may be especially useful in certain situations, particularly in children where there is a need for bolus administration of a large dose for rapid onset of neuromuscular paralysis.

In conclusion, we have demonstrated that Pm is a useful neuromuscular blocking drug in burned children and that the dose–response curve is shifted 2.5-fold to the right and that the dose requirement correlates with the degree of burn injury. The high doses administered also resulted in modest increases in heart rate and blood pressure and a prolonged recovery time.

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Comparison of Continuous Infusion Fentanyl or Ketamine *versus* Thiopental—Determining the Mean Effective Serum Concentrations for Outpatient Surgery

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Recent studies of outpatients undergoing minor surgical procedures indicate that the use of continuous infusion fentanyl or ketamine significantly decreases the drug dosage and recovery time when compared with the traditional intermittent bolus technique.[1] The present study was designed to compare the intraoperative and postoperative effects of the intravenous anesthetics fentanyl and ketamine with thiopental when each drug was administered by continuous infusion in combination with nitrous oxide during midtrimester abortions. Serum samples were obtained during the maintenance infusions in order to determine their therapeutic concentration ranges in the presence of nitrous oxide.

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Materials and Methods

Seventy-five healthy (ASA physical status I), unpremedicated, young women who presented for elective midtrimester abortions (15 ± 1 wk gestation, mean value ± SEM) were studied according to a protocol approved by the local institutional review board. After obtaining informed consent, patients were assigned to one of three infusion groups: a fentanyl group (N = 25), a ketamine group (N = 25), or a thiopental group (N = 25). The three groups were comparable with respect to age (22 ± 1 yr) and weight (57 ± 2 kg), however, the ketamine infusion group had a significantly higher incidence of preoperative nausea (32% *vs.* 12% or 16%) and cramping (48% *vs.* 28% or 24%) than the other two groups.

On the morning of operation, a baseline Trieger test[2] (used to measure recovery of psychomotor function[3]), a POMS mood assessment,¶ and a general information questionnaire were administered in a standardized manner. Patients were taken to the operating room, where an 18-gauge intravenous catheter was inserted into a forearm vein and routine monitoring devices were applied (*e.g.*, EKG, Dinamap® blood pressure cuff, and precordial stethoscope). All patients received droperidol 0.5 mg and glycopyrrolate 0.2 mg intravenously immediately prior to induction of anesthesia.

Anesthesia was induced with sodium thiopental 4 mg/kg intravenously, and when the patient became unresponsive (*i.e.*, loss of response to commands, loss of eyelid reflex), nitrous oxide 70% in oxygen (7:3 1/min) was administered via a tight-fitting face mask using a conventional circle absorber system. Supplemental doses of thiopental 25–75 mg were required occasionally. Inspired oxygen concentration was measured using a calibrated alarm oxygen monitor.** In the thiopental infusion group, thiopental, 3 mg/ml, was used to supplement nitrous oxide during the procedure. In the other two groups, patients received either fentanyl 100 μg or ketamine 50 mg as a "priming" infusion over a 1–2 min time interval, followed by a maintenance infusion of either fentanyl, 2 μg/ml, or ketamine, 1 mg/ml, as an adjuvant to nitrous oxide. An attempt was made to maintain a stable level of anesthesia in all groups (*e.g.*, constant respiratory rate, heart rate, and blood pressure, absence of purposeful movement) by altering the rate of the infusion (over a range of 1–25 ml/min) in response to clinical signs of inadequate anesthesia†† or excessive drug effect.‡‡

Changes in hemodynamic values of 30% or more from the awake (baseline) state on three consecutive measurements over a 3-min interval were considered significant. The time to awakening (min) was defined as the time from discontinuation of the nitrous oxide until the patient was able to respond to simple commands. The orientation time (min) was the time from discontinuation of nitrous oxide until the patient was oriented to person, place, and time. A nurse–observer recorded side effects and administered Trieger tests at 30-min intervals until discharge. Patients were discharged from the recovery room when their vital signs were stable, they were able to ambulate, and they no longer experienced side effects from the anesthesia. Prior to discharge, patients repeated the POMS mood assessment and were given follow-up questionnaires, which they completed approximately 24 h after their surgery.

In 10 patients from each group, blood samples were obtained at 2–5 min intervals during the maintenance infusion through a 19-gauge "butterfly" needle placed in the arm contralateral to the one receiving the infusion. Serum thiopental concentrations were measured with a high performance liquid chromatography assay sensitive to 0.1 μg/ml.[4] Serum fentanyl concentrations were analyzed using a modification§§ of the fentanyl radioimmunoassay method described by Michiels *et al.*[5] The standard curve was linear over a concentration range from 0.2 to 20 ng/ml. Serum ketamine concentrations were analyzed using a gas chromatographic technique described previously.[6] The standard curves were linear over a concentration range from 0.02 to 4 μg/ml for ketamine and from 0.01 to 2 μg/ml for its principal metabolite, norketamine.

Data were analyzed as follows: continuous variables were analyzed using Statistical Analysis System (SAS),¶¶ one-way analysis of variance, and Duncan's multiple range test ($P < 0.05$). Categoric variables were evaluated with SAS chi-square analysis ($P < 0.05$). Trieger tests were scored in terms of the number of dots missed (maximum 40) and the total distance from the missed dots to the nearest line (maximum 200 mm). Serum concentrations during the maintenance infusion period were averaged for each patient and reported as the mean effective serum concentration (±SEM).

¶ McNair DM, Lorr M, Droppleman LF: Profile of Mood States Manual. Educational and Industrial Testing Service, P.O. Box 7234, San Diego, California 92107.

** Instrumentation Laboratory Inc., 113 Hartwell Avenue, Lexington, Massachusetts 02173.

†† Patient movement, lacrimation or diaphoresis, or a progressive increase in respiratory rate, heart rate, or mean arterial blood pressure exceeding 20% of the values that prevailed at the conclusion of the induction sequence.

‡‡ Progressive slowing of respiratory rate (or apnea), decreases in mean arterial blood pressure, or heart rate exceeding 20% of the postinduction values.

§§ Schüttler J, White PF: Optimization of the radioimmunoassays for determining fentanyl and alfentanil in human serum. Anesthesiology (submitted for publication).

¶¶ SAS Institute, Inc., P.O. Box 10066, Raleigh, North Carolina 27605.

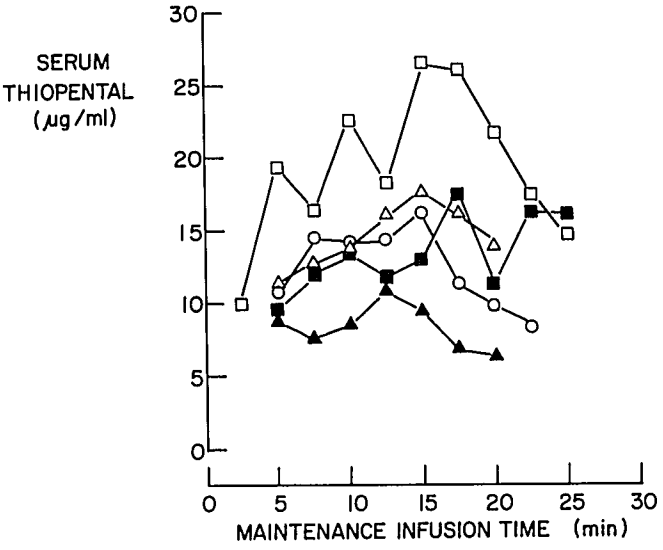

FIG. 1. Serum thiopental concentrations (μg/ml) for five patients in the thiopental infusion group are shown as a function of time during the maintenance infusion.

RESULTS

There were no significant differences in the total amount of thiopental required for induction of anesthesia among the three groups (table 1). The group given no intravenous analgesics required an infusion of thiopental equal to approximately 20 mg/min to supplement nitrous oxide, resulting in a total dose of thiopental equal to 11.4 mg/kg as compared with 4.4 mg/kg and 4.2 mg/kg in the fentanyl and ketamine groups, respectively. The mean thiopental concentrations during the maintenance infusion was 13.7 ± 2.6 μg/ml (range: 8.1–19.4 μg/ml, as illustrated in fig. 1). The overall fentanyl requirement averaged 10 μg/min, however the "maintenance" requirement (*i.e.*, total dose less the loading dose) equaled 6 μg/min or 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the presence of nitrous oxide 70%. The maintenance ketamine requirement equaled 3 mg/min or 53 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the presence of nitrous oxide 70%. The mean "therapeutic" serum levels of fentanyl or ketamine when administered in the presence of nitrous oxide were 2.3 ± 0.2 ng/ml (range: 1.4–4.3 ng/ml) and 1.1 ± 0.1 μg/ml (range: 0.5–1.8 μg/ml), respectively. Additionally, levels of the principal "active" metabolite[6] of ketamine ranged from 0.2–0.8 μg/ml (mean: 0.40 ± 0.05 μg/ml). Examples of fentanyl and ketamine serum concentration curves as a function of time during the maintenance infusion are shown in fig. 2. Variations in serum concentrations with time presumably reflect alterations in the infusion rate in response to changing surgical stimuli, while the individual variability in serum levels might reflect differing individual sensitivities to the drugs. There were no obvious correlations between serum drug levels and the incidence of intraoperative or postoperative side effects.

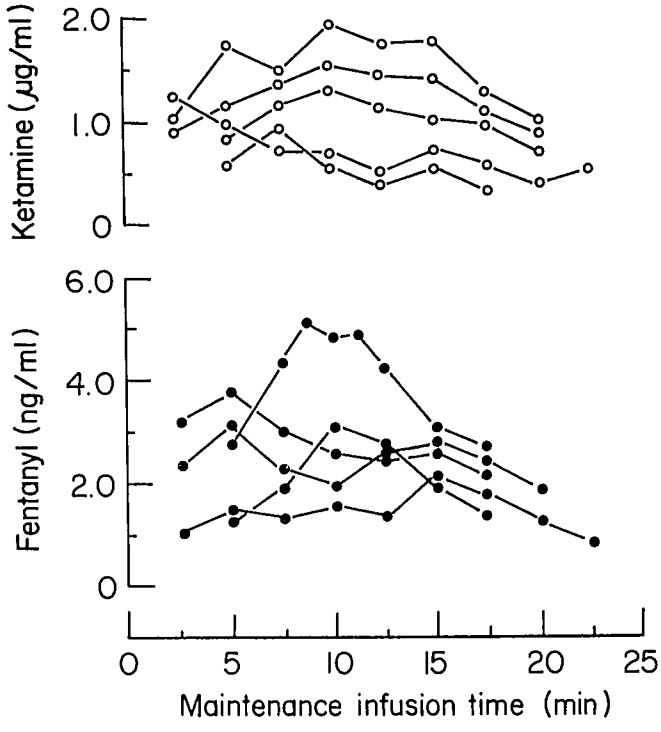

FIG. 2. Serum concentration curves for patients from the fentanyl and ketamine groups demonstrate the range of individual variation in fentanyl (ng/ml) and ketamine (μg/ml) levels as a function of time during the maintenance infusion.

The duration of anesthesia was similar in all groups (table 1). Evaluations of the intraoperative conditions revealed significantly less respiratory depression*** with the thiopental and ketamine infusions. However, the times to awakening, orientation, and discharge were significantly prolonged in these two groups. Trieger test scores also revealed significant differences among the groups during the early postoperative period. Although the baseline values were the same for the three groups (4 ± 1), the number of errors were significantly greater with the thiopental and ketamine infusions than with the fentanyl infusion at the 30 min (26 ± 5, 21 ± 3 *vs.* 10 ± 2) and 60 min (16 ± 3, 13 ± 2 *vs.* 7 ± 1) time intervals after awakening from anesthesia.

The incidences of symptoms experienced by patients during emergence from anesthesia, as well as postoperative side effects, differed significantly among the three groups (table 1). The thiopental group had the highest incidence of pain, excessive tiredness, and sleepiness at the time of discharge from the recovery room. Ketamine was associated with a significantly higher incidence of

*** Decrease in respiratory frequency and/or tidal volume requiring assisted ventilation.

TABLE 1. Assessment of Intravenous Anesthetic Requirements, Intraoperative Conditions, and Postoperative Side Effects (Mean Values ± SEM)

	Thiopental	Fentanyl	Ketamine
Induction			
Thiopental (mg)	232 ± 2	254 ± 8	238 ± 5
Maintenance			
Dose (μg or mg)	428 ± 32 mg	204 ± 13 μg	101 ± 7 mg
Duration of anesthesia* (min)	21 ± 2	20 ± 2	19 ± 1
Conditions (%)			
Motor activity†	16	16	8
Hypoventilation‡	0	36§¶	4
Hypertension‡	4	0	8
Hypotension‡	24	0§	0**
Tachycardia‡	48	8§	20
Bradycardia‡	0	4	0
Laryngospasm	0	8	4
Muscular rigidity††	0	12	4
Recovery			
Awakening time (min)	10.2 ± 1.2	2.1 ± 0.3§¶	3.5 ± 0.5**
Orientation time (min)	20 ± 4	4 ± 1§¶	16 ± 4
Discharge time (h)	1.9 ± 0.2	1.1 ± 0.1§¶	1.5 ± 0.1
Symptoms (%)			
Visual disturbances	20	12¶	56**
Dreaming	8	16	40**
Nausea/vomiting	8	60§¶	28
Dizziness	28	32	64**
Confusion	4	8¶	52**
Excessive sedation‡‡	92	8§	16**
Pain/cramping	56	4§	4**

* Time from injection of initial dose of thiopental until discontinuation of nitrous oxide.

† Purposeful movement requiring temporary cessation of surgical stimulus.

‡ Changes in respiratory rate, mean arterial pressure or heart rate exceeding 30% of pre-induction (baseline) values and lasting longer than 3 min.

§ Fentanyl group significantly different from thiopental group, $P < 0.05$.

¶ Fentanyl group significantly different from ketamine group, $P < 0.05$.

** Ketamine group significantly different from thiopental group, $P < 0.05$.

†† Increases in muscle tone requiring use of succinylcholine, 10–20 mg iv.

‡‡ Feelings of excessive tiredness and sleepiness at the time of discharge from the recovery room.

visual disturbances, dreaming, dizziness, and confusion, while fentanyl produced the highest incidence of nausea and vomiting. In spite of the fact that ketamine was associated with more frequent disturbances in CNS function during emergence from anesthesia, overall patient acceptance and future anesthetic preference did not significantly differ among the three groups.

The comparative effects of the three intravenous anesthetics on the patients' postoperative mood states demonstrated comparable decreases in tension, depression, anxiety, and vigor scores, with corresponding increases in fatigue scores. The ketamine group had a significant increase in the confusion score during recovery, compared with fentanyl or thiopental. At the subsequent follow-up evaluation, vigor scores were increased and fatigue scores were decreased to a comparable degree in all groups.

DISCUSSION

In outpatient anesthesia, a rapid recovery with minimal side effects is of primary importance. Although volatile anesthetics (*e.g.*, isoflurane) are popular in this setting, intravenous anesthetics in combination with nitrous oxide offer important advantages for midtrimester abortions because of decreased blood loss and postoperative pain. Given the large individual variation in the therapeutic serum concentrations of fentanyl and ketamine (fig. 2), a technique that would allow the anesthetist to titrate these drugs in a manner analogous to the volatile anesthetics would be of obvious clinical advantage in outpatient surgery.

My recent study[1] indicated that continuous infusion fentanyl or ketamine significantly decreased the drug dosage requirement compared with the traditional intermittent bolus technique. More importantly, continuous infusion techniques decreased recovery time following outpatient procedures. Although numerous reports regarding administration of ketamine by continuous infusion have appeared in the literature over the last 10 yr,[7] this technique had not been compared with other analgesic infusion techniques.[8–10] Recently, Benumof *et al.*[11] reported that the duration of postoperative analgesia was

significantly longer when ketamine (*vs.* fentanyl) was used to supplement nitrous-oxide–relaxant anesthesia. While prolonged postoperative analgesia is desirable in most situations, concomitant sedation may contribute to a delayed recovery following outpatient surgical procedures. Our current investigation comparing fentanyl or ketamine infusions (*vs.* thiopental infusion) for maintenance anesthesia in combination with nitrous oxide, revealed significantly better respiratory stability intraoperatively with ketamine (and thiopental) than with fentanyl. Although there was a high incidence of ventilatory depression intraoperatively in the fentanyl group (table 1), there was no evidence of clinically important postoperative respiratory depression (*i.e.*, requiring naloxone administration). The use of ketamine was associated with a higher incidence of postoperative side effects and a more prolonged recovery than fentanyl. The use of thiopental without an intravenous analgesic was associated with a higher incidence of intraoperative tachycardia as well as a more prolonged recovery (as a result of excessive sedation) compared with the fentanyl group.

Even though ketamine has a shorter elimination half-life ($t_{1/2}$ β equal to 1.5–3 h[12,13]) than fentanyl ($t_{1/2}$ β equal to 3–5 h[14,15]), it was associated with a more prolonged recovery. Our data suggest that the relatively slow distribution phase ($t_{1/2}$ α equal to 13 min[14]), associated with the redistribution of fentanyl from vessel-rich tissues to lean muscle tissues, was most important in terminating the clinical effects of fentanyl when administered by a continuous infusion for brief surgical procedures. Termination of ketamine's anesthetic effects would appear to be due to a combination of redistribution from brain to other tissues and hepatic metabolism.

Therapeutic blood levels of analgesics when used as intravenous adjuvants during anesthesia are unknown. Earlier fentanyl infusion studies[8,9] have reported steady state plasma concentrations of 5–25 ng/ml for intraabdominal procedures. Because we did not use muscle relaxants in our studies, we were able to make adjustments in the infusion rate based on clinical criteria (without the "masking" effect of muscle relaxants) to meet the changing surgical needs. The titration method used in this study allowed us to regulate the amount of drug administered closely and thereby to determine the mean effective fentanyl concentration (2.3 ± 0.2 ng/ml) for minor procedures in the presence of nitrous oxide 70%.

In a study involving patients undergoing intraabdominal surgery, Idvall *et al.*[13] found a steady state plasma ketamine concentration of 2.2 μg/ml was required as an adjuvant to nitrous oxide 65%. Our data indicate that lower serum levels (1.1 ± 0.1 μg/ml) are adequate for superficial surgical procedures. Because analgesic effects of ketamine have been reported at plasma levels of 0.1–0.2 μg/ml,[16] it is clear that significantly higher levels are required for anesthesia, even in the presence of nitrous oxide 70%.

To rapidly achieve a steady state concentration, a loading ("priming") dose usually is administered. However, because of the short duration of these cases and our desire to titrate the drug closely, only small loading doses were given (*i.e.*, fentanyl 100 μg or ketamine 50 mg). Thus, it was necessary to use high-maintenance infusion rates in order to maintain therapeutic drug levels in the presence of both redistributional and metabolic processes. If the averaged infusion rates in our study were maintained, steady state fentanyl and ketamine concentrations (calculated by dividing the maintenance infusion rate by the clearance) would approach 8 ng/ml and 3.1 μg/ml, respectively.

Becker[17] determined that a thiopental concentration of 14 μg/ml was required to produce loss of response to squeezing the trapezius muscle in the presence of nitrous oxide 67%. Similar thiopental levels were required in outpatients undergoing superficial surgical procedures (fig. 1). Subsequent studies will evaluate the effects of fentanyl, 1–3 μg/kg, on the therapeutic level of thiopental.

The use of adjunctive intravenous analgesics such as fentanyl and ketamine significantly decreased the thiopental requirement. Both fentanyl and ketamine infusions in combination with nitrous oxide decreased the intraoperative cardiovascular changes and shortened the recovery times, compared with a group receiving a combination of thiopental and nitrous oxide. The use of fentanyl was associated with a high incidence of nausea and retching during the early postoperative period as a result of its emetogenic properties and the need for assisted ventilation, however, this rarely delayed discharge from the recovery room. Fentanyl seems to offer significant advantages over ketamine when administered as a continuous infusion in combination with nitrous oxide for short outpatient surgical procedures.

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New and Easy Techniques for Fiberoptic Endoscopy-aided Tracheal Intubation

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Whenever tracheal intubation by direct laryngoscopy is considered very difficult or dangerous, fiberoptic endoscopy-aided tracheal intubation often is considered.[1–5] However, current fiberoptic intubation techniques require that the endoscopist have considerable experience and frequent practice in order to maneuver the fiberoptic instrument efficiently and safely past irregularly shaped, often moving, and sometimes secretion-filled upper airway segments.[2,6–8] Since the fiberoptic bronchoscope has been introduced only recently, many practicing anesthesiologists have received no organized instruction in its use. Consequently, they do not include fiberoptic endoscopy-aided tracheal intubation in their therapeutic armamentarium.

We report our successful experience with two newly developed airway devices that make fiberoptic endoscopy-aided tracheal intubation simple and easy, even in the hands of inexperienced operators. The oral Airway Intubator[9] is a plastic oropharyngeal airway with a cylindric passage down the midlongitudinal axis, which permits the concentric insertion of a fiberoptic bronchoscope and endotracheal tube; the distal end of the device locates in close proximity to the laryngeal aperture. The anesthesia mask with diaphragm[10] permits introduction of a fiberoptic bronchoscope into the airway without the loss of a seal for positive-pressure ventilation. These two airway adjuncts allow fiberoptic tracheal intubation to be performed easily and safely by the oral route in both awake and positive-pressure ventilated anesthetized patients.

METHODS

The tracheas of 25 adult patients who required general endotracheal anesthesia and either had a history of difficult tracheal intubation or were considered at preoperative evaluation to be potentially difficult to intubate were intubated fiberoptically using the techniques described below. Approval to perform this study was obtained from our local committee on human research. Tracheal intubation was performed under local anesthesia in 16 patients and under general anesthesia in the remaining nine. Patients were unpremedicated or received diazepam 5–10 mg po or morphine 5–10 mg im prior to arrival in the operating room.

Patients undergoing fiberoptic tracheal intubation under local anesthesia first gargled with 30 ml of viscous

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