3±14.2	12.3±8.1
Nausea and/or Vomiting	4/18 (22%)	5/22 (23%)
Needing Analgesia in 1st Hour	16/18 (89%)	18/22 (82%)



References: 1) MacKenzie N, Grant IS: Propofol ("Diprivan") for continuous intravenous anaesthesia. A comparison with methohexitone. Postgrad Med J 61(Sup 3):70-75, 1985; 2) Alvis JM, Reves JG, Govier AV, Menkhaus PG, Henling CE, Spain JA, Bradley E: Computer-assisted continuous infusion of fentanyl during cardiac anesthesia: comparison with a manual method. Anesthesiology 63:41-49, 1985.