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Propofol-Nitrous Oxide Versus *Thiopental-isoflurane-nitrous Oxide for General Anesthesia*

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One hundred and twenty patients undergoing elective operations were randomly assigned to receive anesthesia with either thiopental, 4 mg/kg-isoflurane, 0.2–3%-nitrous oxide, 60–70% (control) or propofol, 2 mg/kg-propofol infusion, 1–20 mg/min-nitrous oxide, 60–70% (propofol). Although anesthetic conditions were similar during the operation, differences were noted in the recovery characteristics. For non-major (superficial) surgical procedures, the times to awakening, responsiveness, orientation, and ambulation were significantly shorter in the propofol group (4 ± 3, 5 ± 4, 6 ± 4, and 104 ± 36 min) than in the control group (8 ± 7, 9 ± 7, 11 ± 9, and 142 ± 61 min, respectively). In addition, less nausea and vomiting (20 *vs.* 45%) and significantly less psychomotor impairment was noted in the non-major propofol (*vs.* control) group. Following major abdominal operations, recovery characteristics did not differ between propofol and control groups. Delayed emergence (>20 min), significant psychometric impairment, and a high overall incidence of postoperative side effects (55–60%) were noted in both drug treatment groups. The authors conclude that propofol-nitrous oxide compares favorably to thiopental-isoflurane-nitrous oxide for maintenance of anesthesia during short outpatient procedures. However, for major abdominal operations, propofol anesthesia does not appear to offer any clinically significant advantages over a standard inhalational anesthetic technique. (Key words: Anesthesia: general. Anesthetics, inhaled: nitrous oxide. Anesthetics, intravenous: propofol; thiopental. Anesthetics, volatile: isoflurane. Anesthetic technique: continuous infusion; inhalational.)

THE AVAILABILITY OF RAPID and short-acting intravenous (iv) anesthetics and analgesics has increased interest in the use of continuous iv infusions as alternatives to standard inhalational techniques for maintenance of anesthesia. Propofol (Diprivan®) is a sedative-hypnotic compound with a pharmacokinetic-dynamic profile that favors continuous iv administration for maintenance of anesthesia. Previous clinical studies have shown that propofol is an effective induction agent.[1–3] In addition, propofol has been used as an alternative to methohexital for maintenance of general anesthesia during brief, outpatient procedures,[4,5] and as an alternative to nitrous oxide during total intravenous anesthesia.[6,7]

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The most widely used general anesthetic technique consists of thiopental for induction, followed by the combination of a volatile agent and nitrous oxide, with incremental doses of an opioid (narcotic) analgesic, for maintenance of anesthesia. This study was designed to evaluate the intraoperative hemodynamic responses and recovery characteristics of propofol when used for the induction and maintenance of general anesthesia with nitrous oxide, compared to a combination of thiopental and isoflurane-nitrous oxide.

Materials and Methods

One hundred and twenty adult ASA physical status I–III patients scheduled for elective operations were studied. The protocol was approved by the Committee for the Protection of Human Subjects in Research at Stanford University, and written informed consent was obtained from each patient. Eighty patients presenting for non-major (*e.g.*, superficial) surgical procedures and 40 patients scheduled to undergo major (*e.g.*, intra-abdominal) operations were randomly assigned to either a thiopental-isoflurane-nitrous oxide (control) or a propofol-nitrous oxide treatment group using an open (non-blinded) protocol design. Patients with a history of allergic reactions to any of the study drugs and patients with clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, metabolic, or neurologic disease were excluded.

Upon arrival in the pre-induction area, all patients were asked to complete the following psychometric tests: 1) a Trieger test (to measure psychomotor function),[8] 2) p-deletion test (to evaluate cognitive function),[9] and 3) a series of visual analog scales (to assess the degree of sedation).[10] In the operating room, an 18-gauge iv cannula was inserted and routine monitoring devices (including a precordial stethoscope, ECG, Puritan-Bennett/Datex™ capnograph, and Dinamap™ vital signs monitor) were applied. Mean arterial pressure (MAP) and heart rate (HR) were recorded at 1–5-min intervals, and the end-tidal carbon dioxide tension ($P_{ET_{CO_2}}$) and respiratory rate (RR) were continuously monitored.

All patients were administered meperidine, 1 $mg \cdot kg^{-1}$ iv, and d-tubocurarine, 2–3 mg iv, 3–5 min prior to induction of anesthesia. In the control treatment groups, anesthesia was induced with thiopental, 4.0 $mg \cdot kg^{-1}$ iv, over 15 s. The propofol treatment

groups received propofol, 2.0 mg·kg^{-1} iv, over 15 s, for induction of anesthesia. If the patient did not exhibit signs of unconsciousness (*e.g.*, loss of the eyelash reflex) within 1 min from the start of the induction dose of either thiopental or propofol, supplemental injections of the study drugs (*e.g.*, thiopental, 25–50 mg iv, or propofol, 10–20 mg iv) were administered. The time from the start of the bolus injection to abolition of the eyelash reflex was recorded as induction (onset) time. Following administration of succinylcholine, 1.5 mg·kg^{-1} iv, and endotracheal intubation, maintenance of anesthesia was initiated with either isoflurane, 1.0%, and nitrous oxide (N_2O), 70% in oxygen (control group), or a continuous iv infusion of propofol, 10 mg·min^{-1}, and N_2O, 70% in oxygen (propofol group). If muscle relaxation was required during the operation, incremental doses of pancuronium, 1–2 mg iv, were administered.

In an attempt to maintain a comparable depth of anesthesia with the two anesthetic techniques, the inspired isoflurane concentration and the propofol infusion were administered in a variable-rate fashion depending on clinical signs of "anesthetic depth." The inspired isoflurane concentration and the propofol infusion rate were increased in response to elevations in MAP and HR exceeding 20% of baseline values, or in anticipation of an increased level of surgical stimulation (*e.g.*, upon entry into the abdominal cavity). Conversely, the inspired concentration of isoflurane and the maintenance propofol infusion were decreased in response to a decrease in MAP and HR exceeding 20% of baseline values, as well as in response to a reduced level of surgical stimulation (*e.g.*, upon closure of the surgical incision).

If rapid suppression of clinical signs of inadequate anesthesia (*e.g.*, spontaneous movement, hiccoughing, or blood pressure exceeding 30% of the baseline value) was required during the maintenance period, small supplemental doses of propofol, 10–20 mg iv, or thiopental, 25–50 mg iv (control), were administered. During the longer, more stressful surgical procedures (major operations), persistent hypertension (MAP > 120% of the baseline value) and tachycardia (HR > 120% of the baseline value) was treated by administering supplemental doses of meperidine, 10–20 mg iv. Conversely, episodes of bradycardia (HR < 40 bpm) associated with a decrease in MAP (<60 mmHg) were treated with atropine, 0.1–0.2 mg iv. Alternatively, ephedrine, 5–10 mg iv, was given if a patient experienced hypotension (MAP < 60 mmHg) during induction or maintenance of anesthesia.

At the end of the operation, residual neuromuscular blockade was reversed with a combination of neostigmine, 3–5 mg iv, and glycopyrrolate, 0.6–1.0 mg iv, and the maintenance anesthetic agents were discontinued. Anesthesia times were calculated as follows: 1) duration of anesthesia (time from the start of induction until discontinuing N_2O), and 2) maintenance anesthetic time (elapsed time from the start of the maintenance anesthetic drug until its discontinuation). The average inspired isoflurane concentration was determined by multiplying the time by the calibrated vaporizer outflow concentration, summating these values, and then dividing by the maintenance anesthetic time. The mean propofol infusion rate (mg·min^{-1}) was calculated by dividing the total propofol maintenance dose by the maintenance anesthetic time.

Early postoperative recovery times were evaluated at 30–90 s intervals and recorded as follows: 1) awakening time (elapsed time from discontinuation of the nitrous oxide until the patient spontaneously opened their eyes), 2) time to responsiveness (time from N_2O off until the patient responded to simple verbal commands), and 3) orientation time (time from N_2O off until the patient was oriented to person and place). For outpatients in the non-major group, the elapsed time from discontinuation of N_2O until the patient could walk unassisted was recorded as ambulation time. A nurse who was unaware of the anesthetic technique determined the time to ambulation. In addition, the psychometric tests were administered at 30-min intervals until the patient achieved baseline (preoperative) scores or the patient was discharged from the post-anesthesia care unit (PACU). All side effects were recorded in the PACU by a nurse who was not involved in the study. Postoperatively, antiemetics (*e.g.*, droperidol, metoclopramide) were administered for protracted nausea and vomiting, and opiates (*e.g.*, morphine or meperidine) were given for moderate-severe pain. Outpatients were discharged from the PACU as soon as they were able to void and ambulate without assistance.

Trieger and p-deletion tests were scored according to the absolute number of dots missed (maximum score of 42) and by the total number of letter p's correctly deleted in a 60-s time period (maximum score of 50), respectively. The sedation analog scales consisted of five 100-mm lines arranged such that a score of 100 on the analog scale represented maximal sedation, while a score of zero indicated no sedation (maximum score of 500). Data are reported as mean (or median) values with measures of variability expressed as either standard deviation (SD) in the tables or standard error of the mean (SEM) in the figures.

Data analysis consisted of Statistical Analysis System analysis of variance with Wilcoxon Rank-Sum test (for continuous variables) and Chi-square analysis (for categorical variables), with P values < 0.05 considered statistically significant. The psychometric test results and

TABLE 1. Demographic Characteristics of the Four Study Groups

	Non-major		Major	
	Control	Propofol	Control	Propofol
Number of patients (n)	40	40	20	20
Age (yr)*	41 ± 14	44 ± 15	48 ± 16	46 ± 16
Sex (M/F)	22/18	24/16	7/13	5/15‡
Weight (kg)*	71 ± 14	72 ± 17	66 ± 14	69 ± 17
A.S.A. physical status (I/II–III)	22/18	19/21	5/15‡	4/16‡
Smoking history (%)	55	45	40	55
Alcohol/drug abuse (%)	12	10	10	15
Patient status (n) (inpatient/outpatient)	17/23	14/26	20/0‡	20/0‡
Premedication† (%)	17	15	40	35
Systolic BP (mmHg)	124 ± 17	126 ± 14	120 ± 18	119 ± 13
Diastolic BP (mmHg)	76 ± 12	75 ± 11	73 ± 11	73 ± 9
Heart rate (beats/min)	76 ± 12	76 ± 11	75 ± 11	79 ± 16

* Values are expressed as mean ± SD.

† Percentage of patients who received any sedative or anxiolytic medication (*e.g.*, benzodiazepines) on the day of surgery prior to their arrival in the operating room.

‡ Significantly different from respective non-major groups, $P < 0.05$.

hemodynamic values were analyzed both in terms of the mean values at each time interval, and with respect to changes in the values compared to the preoperative baseline values using repeated measures of analysis of variance.

Results

The two non-major groups were similar, as were the two major groups, with respect to patient demographics and preoperative vital signs (table 1). However, relative to the non-major groups, the major groups had a greater proportion of female subjects and patients with higher ASA physical status designations. In addition, while the major groups consisted entirely of inpatients, most patients in the non-major groups were unpremedicated outpatients. No significant differences existed between groups with respect to history of smoking and alcohol/drug abuse or preoperative vital signs.

Induction of anesthesia was associated with a rapid loss of consciousness (≤30 s) in all groups. Only nine patients (15%) receiving thiopental for induction and 11 patients (18%) receiving propofol required additional bolus doses. The total induction doses of thiopental or propofol were similar in the non-major and major groups (table 2). Pain on injection was noted in 7% of patients receiving propofol (*versus* none in the thiopental group). Of the intraoperative side effects, excessive oral secretions were only observed in the non-major groups (table 3). Heart rate and mean arterial pressure increased significantly following tracheal intu-

TABLE 3. Incidences of Adverse Intraoperative Reactions in the Control and Propofol Groups (%)

	Non-major		Major	
	Control	Propofol	Control	Propofol
Induction*				
Pain on injection	0	10	0	0
Excitatory effects†	0	2	0	0
Oral secretions	5	12	0	0
Maintenance				
Tachycardia‡	2	0	5	5
Bradycardia‡	5	2	10	5
Hypertension‡	2	0	5	10
Hypotension‡	0	0	5	5

* Adverse reactions occurring within 3–5 min following induction of anesthesia with thiopental or propofol.

† Excitatory effects including twitching, tremor, and myoclonus.

‡ Changes in mean arterial pressure or heart rate exceeding 30% of pre-induction (baseline) values and persisting longer than 5 min.

TABLE 2. Intraoperative Anesthetic Requirements in Patients Receiving Either Thiopental-Isoflurane-N_2O (Control) or Propofol-N_2O (Propofol) during Non-major or Major Surgery†

	Non-major		Major	
	Control	Propofol	Control	Propofol
Induction				
Thiopental (mg)	290 ± 62		293 ± 77	
Propofol (mg)		151 ± 31		143 ± 31
Onset time (s)	29 ± 5	29 ± 9	30 ± 13	28 ± 5
Maintenance				
Anesthetic time (min)	66 ± 29	67 ± 28	156 ± 54*	158 ± 54*
Isoflurane (%)	0.9 ± 0.3		1.0 ± 0.2	
Propofol ($mg \cdot min^{-1}$)		7.8 ± 2.8		8.3 ± 2.4
Propofol (mg)		490 ± 215		1326 ± 580*
Muscle relaxants (%)	50	57.5	90*	100*
Meperidine (mg)			41 ± 24* (n = 9)	45 ± 43* (n = 12)
Duration of Anesthesia				
Total time (min)	74 ± 29	75 ± 28	167 ± 53*	171 ± 53*

* Significantly different from respective non-major groups, $P < 0.05$.

† Values are expressed as mean ± SD.

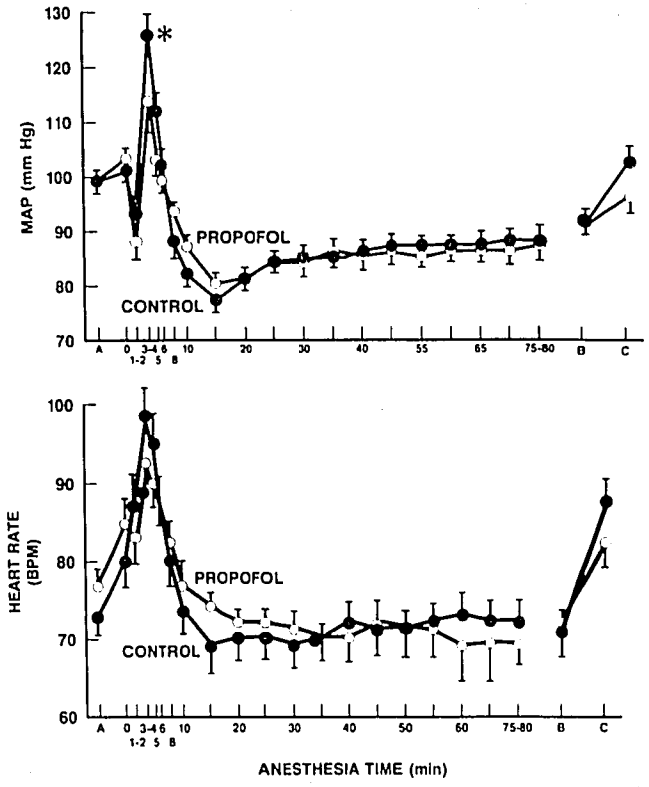

FIG. 1. Comparative effects of thiopental-isoflurane (●) and propofol (○) on mean arterial blood pressure and heart rate during non-major surgical procedures. The letters on the abscissa correspond to the following events: A, pre-induction (3–5 min prior to the administration of meperidine, 1 mg · kg^{-1} iv, and d-tubocurarine, 2–3 mg iv); B, end of anesthesia (upon the discontinuation of N_2O), and C, post-extubation (5 min after removal of the endotracheal tube). An asterisk denotes significant differences ($P < 0.05$).

bation in all groups (fig. 1, table 4). However, the increase in MAP associated with laryngoscopy and intubation was significantly greater in the groups that received thiopental for induction compared to the propofol groups (fig. 1, table 4).

TABLE 4. Hemodynamic Values in the Two Treatment Regimens during the Major Operations‡

	Heart Rate		Mean Arterial Pressure	
	Control	Propofol	Control	Propofol
Induction	80 ± 16	85 ± 20	100 ± 14	98 ± 14
Post-induction	89 ± 18	85 ± 17	96 ± 12	94 ± 16
Intubation	103 ± 16	98 ± 18	125 ± 20	110 ± 22†
Prior incision	75 ± 20	81 ± 15	74 ± 9	76 ± 11
Incision	78 ± 18*	82 ± 17*	96 ± 16*	95 ± 13*
Intraoperative	78 ± 16*	80 ± 16*	86 ± 8	91 ± 10
Post-extubation	79 ± 18	75 ± 16	93 ± 13	91 ± 13

* Significantly different from respective non-major groups, $P < 0.05$.

† Significantly different from major control group, $P < 0.05$.

‡ Mean values ± SD.

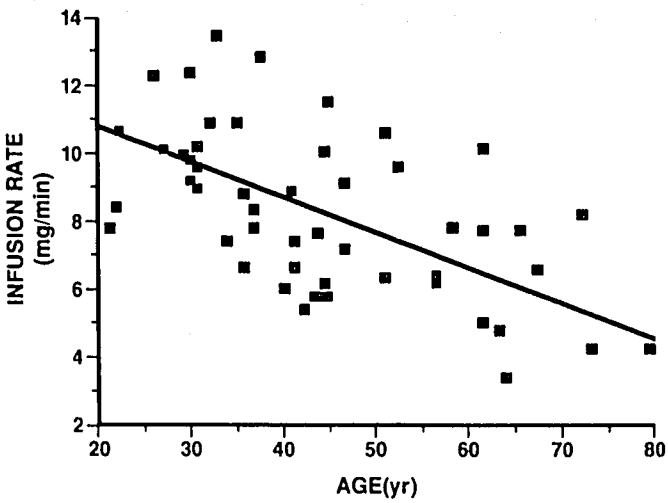

FIG. 2. Relationship between the mean propofol infusion rate as a function of the patient's age. The regression line was calculated using data points for the major and non-major propofol treatment groups. The regression is given as: dose [mg/min] = 12.5 − 0.10 × age (yr).

In response to clinical signs of anesthetic depth, the inspired isoflurane concentration was varied from 0.2 to 3.0% and the propofol infusion rate was varied from 1 to 20 mg · min^{-1}. Although maintenance anesthetic times were similar for the two non-major and two major groups, times were significantly longer in the major than the non-major groups. During the maintenance period, the average inspired isoflurane concentration and the mean propofol infusion rate were not significantly different between the non-major and major groups (table 2). In addition, the mean propofol infusion rate decreased linearly with age (fig. 2). Using the data from both the non-major and major groups did not change the slope of the curve for the mean infusion rate *versus* age ($r = 0.61$, $P < 0.05$). For each 10-yr increase in age, the mean infusion rate of propofol required to maintain satisfactory anesthetic conditions decreased approximately 1 mg · min^{-1}.

Maintenance hemodynamic values were comparable in the two non-major and in the two major groups (fig. 1, table 4). In all groups, hemodynamic values returned to pre-induction (baseline) levels within 10 min following tracheal intubation. The lowest hemodynamic values were recorded immediately prior to the start of operation. MAP and HR following surgical incision were higher in the major groups compared to the non-major groups. Although the average MAP during surgery did not differ significantly among the four groups, the mean HR during surgery was significantly higher in the major groups compared to the non-major groups. Within 5 min after tracheal extubation, MAP and HR values had returned to pre-induction levels in the non-major groups, but remained depressed in the two major

TABLE 5. Recovery Times (Minutes) after Either Thiopental-Isoflurane-Nitrous Oxide (Control) or Propofol-Nitrous Oxide Anesthesia§

	Non-major		Major	
	Control	Propofol	Control	Propofol
From discontinuance of nitrous oxide to:				
Awakening	8 ± 7	4 ± 3*	10 ± 9	8 ± 12†
Responsiveness	9 ± 7	5 ± 4*	12 ± 10	10 ± 13†
Orientation	11 ± 9	6 ± 4*	22 ± 16†	20 ± 22†
Ambulation	142 ± 61	104 ± 36*	N/A‡	N/A‡

* Significantly different from non-major control group, $P < 0.05$.
† Significantly different from non-major groups, $P < 0.05$.
‡ Ambulation time in patients who underwent major operations were not assessed (N/A).
§ Values are expressed as mean ± SD.

groups. Adverse reactions occurring during the maintenance period were similar in the two non-major groups, as well as in the two major groups (table 3). As expected, hemodynamic responses requiring treatment (*e.g.*, hypertension and tachycardia) were noted more frequently in the major than in the non-major groups.

Recovery times for awakening, responsiveness, orientation, and ambulation were significantly shorter in the non-major propofol group than in the non-major control group (table 5). Recovery times were significantly longer in the major *versus* the non-major groups, but there were no differences in the awakening, response, and orientation times between the two major groups (table 5). The time from discontinuation of the maintenance study agent to discontinuation of the nitrous oxide averaged 5 ± 4 min and 9 ± 7 min for the non-major and major groups, respectively, and did not differ between the respective drug treatment groups. Delayed emergence (>20 min) occurred more frequently in the major groups than in the non-major treatment groups (table 6). A higher incidence of dizziness/fainting was observed in the non-major (*versus* major) treatment groups (table 6). Although the incidence of nausea and vomiting did not differ between the two major groups, nausea and vomiting occurred more frequently in the non-major control (*versus* propofol) group. Emotional lability (*i.e.*, euphoria and dysphoria) was occasionally observed in patients who had received propofol for non-major outpatient procedures. Postoperatively, analgesic requirements were similar in the two non-major and two major study groups (table 6). As expected, a significantly higher percentage of patients received opiates following major operations than after non-major procedures (table 6). Irrespective of their study drug, patients administered narcotic analgesics in the PACU had a higher incidence of nausea and/or vomiting than patients who did not receive opiates (table 7).

TABLE 7. The Effect of Opioid Administration in the Post-anesthesia Care Unit on the Incidence (%) of Nausea and Vomiting in the Early Postoperative Period

	Opioid		No Opioid	
Treatment	Non-major	Major	Non-major	Major
Control	57*	50*	23	25
Propofol	38*	41	16	33
Overall	50*	43	19	26

* Significantly different from groups receiving no opiates, $P < 0.05$.

Psychometric test scores were significantly different at 30 min, 60 min, 90 min, and 120 min postoperatively

TABLE 6. Incidence of Postoperative Side Effects and Analgesic Requirements in the PACU following Operative Procedures with Either Thiopental-Isoflurane-Nitrous Oxide (Control) or Propofol-Nitrous Oxide Anesthesia (%)

	Non-major		Major	
	Control	Propofol	Control	Propofol
Emergence				
Prolonged sedation*	12	0	40‡	25‡
Recovery				
Emotional lability†	0	10	0	0
Dizziness/fainting	10	15	5	5
Diaphoresis	2	2	5	0
Headache	2	2	5	0
Nausea	45	20§	30	40
Vomiting	27	5§	10	15
Analgesic requirements				
Acetoaminophen with codeine	45	47	—	—
Opiates (morphine or meperidine)	35	30	80‡	85‡
Mean meperidine dose (mg)	47 ± 4	45 ± 31	74 ± 40‡	71 ± 34‡

* Prolonged sedation is defined as orientation times exceeding 20 min.
† Emotional lability includes euphoria and dysphoria.
‡ Significantly different from respective non-major groups, $P < 0.05$.
§ Significantly different from respective control groups, $P < 0.05$.

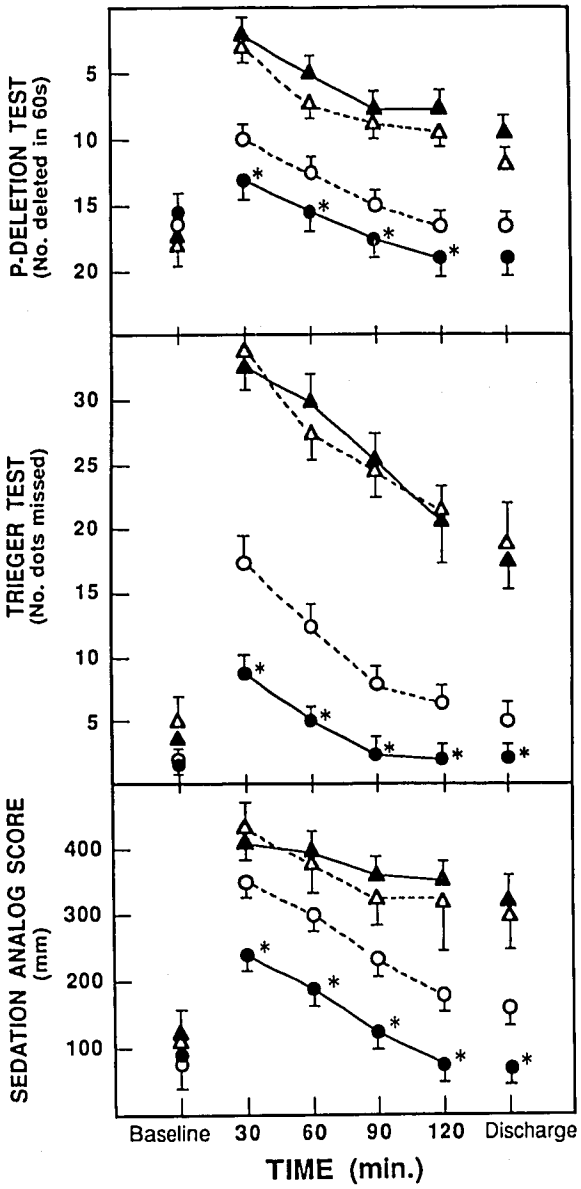

FIG. 3. Changes in psychometric test scores as a function of time after discontinuation of nitrous oxide for the major (control, △- - -△; propofol, ▲——▲) and non-major (control, ○- - -○; propofol, ●——●) groups. An asterisk denotes significant differences ($P < 0.05$) between values for the non-major study groups. Psychometric test scores were comparable for both major groups, but were significantly different in the major groups compared to the non-major groups ($P < 0.05$). Upper panel: p-deletion test; middle panel: Trieger test; lower panel: sedation analog scales.

in the non-major groups, but were similar in both major surgery groups (fig. 3). Following the non-major procedures, a significantly greater percentage of patients receiving propofol returned to baseline psychometric test scores within 120 min postoperatively than in the control group (fig. 4). However, less than 10% of the patients in the major surgery groups achieved baseline levels on the psychometric tests prior to their transfer to the ward. Overall, the postoperative psychometric test scores demonstrated significantly greater impairment following major (*versus* non-major) operations (fig. 3, 4). Finally, patients in the non-major groups receiving opiate analgesics (*e.g.*, meperidine) and centrally acting antiemetics (*e.g.*, droperidol) in the PACU demonstrated significantly greater impairment of psychomotor function in the early postoperative period (fig. 5).

Discussion

Propofol, a rapid and short-acting intravenous anesthetic, can be administered as a variable-rate infusion for both induction and maintenance of general anesthesia.[4] In this study, propofol provided a rapid, smooth, and pleasant loss of consciousness comparable to that produced by thiopental. Consistent with previous stud-

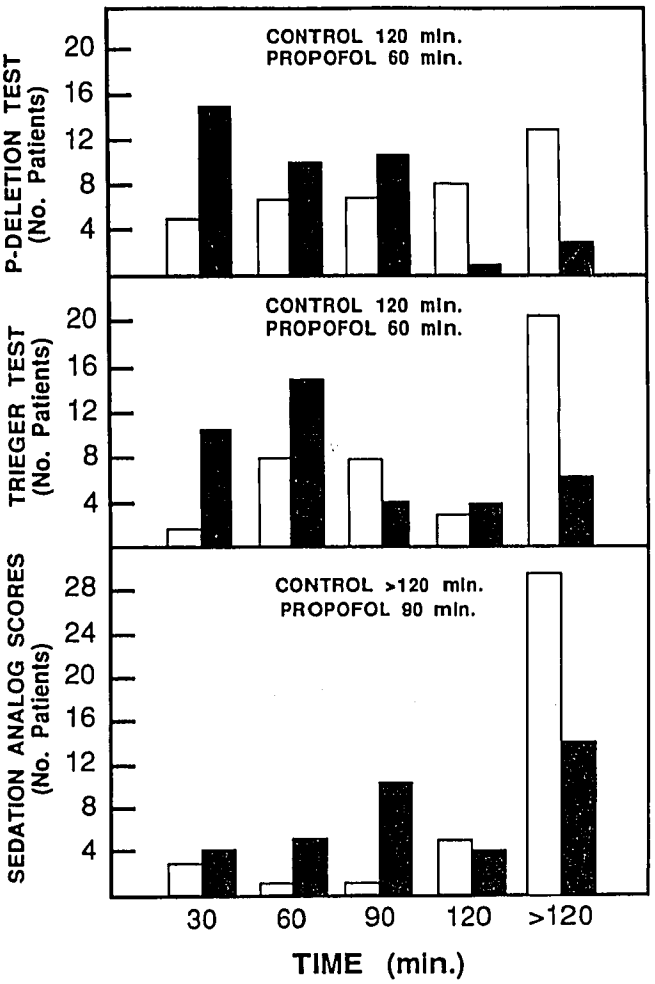

FIG. 4. Distribution of times for patients in the non-major propofol (■) and control (□) groups to achieve baseline levels as measured by psychometric testing. A median score is reported for each distribution. Upper panel: p-deletion test; middle panel: Trieger test; lower panel: sedation analog scales.

ies, the frequency of injection pain appeared to be related to the site or size of the vein into which propofol was injected.[10-13] In three of the four patients who experienced pain on injection, the drug was injected into a small hand or forearm vein. The incidence of excessive oral secretions was higher following induction with propofol, suggesting that it may possess cholinergic (vagotonic) activity.

The pattern of hemodynamic response to induction of anesthesia and tracheal intubation was similar for propofol and thiopental. Consistent with other studies, both induction agents depressed arterial pressures, with propofol producing significantly greater depression than thiopental (fig. 1, table 4).[1-3,14-16] However, propofol more effectively attenuated the blood pressure response to laryngoscopy and tracheal intubation. Studies of the hemodynamic effects of propofol in patients with coronary artery disease would suggest that the decrease in heart rate and arterial pressure is probably due to both direct myocardial depression[17] and a decrease in systemic vascular resistance.[17,18] In a recent study, the investigators concluded that the hemodynamic effects of propofol may be related to central sympatholytic and/or vagotonic mechanisms.[19] Following administration of propofol, significant decreases have been reported in arterial blood pressure,[17-24] cardiac index[22] or output,[23,24] stroke volume,[20,22] systemic vascular resistance,[17,24] and pulmonary artery occlusion pressure.[21,22] One elderly patient in the major treatment group experienced a marked decrease in blood pressure (>50% decrease in MAP) following induction of anesthesia with propofol. Severe hypotension following induction of anesthesia with propofol has been reported by other investigators in elderly patients and in patients with limited cardiovascular function.[18,25]

During maintenance of anesthesia, propofol produced hemodynamic effects similar to those produced by isoflurane. Although propofol and isoflurane both provided satisfactory anesthetic conditions, hemodynamic values were decreased during the maintenance period compared to pre-induction values. The hemodynamic responses to the stress of surgical stimulation was significantly greater in the major than the non-major groups. Overall, the incidence of adverse reactions was low for both propofol and isoflurane during the maintenance period (table 3).

The average maintenance anesthetic requirements for propofol and isoflurane did not differ significantly between the non-major and major groups. Mean infusion rates for propofol (108–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$) are consistent with infusion rates (*i.e.*, ED_{50} and ED_{95}) reported by other investigators.[26,27] We speculate that the similarity in maintenance anesthetic infusion rates between non-major and major groups may be related, in part, to the supplemental doses of meperidine administered during the major procedures, as well as to the possible cumulative effects of propofol. Administration of opiate analgesics prior to and during the operative procedure has been shown to decrease the intravenous anesthetic requirement.§ The fact that the propofol in-

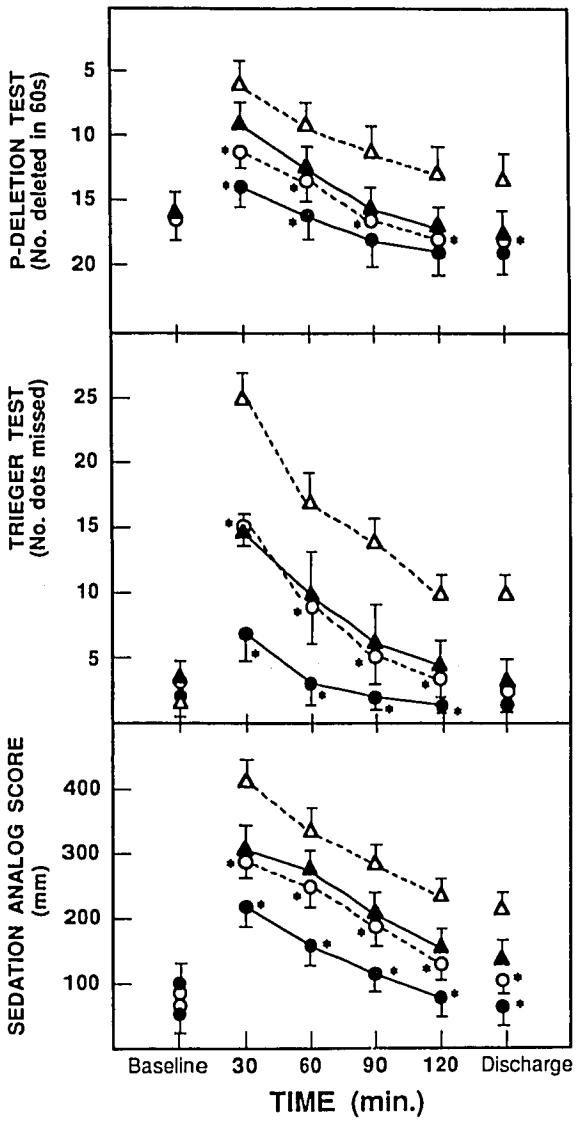

FIG. 5. Effect of opiate analgesics and centrally acting antiemetics on postoperative psychometric test scores in the non-major groups as a function of time after discontinuation of nitrous oxide. Patients in the non-major groups (control O – – – O; propofol ● —— ●) that did not receive centrally active medications in the PACU, were compared to those who received centrally active medications (control Δ – – – Δ; propofol ▲ —— ▲). An asterisk denotes significant differences ($P < 0.05$). Upper panel: p-deletion test; middle panel: Trieger test; lower panel: sedation analog scales.

§ White PF, Chang T: Effect of narcotic premedication on the intravenous anesthetic requirement (abstract). ANESTHESIOLOGY 61:A389, 1984.

fusion rates decreased progressively during longer major (intra-abdominal) procedures would be consistent with progressive accumulation of the study drug. Other investigators have also noted a progressively decreasing propofol requirement during the course of anesthesia.[28]

Compared with young adults, elderly patients are more sensitive to induction doses of propofol.[29] A decreased propofol clearance rate has also been observed in patients 65–80 yr of age.¶ In agreement with these studies, we noted an age-related decrease in the mean propofol infusion rate for both the non-major and major study groups (fig. 2). A similar age-related decrease has been reported for thiopental[30,31] and isoflurane.[32]

Following the non-major procedures, the recovery profile was significantly more rapid with propofol than thiopental-isoflurane. Emergence times were statistically shorter in the propofol (*versus* control) group, and there was significantly less nausea and vomiting after propofol-N_2O anesthesia. In addition, patients receiving propofol for non-major procedures exhibited significantly less impairment on the postoperative psychometric tests, achieving baseline levels of psychomotor function 30–60 min faster than patients in the non-major control group. Other investigators have also reported a more rapid recovery with fewer postoperative emetic sequelae following propofol (*versus* thiopental, methohexital, or etomidate) administration during short, minimally stressful operations.[1–4]

Delayed emergence, significant psychometric impairment, and a higher incidence of postoperative side effects were noted in the major (*versus* non-major) treatment groups. Recovery after more prolonged and stressful surgical procedures is obviously affected by both anesthetic and non-anesthetic factors (*e.g.*, surgical pain, fluid shifts). Supplemental doses of narcotic analgesics not only increased postoperative sedation and impaired psychomotor function (fig. 5), but were also associated with an increased incidence of nausea and vomiting (table 7). Other investigators have also noted an association between the frequency of nausea and vomiting and postoperative opiate administration.[33] Finally, the delayed emergence and recovery observed in the major (propofol) group may have been related to a prolongation of propofol's elimination half-life.[34]

In order to minimize investigator bias in the postoperative assessments, objective measures of recovery were used. Unfortunately, it was not possible to conduct this study in a double-blind fashion because of propofol's unique "milky" white appearance. In addition, the logistics of administering an intravenous anesthetic infusion during the maintenance period differ from those involved in using a volatile agent. Although the study design precluded use of a double-blind technique, an attempt was made to provide comparable levels of anesthesia by varying the rate of administration of the study drugs in response to autonomic and somatic signs of anesthetic depth. In addition, the nitrous oxide was discontinued at a similar time relative to the discontinuation of study drugs. Furthermore, all postoperative side effects were recorded by a blinded observer, and patients were not informed of their treatment regimen until after discharge from the recovery room.

In summary, propofol can be used as an alternative to thiopental-isoflurane for induction and maintenance of general anesthesia with nitrous oxide. Propofol's hemodynamic effects are similar to those of thiopental and isoflurane. The rapid recovery profile for propofol following its use during short, non-major procedures makes it a useful alternative to the conventional anesthetic drugs in situations in which a rapid and complete recovery from general anesthesia may be of benefit (*e.g.*, ambulatory surgery). For longer, more stressful operations, the use of propofol does not appear to offer any clinically significant advantages over a standard intravenous-inhalational anesthetic technique. Further studies are needed to determine the role of propofol anesthesia during major operative procedures.

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