# Pretreatment with Sedative-Hypnotics, but Not with Nondepolarizing Muscle Relaxants, Attenuates Alfentanil-Induced Muscle Rigidity

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Study Objective: *To evaluate and compare the efficacy of various pretreatment agents to attenuate or prevent opioid-induced muscle rigidity using a well-established, previously described clinical protocol.*
Design: *Prospective, controlled, single-blind, partially randomized study.*
Setting: *Large medical center.*
Patients: *ASA physical status I–III patients undergoing elective surgical procedures of at least 3 hours' duration.*
Interventions: *The effect of pretreatment with nondepolarizing muscle relaxants (atracurium 40μg/kg or metocurine 50μg/kg), benzodiazepine agonists (diazepam 5 mg or midazolam 2.5 mg), or thiopental sodium 1 mg/kg on the increased muscle tone produced by alfentanil 175 μg/kg was compared with a control group (given no pretreatment).*
Measurements and Main Results: *Rigidity was assessed quantitatively by measuring the electromyographic activity of five muscle groups (biceps, intercostals, abdominals, quadriceps, and gastrocnemius). Rigidity also was rated qualitatively by attempts to initiate and maintain mask ventilation, attempts to flex an extremity, and the occurrence of myoclonic movements. Pretreatment with the two nondepolarizing muscle relaxants had no effect on the severe muscle rigidity produced by high-dose alfentanil. Whereas thiopental was only mildly effective, the benzodiazepines midazolam and diazepam significantly attenuated alfentanil rigidity ($p < 0.05$).*
Conclusion: *This study suggests that benzodiazepine pretreatment is frequently, but not always, effective in preventing opioid-induced muscle rigidity.*

**Keywords:** Alfentanil; electromyography; muscle rigidity, opioid-induced; premedication.

## Introduction

The muscle rigidity associated with opioid administration was first described by Hamilton *et al.* in 1953.[1] However, opioid-induced muscle rigidity was not appreciated as a clinical problem until the introduction of high-dose opioid techniques for cardiac and other major surgery. Opioid-induced muscle rigidity most commonly occurs with induction of anesthesia. It has been shown to impede bag and mask ventilation, causing hypercarbia,[2] to elevate central venous pressure (CVP) and pulmonary artery pressure,[3] to increase intracranial pressure,[4] and, in some situations, to require the administration of muscle relaxants before the patient is unresponsive.[5]

Early suggestions for preventing or controlling opioid rigidity were largely based on empiric or anecodotal data and included eliminating nitrous oxide ($N_2O$) supplementation,[6] limiting the dose of opioid,[7] and administering three times the "sleep dose" of opioid.[8] More recently, clinical studies have led to the suggestion that opioid rigidity may be ameliorated by pretreatment with either small doses of nondepolarizing muscle relaxants*,[9–12] or sedative-hypnotics such as thiopental sodium[13] and midazolam.[14] However, these clinical studies have generally used subjective measures of muscle tone, and they have only rarely compared directly different pretreatment regimens (and then only two regimens). As a result, the present data are conflicting regarding the optimum pretreatment regimen to prevent opioid-induced muscle rigidity. In addition, the potential benefit of pretreatment with either nondepolarizing muscle relaxants or sedative-hypnotics may be offset by undesirable side effects (*e.g.*, premature muscle paralysis or cardiovascular depression, respectively).

Therefore, a prospective, controlled, objective clinical study was undertaken to evaluate and compare the efficacy of various pretreatment drugs to attenuate or prevent opioid-induced muscle rigidity using a well-established, previously described clinical protocol employing the potent opioid agonist alfentanil.[3]

## Materials and Methods

The experimental protocol was approved by both the University of California, San Diego, and the San Diego Veterans Affairs Medical Center Human Subjects Committees. All patients gave written informed consent.

Five pretreatment drugs were chosen for study based on previous clinical or basic scientific investigations that suggested their potential efficacy in preventing or attenuating opioid-induced rigidity. The pretreatment drugs represented two types of drugs: nondepolarizing muscle relaxants [atracurium 40μg/kg (n = 4) or metocurine 50μg/kg (n = 4)] and sedative-hypnotics known to act at the gamma-amino butyric acid (GABA) receptor-chloride channel ionophore[15] [the benzodiazepines diazepam 5 mg (n = 5) and midazolam 2.5 mg (n = 5) and the barbiturate thiopental 1 mg/kg (n = 4)]. The control patients (n = 11) did not receive any pretreatment injection but otherwise were subjected to an identical experimental protocol. All drugs were administered intravenously (IV).

The dose and timing of administration of each drug were selected to optimize potential efficacy without causing disturbing effects on their own. For example, the doses of the nondepolarizing muscle relaxants were chosen to minimize the risk of preinduction muscle paralysis or respiratory deficiency. In addition, the timing of drug administration was selected to attempt to align the peak effect of the pretreatment drug with the expected peak alfentanil serum levels.

Patients were randomly assigned by randomization table to receive one of the five pretreatment agents. (The midazolam group was added toward the end of the study and thus was not able to be included in this randomization.) Nevertheless, the technician collecting and analyzing the data was blinded as to which pretreatment agent had been administered.

Thirty-one male ASA physical status I–III patients scheduled for elective orthopedic, ear, nose, and throat, or general surgical procedures expected to last longer than 3 hours were studied. Patients were excluded if they had significant cardiovascular or pulmonary disease (*e.g.*, myocardial ischemia, cerebrovascular disease, diminished pulmonary reserve). All patients were monitored identically to those in the report by Benthuysen *et al.*,[3] who studied unmodified alfentanil-induced rigidity. Cardiovascular monitoring consisted of an ECG, intra-arterial pressure, CVP, and continuous beat-to-beat pulse-contour cardiac output (CO) measurements calibrated with triplicate green-dye CO determinations.[16] Patient oxygenation was monitored continuously via pulse oximetry ($SpO_2$) (Nellcor Model 100, Nellcor, Hayward, CA) and transcutaneous $PO_2$ ($TcO_2$) recordings (Novametrix Model 810, Wallingford, CT).

Electrophysiologic measurements included bilateral electroencephalogram (EEG) recordings (frontal-mastoid configuration—$FP1\text{-}M_1/FP2\text{-}M_2$) with a Lifescan processed on-line EEG (Diatek, San Diego, CA) and five widely distributed surface electromyograms (EMGs). Following Omniprep skin preparation, triplets of EMG electrodes placed 8 cm apart were arranged over each of the following muscle groups: biceps, gastrocnemius, intercostals (seventh, eighth, or ninth interspace), rectus abdominis muscles, and quadriceps. Both EEG and EMG electrodes were connected via shielded cables to Hewlett-Packard 8811A bioelectric amplifiers (Palo Alto, CA), with band-pass filtering from 0.5 to 1,000 Hz (EEG) or 1 to 1,500 Hz (EMG). In addition to polygraphic recordings, all analog data were recorded on magnetic tape using Crown Vetter A-1 8-channel and Ampex 14-channel FM recorders. Concurrently recorded on each strip-chart and tape recorder channel was a 10 Hz sine wave calibration signal equivalent to a 100 μV EEG or EMG signal.

*Gratz I, Larijani GE, Boxer L, Valvamp E, Jacobi AG: The effect of a priming dose of vecuronium on sufentanil-induced rigidity [Abstract]. *Anesth Analg* 1989;68:S110.

EMG activity was measured continuously after administration of the pretreatment drug and for up to 7 minutes after alfentanil induction (until just after an intubating dose of nondepolarizing muscle relaxants was administered). Time zero was measured when the alfentanil infusion was initiated. In addition, rigidity was assessed by the occurrence of nonconvulsive myoclonic movements, the ability of an observer to flex either an upper or lower extremity at 5 minutes, and the ability of the anesthesiologist to initiate and maintain mask ventilation at the time of muscle relaxant administration (see below).

All patients received lorazepam 1 to 3 mg and cimetidine 300 mg orally the evening before the study. Cimetidine 300 mg orally and morphine 0.1 to 0.15 mg/kg intramuscularly were administered 60 minutes prior to induction. Before beginning anesthetic induction, each patient received lactated Ringer's solution 7 ml/kg IV over a 5-minute period. This was followed by 100% oxygen ($O_2$) 5 L/min by mask for at least 5 minutes, or until $TcO_2$ was greater than 200 mmHg. All pretreatment drugs except diazepam were administered 1 minute before anesthetic induction. Diazepam was administered 5 minutes before induction. Induction of anesthesia was accomplished with alfentanil 175 μg/kg infused over 1 minute. The patient was then observed in an apneic, unstimulated state.

During these observations, an independent anesthesiologist continuously evaluated patient status and guided clinical management using preestablished, well-defined criteria. The independent anesthesiologist immediately terminated the period of alfentanil-induced apnea when the patient showed (1) $SpO_2$ less than 98%, (2) a decrease in $TcO_2$ of more than 75 mmHg per minutes, or (3) adverse hemodynamic changes [mean blood pressure greater than 120 mmHg, heart rate (HR) greater than 110 beats per minute or dysrhythmias]. When any of these events occurred, pancuronium 50 μg/kg and metocurine 100 μg/kg were administered, and the patient was manually ventilated by mask with 100% $O_2$. If signs of light anesthesia [*e.g.*, hypertension/tachycardia as defined above or the reappearance of higher EEG frequencies (10 to 30 Hz)] occurred prior to endotracheal intubation, supplemental thiopental was administered. After intubation, data collection ceased, isoflurane-$N_2O$ was administered as required, and anesthesia proceeded in the usual fashion.

The EMG signals were rectified and integrated to yield root mean square EMG values for each muscle group.[3] EMG activity over time (every 30 seconds) for each pretreatment drug was compared with that of control patients using two-way analysis of variance (ANOVA) with one between-subjects factor (drug) and one within-subjects repeated-measures factor (time). Significant interactions were explored with Newman-Keuls post hoc tests.[17] Differences between groups with respect to the ability to mask-ventilate and the need for thiopental supplementation were examined using contingency table analysis. CVP values were compared using two-way ANOVA at five time points: prior to IV fluid administration, after hydration (but before alfentanil), and at 1, 2, and 5 minutes after alfentanil infusion. A $p$-value of 0.05 was considered statistically significant. All values are presented as means ± SEM.

## Results

There were no differences in patient demographics. The average age was 52.6 ± 12 years. All patients were ASA physical status I, II, or III. Two patients (one in the diazepam group and one control patient) required early administration of muscle relaxants because of rapidly decreasing $TcO_2$ following alfentanil administration. No patient in any group reported intraoperative awareness. There were no postoperative complaints of muscle pain.

Complete EMG data were able to be collected for the 5-minute period following initiation of alfentanil administration in the truncal (rectus abdominis muscles and intercostals) *(Table 1)* and peripheral (biceps, gastrocnemius, and quadriceps) *(Table 2)* muscle groups. There were no statistically significant differences in baseline EMG values between pretreatment groups in any muscle group.

### *Control Group*

Patients receiving no pretreatment drug prior to alfentanil administration displayed spontaneous, progressive, rapid increases in muscle rigidity that began just prior to the completion of the alfentanil infusion. There were statistically significant increases in EMG activity over time in *all* muscle groups *(Table 1* and *2)*. The alfentanil-induced muscle rigidity was most notable in the rectus abdominis muscles ($p < 0.001$), gastrocnemius ($p < 0.001$), and biceps ($p < 0.001$). None of the nine patients could be ventilated adequately by bag and mask prior to the onset of the effects of the nondepolarizing muscle relaxant. Patients in this group also manifested significant increases in CVP [$F(4,100) = 2.69$; $p < 0.05$], with a peak value at 2 minutes after alfentanil administration *(Table 3)*. In addition, four of the nine patients required thiopental supplementation at the time of intubation.

### *Metocurine Pretreatment*

There was no difference in the magnitude of rigidity in the metocurine pretreatment group when compared with the control group. Significant muscle rigidity occurred in the intercostals [$F(10,230) = 3.52$; $p < 0.001$] quadriceps [$F(10,240) = 2.90$; $p < 0.005$], and gastrocnemius 1; [$F(10,240) = 2.61$; $p < 0.005$]. Bag and mask ventilation was possible in only one of the four patients. Rigidity increased markedly in one patient upon attempting mask ventilation. There were significant increases in CVP ($p < 0.05$), with a peak value at 1 minute after alfentanil administration. One patient required supplemental thiopental.

**Table 1.** Electromyographic Activity in the Truncal Muscle Groups

| | Time (min) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 | 5 |
| Rectus abdominis | | | | | | | | | | | |
| Control | 6.8 ± 2.2 | 7.5 ± 1.9 | 10.7 ± 3.0 | 23.1 ± 6.1* | 24.9 ± 3.8* | 32.3 ± 5.9* | 33.1 ± 5.9* | 36.1 ± 6.9* | 35.3 ± 6.1* | 40.3 ± 9.2* | 35.0 ± 7.8* |
| Metocurine | 7.8 ± 1.6 | 21.1 ± 9.9 | 20.1 ± 9.4 | 25.3 ± 6.9 | 25.7 ± 6.8 | 27.2 ± 8.1 | 27.6 ± 7.4 | 29.3 ± 7.3 | 23.5 ± 11.4 | 15.8 ± 5.9 | 24.0 ± 11.2 |
| Atracurium | 4.1 ± 2.4 | 4.1 ± 2.4 | 3.9 ± 2.1 | 24.0 ± 13.6* | 33.8 ± 16.7* | 41.0 ± 16.8* | 42.3 ± 16.9* | 37.8 ± 14.2* | 38.8 ± 14.8* | 37.5 ± 13.4* | 37.8 ± 13.8* |
| Thiopental | 9.4 ± 5.5 | 15.4 ± 9.2 | 9.1 ± 5.0 | 10.1 ± 5.7 | 19.3 ± 13.8 | 10.2 ± 6.1† | 11.5 ± 6.2† | 12.0 ± 7.2 | 10.1 ± 2.9 | 10.1 ± 2.6‡ | 9.1 ± 2.5 |
| Diazepam | 10.4 ± 1.9 | 9.8 ± 2.0 | 10.1 ± 2.0 | 9.8 ± 1.8 | 9.8 ± 1.8 | 9.8 ± 1.8† | 10.3 ± 1.9† | 10.3 ± 1.8 | 10.3 ± 1.8 | 10.8 ± 1.3 | 13.3 ± 2.6 |
| Midazolam | 3.2 ± 1.5 | 3.8 ± 1.2 | 5.7 ± 1.9 | 7.9 ± 4.5 | 8.4 ± 4.4 | 10.0 ± 4.9† | 10.2 ± 4.5† | 11.3 ± 4.3 | 14.4 ± 5.6 | 12.4 ± 4.2 | 8.4 ± 3.2 |
| Intercostal | | | | | | | | | | | |
| Control | 26.8 ± 9.0 | 28.8 ± 13.2 | 20.1 ± 5.3 | 39.3 ± 11.8 | 36.7 ± 5.4 | 41.6 ± 5.9§ | 44.5 ± 5.2§ | 48.6 ± 4.4§ | 49.2 ± 6.0§ | 55.4 ± 5.3*§ | 56.8 ± 6.5*§ |
| Metocurine | 13.0 ± 2.7 | 23.6 ± 13.2 | 35.5 ± 14.1 | 40.9 ± 16.8 | 45.5 ± 20.8 | 56.0 ± 29.9* | 54.0 ± 26.6* | 54.6 ± 24.9* | 29.6 ± 11.0 | 23.8 ± 6.8 | 23.8 ± 6.7 |
| Atracurium | 14.1 ± 3.2 | 13.3 ± 3.3 | 13.0 ± 3.3 | 17.8 ± 5.9 | 30.6 ± 12.3 | 34.3 ± 12.1 | 38.0 ± 12.7 | 39.4 ± 12.8 | 41.0 ± 13.7 | 41.0 ± 13.7 | 41.1 ± 13.1 |
| Thiopental | 15.3 ± 0.8 | 15.6 ± 1.9 | 17.1 ± 3.0 | 17.9 ± 3.4 | 18.5 ± 3.1 | 19.4 ± 3.7‖ | 23.3 ± 4.2 | 28.8 ± 5.0 | 25.6 ± 8.5 | 31.7 ± 16.8 | 33.6 ± 14.5 |
| Diazepam | 12.9 ± 3.1 | 12.3 ± 3.2 | 12.1 ± 3.5 | 11.5 ± 2.7 | 13.7 ± 3.8 | 13.7 ± 2.9‖ | 13.9 ± 3.3‖ | 14.4 ± 3.9‖ | 14.1 ± 3.3 | 15.1 ± 3.1‡ | 16.6 ± 3.5‡ |
| Midazolam | 10.2 ± 1.5 | 9.7 ± 1.7 | 9.8 ± 1.7 | 10.9 ± 2.2 | 10.4 ± 2.6 | 12.0 ± 2.5‖ | 14.6 ± 2.8‖ | 16.5 ± 3.2‖ | 18.0 ± 3.6 | 18.7 ± 3.8‡ | 13.9 ± 3.3‡ |

*$p < 0.05$ compared with the 0-minute time point in this group. †$p < 0.05$ compared with atracurium at this time point. ‡$p < 0.05$ compared with control group at this time point. §$p < 0.05$ compared with the 1-minute time point in this group. ‖$p < 0.05$ compared with metocurine at this time point. Note: Data are means ± SEM.

**Table 2.** Electromyographic (EMG) Activity in the Peripheral Muscles

| | Time (min) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 | 5 |
| Quadriceps | | | | | | | | | | | |
| Control* | 5.0 ± 4.6† | 7.1 ± 4.5† | 9.6 ± 4.4 | 19.0 ± 6.7 | 19.4 ± 4.4 | 18.3 ± 4.5 | 23.2 ± 8.2 | 19.1 ± 5.3 | 22.8 ± 5.2 | 26.3 ± 7.3 | 17.6 ± 5.0 |
| Metocurine* | 1.6 ± 0.6† | 1.9 ± 0.9† | 1.4 ± 0.8† | 1.6 ± 0.6† | 17.4 ± 9.6 | 16.0 ± 9.1 | 24.0 ± 16.3 | 21.0 ± 17.6 | 19.0 ± 13.8 | 32.2 ± 22.1 | 17.8 ± 11.1 |
| Atracurium* | 3.0 ± 0.7 | 3.0 ± 0.8 | 7.1 ± 4.5 | 21.9 ± 14.1 | 29.1 ± 18.2 | 24.6 ± 12.2 | 25.9 ± 14.2 | 15.0 ± 8.9 | 18.8 ± 9.2 | 10.8 ± 5.0 | 18.8 ± 9.2 |
| Thiopental | 5.1 ± 2.3 | 12.4 ± 9.6 | 5.4 ± 2.9 | 8.9 ± 6.4 | 11.4 ± 7.0 | 21.8 ± 17.8 | 17.2 ± 11.0 | 23.1 ± 16.8 | 11.6 ± 6.1 | 7.2 ± 4.5 | 12.7 ± 5.9 |
| Diazepam | 3.7 ± 0.7 | 3.3 ± 0.8 | 3.3 ± 0.8 | 2.7 ± 0.3 | 2.3 ± 0.1 | 2.1 ± 0.2 | 2.1 ± 0.2 | 2.0 ± 0.3 | 1.9 ± 0.3 | 1.7 ± 0.6 | 1.7 ± 0.6 |
| Midazolam | 3.9 ± 1.2 | 3.6 ± 1.2 | 3.9 ± 1.2 | 3.6 ± 1.0 | 4.7 ± 1.0 | 4.5 ± 1.0 | 3.8 ± 1.3 | 3.4 ± 0.9 | 9.9 ± 5.6 | 7.5 ± 3.7 | 17.3 ± 11.0 |
| Biceps | | | | | | | | | | | |
| Control* | 4.0 ± 1.5 | 4.6 ± 1.6 | 5.9 ± 2.3 | 31.5 ± 10.8‡ | 34.1 ± 13.8‡ | 30.3 ± 9.9‡ | 33.5 ± 12.8‡ | 31.2 ± 10.5‡ | 34.6 ± 12.2‡§ | 35.3 ± 12.9‡ | 34.7 ± 12.3‡ |
| Metocurine | 5.1 ± 2.0 | 5.9 ± 2.3 | 10.9 ± 4.0 | 19.2 ± 9.6 | 18.0 ± 8.2 | 20.0 ± 10.0 | 17.5 ± 7.2 | 21.0 ± 9.8 | 20.5 ± 8.2§ | 9.9 ± 5.7 | 22.1 ± 14.9 |
| Atracurium | 8.6 ± 5.2 | 8.6 ± 5.2 | 6.2 ± 3.6 | 9.5 ± 3.2 | 12.4 ± 4.7 | 14.9 ± 3.6 | 16.5 ± 5.0 | 15.4 ± 3.8 | 14.5 ± 4.0§ | 15.4 ± 6.0 | 14.2 ± 5.4 |
| Thiopental* | 5.7 ± 2.1 | 15.4 ± 10.4 | 23.9 ± 8.7‖ | 36.2 ± 22.3‖ | 38.9 ± 24.4‖ | 42.9 ± 26.6# | 44.1 ± 27.4# | 50.4 ± 30.6** | 76.7 ± 60.0**,†† | 57.0 ± 23.8**,†† | 56.6 ± 29.2**,†† |
| Diazepam | 3.4 ± 0.3 | 3.4 ± 0.3 | 3.7 ± 0.5 | 3.4 ± 0.3 | 6.5 ± 3.3 | 6.2 ± 3.0 | 6.5 ± 3.3 | 6.2 ± 2.6 | 6.2 ± 2.6§ | 6.5 ± 3.3 | 5.9 ± 2.7 |
| Midazolam | 4.6 ± 1.4 | 4.5 ± 1.6 | 5.6 ± 1.9 | 9.8 ± 5.3 | 8.5 ± 4.4 | 8.4 ± 4.0 | 8.7 ± 4.0 | 9.0 ± 3.1 | 23.2 ± 12.1§ | 18.8 ± 9.0 | 11.7 ± 5.0 |
| Gastrocnemius | | | | | | | | | | | |
| Control* | 3.7 ± 2.3 | 4.9 ± 2.6 | 8.8 ± 4.7 | 31.0 ± 10.5‡ | 32.8 ± 9.1‡ | 32.5 ± 8.0‡ | 35.0 ± 8.0‡ | 32.6 ± 7.1‡ | 31.2 ± 6.4‡ | 33.8 ± 5.8‡ | 36.9 ± 6.4‡ |
| Metocurine* | 4.7 ± 3.0 | 4.8 ± 3.2 | 4.2 ± 2.5 | 8.2 ± 3.7 | 26.6 ± 14.3 | 28.4 ± 16.6 | 26.9 ± 16.5 | 57.6 ± 25.9 | 25.8 ± 12.5 | 20.1 ± 10.4 | 24.3 ± 13.3 |
| Atracurium* | 5.3 ± 0.6 | 4.1 ± 0.8 | 13.5 ± 7.0 | 34.0 ± 9.6‡‡ | 37.5 ± 1.9‡‡ | 39.3 ± 2.5‡‡ | 37.9 ± 3.0‡‡ | 33.0 ± 2.0‡‡ | 31.8 ± 3.7‡‡ | 24.2 ± 0.9 | 22.9 ± 3.6 |
| Thiopental* | 4.6 ± 1.8 | 3.8 ± 1.1 | 3.0 ± 0.7 | 18.4 ± 15.5 | 15.9 ± 13.0† | 14.7 ± 11.8† | 25.7 ± 22.1 | 23.2 ± 15.1 | 29.6 ± 12.3 | 44.8 ± 22.6‡ | 23.3 ± 10.0 |
| Diazepam | 3.6 ± 0.5 | 3.4 ± 0.9 | 3.2 ± 1.0 | 3.0 ± 0.8 | 3.2 ± 0.6 | 3.7 ± 0.9 | 3.2 ± 0.6 | 3.2 ± 0.6 | 3.0 ± 0.8 | 4.9 ± 0.2 | 5.2 ± 1.4 |
| Midazolam* | 5.0 ± 1.2 | 7.1 ± 2.0 | 10.1 ± 4.9 | 9.5 ± 4.2 | 10.5 ± 4.9 | 10.1 ± 4.7 | 10.1 ± 4.3 | 10.4 ± 5.3 | 26.1 ± 14.4 | 26.9 ± 14.8 | 27.9 ± 11.5 |

*Significant increase in EMG activity over time in this group. †$p < 0.05$ compared with the 4.5-minute time point in this group. ‡$p < 0.01$ compared with the 0-, 0.5-, and 1-minute time points in this group. §$p < 0.05$ compared with thiopental at this time point. ‖$p < 0.05$ compared with the 4-minute time point in this group. #$p < 0.05$ compared with the 0-minute time point in this group. **$p < 0.01$ compared with the 0-minute time point in this group. ††$p < 0.05$ compared with the 0.5-minute time point in this group. ‡‡$p < 0.05$ compared with the 0- and 0.5-minute time points in this group. Note: Data are means ± SEM.

### *Atracurium Pretreatment*

When compared with controls, atracurium did not attenuate rigidity in any muscle group. Significant muscle rigidity was expressed in the rectus abdominis muscles [$F(10,240) = 8.14$; $p < 0.001$], gastrocnemius [$F(10,240) = 3.83$; $p < 0.001$], intercostals [$F(10,230) = 2.40$; $p < 0.01$], and quadriceps [$F(10,240) = 2.03$; $p < 0.05$]. Bag and mask ventilation was possible but difficult in two of the four patients and impossible in the other two. There was a greater increase in CVP [$F(4,100) = 9.67$; $p < 0.001$] after atracurium than after any of the other drugs. Peak CVP at 1 minute after alfentanil administration was significantly higher than the comparable value in the midazolam group (*Table 3*; $p < 0.01$). Because of hypertension, two patients required thiopental supplementation prior to intubation.

### *Thiopental Pretreatment*

Following pretreatment with thiopental, significant alfentanil rigidity could be demonstrated only in the biceps [$F(10,230) = 5.26$; $p < 0.001$] and gastrocnemius [$F(10,240) = 3.62$; $p < 0.001$]. There was an increase in rigidity in the quadriceps, but this was insufficient to attain statistical significance. Interestingly, there was no significant change in EMG activity over time in the rectus abdominis muscles, and, although, EMG activity appeared to increase over time in the intercostal muscles, this increase did not attain statistical significance. Consistent with the absence of appreciable truncal muscle rigidity, CVP did not change significantly following alfentanil administration. However, mask ventilation was possible in only one of the four patients. No patient required an additional dose of thiopental prior to intubation.

### *Diazepam Pretreatment*

Diazepam was the only pretreatment regimen that prevented the occurrence of statistically significant rigidity in *all* muscle groups (*Tables 1* and *2*). In the rectus abdominis muscles, the EMG values at the 2.5 to 3-minute time points were significantly lower than in the atracurium group. Similarly, diazepam pretreatment attenuated rigidity in the intercostal muscles when compared with the control and the metocurine groups. Interestingly, however, CVP was still significantly elevated after diazepam [$F(4,100) = 4.08$; $p < 0.005$] (*Table 3*). Mask ventilation was considered easy in four of the five patients ($p < 0.02$ compared with controls). However, in the fifth patient, severe rigidity occurred, and the study had to be terminated approximately 3 minutes after alfentanil when $TcO_2$ began to decrease rapidly. This patient required thiopental supplementation. Two other patients experienced bradycardia and hypotension, which responded to atropine administration.

### *Midazolam Pretreatment*

After midazolam pretreatment, there was still statistically significant alfentanil-induced rigidity over time in the gastrocnemius [$F(10,240) = 2.07 = p < 0.05$] but not in the other extremity muscles (*Table 2*). Interestingly, the increased EMG activity did not occur until 4 minutes after alfentanil. The EMG activity in the rectus abdominis and intercostal muscles (*Table 1*) did not show statistically significant changes, suggesting a protection against alfentanil-induced muscle rigidity. Of note, in contrast to diazepam, there were no changes in CVP after midazolam pretreatment, and the postalfentanil CVP values were actually significantly lower in this group than in either the diazepam or the thiopental group. Mask ventilation was possible in four of the five patients ($p < 0.02$ compared with controls). In the fifth patient, attempts at ventilation produced severe rigidity, and mask ventilation was impossible. Thiopental was required for hypertension immediately after intubation in one patient.

## Discussion

In this study, the two nondepolarizing muscle relaxants atracurium and metocurine were completely ineffective,

**Table 3.** Effects of Pretreatment Drugs on Central Venous Pressure (in mmHg)

| | Before Fluids (t = −5 min) | At Start of Alfentanil (t = 0 min) | At End of Alfentanil (t = 1 min) | At End of Alfentanil (t = 2 min) | After Muscle Relaxant (t = 5 min) |
|---|---|---|---|---|---|
| Control | 8.2 ± 1.4 | 7.9 ± 1.0 | 9.6 ± 1.3 | 11.1 ± 1.3* | 7.3 ± 0.8 |
| Metocurine | 6.3 ± 1.7 | 8.0 ± 2.7 | 11.3 ± 4.4* | 9.0 ± 1.9 | 5.5 ± 1.0 |
| Atracurium | 4.8 ± 1.4† | 7.5 ± 2.2† | 16.0 ± 3.1‡ | 8.0 ± 0.8† | 6.8 ± 1.5† |
| Thiopental | 5.7 ± 1.4 | 7.8 ± 2.3 | 9.3 ± 1.7 | 8.8 ± 2.1 | 7.5 ± 2.2 |
| Diazepam | 7.6 ± 1.7 | 12.0 ± 1.5 | 11.2 ± 1.6 | 14.6 ± 2.8‡,§ | 11.0 ± 2.1 |
| Midazolam | 4.4 ± 1.2 | 6.2 ± 0.6 | 4.6 ± 0.9 | 5.0 ± 0.8 | 4.2 ± 1.0 |

*$p < 0.05$ compared with t = 5 min.

†$p < 0.01$ compared with t = 1 min (post-alfentanil).

‡$p < 0.01$ compared with midazolam at the same time point.

§$p < 0.01$ compared with baseline (t = −5 min).

Note: Data are means ± SEM.

at the doses studied, in attenuating alfentanil-induced muscle rigidity. The barbiturate thiopental produced mild attenuation of alfentanil rigidity in the truncal muscles, but it failed to reduce rigidity in the extremities. In contrast, the benzodiazepine agonists diazepam and midazolam significantly, though incompletely, attenuated alfentanil-induced rigidity. Another objective, albeit indirect, sign of opioid rigidity, elevated CVP,[3] was attenuated after pretreatment with thiopental and midazolam. Thus, clinically and statistically significant reductions in alfentanil rigidity following pretreatment with the sedative-hypnotics were demonstrated despite the relatively small numbers of subjects studied.

Specific consideration went into the selection of each pretreatment drug. Based on previous studies using low doses of muscle relaxants,*[9–12] metocurine and atracurium were chosen in an attempt to attenuate rigidity via the peripheral myoneural junction. Some investigators have implied that by hastening the onset of deep anesthesia, the barbiturate thiopental blocks rigidity.[13,18] Benzodiazepines have been cited in the basic science literature as capable of preventing opioid-induced rigidity in animals.[19,20] This hypothesis is supported by at least one prior clinical study.[14]

It was somewhat surprising that the nondepolarizing muscle relaxants were completely ineffective at attenuating rigidity. These quantitative data contradict three previous reports suggesting that small, defasciculating doses of nondepolarizing neuromuscular blocking drugs prevented opioid rigidity.[10–12] In these other studies, quantitative data analysis was not performed, and thiopental was administered in conjunction with the opioid for anesthetic induction, thereby clouding interpretation of the results.

The doses of atracurium and metocurine were not precisely equivalent from a neuromuscular blocking standpoint, although the dose of each drug was chosen to be approximately 20% of the $ED_{95}$ for complete twitch depression. However, the dose of each muscle relaxant drug was modified to be closer to the "priming" dose typical of our institution's routine clinical practice. The dose also had to be clinically safe and not produce unwanted side effects (*e.g.*, weakness before loss of consciousness, cardiovascular changes). Curariform-like neuromuscular antagonists have a greater degree of prejunctional (*vs.* postjunctional) effect. If opioid rigidity is comparable to tetanus (a sustained increase in muscle tone), then, theoretically, atracurium or metocurine might be expected to be more effective at attenuating rigidity than equivalent doses of pancuronium or vecuronium. Nevertheless, larger doses and/or other nondepolarizing muscle relaxants might have produced different results.

Thiopental attenuated rigidity in the abdominal and intercostal muscle groups, but rigidity in the extremities remained severe. This differential effect on truncal *versus* extremity muscles is interesting. In a pilot study using identical methodology, benztropine, a centrally acting anticholinergic drug with mild antihistaminic action, produced EMG results almost opposite those of thiopental. There appeared to be attenuation of rigidity in the proximal extremity muscles (biceps and gastrocnemius), but severe rigidity occurred in the truncal muscles. The cause of the differential effects of opioids on muscle tone in the truncal *versus* the peripheral muscle groups following different pretreatment drugs is unknown. Thiopental's ability to increase venous compliance, combined with minimal rigidity of the thoracoabdominal musculature, probably explains the stable CVP values.[21]

Midazolam was incorporated into this study after completion of the randomization table and initiation of the study. Initially, midazolam 5 mg was administered 5 minutes before induction in two patients. This dose and time of administration resulted in patient unresponsiveness *prior to* alfentanil administration. As a result of these preliminary findings, the study dose was decreased to 2.5 mg and administered 1 minute prior to alfentanil administration.

Pretreatment with midazolam resulted in significant protection against opioid rigidity in the truncal muscles. The onset of alfentanil rigidity in the extremity muscles was delayed for up to 4 minutes. It is also noteworthy that the administration of midazolam 2.5 mg did not result in loss of consciousness or adverse cardiovascular side effects in any patient.

Of all the drugs tested, diazepam provided the best quantitative protection against alfentanil rigidity. Diazepam was administered 5 minutes before induction because of its relatively slow onset of action. All muscle groups were spared from opioid rigidity, and this beneficial effect lasted throughout the 5-minute observation period in all but one patient. This patient did, however, develop severe rigidity when mask ventilation was attempted. In two patients, there was a significant decrease in blood pressure and CO that appeared to be due primarily to decreased HR. Both patients responded promptly to atropine administration. The combination of diazepam and fentanyl has been reported to cause significant hypotension.[22,23]

Following diazepam pretreatment, there was an increase in CVP at 2 minutes after alfentanil administration. This contrasts with the absence of increased CVP following thiopental or midazolam pretreatment. In a previous study, it was demonstrated that elevated CVP measurements correlated with the intensity of thoracoabdominal rigidity.[3] It has been suggested that the shunting of venous blood from the periphery to the central pool during rigidity is an important factor in the elevation of CVP.[21] However, in the case of diazepam, in light of the absence of truncal muscle rigidity by other criteria, it seems more likely that increased CVP was due to altered hemodynamics resulting from the synergistic effects of diazepam and alfentanil.[23]

One potential criticism of this study could be that the

*Gratz I, Larijani GE, Boxer L, Valvamp E, Jacobi AG: The effect of a priming dose of vecuronium on sufentanil-induced rigidity [Abstract]. *Anesth Analg* 1989;68:S110.

induction dose of alfentanil (175 μg/kg), though within the accepted clinical range, was somewhat higher than what might typically be used. This dose was selected because a previous study showed that it reliably and rapidly produced profound rigidity.[3] Although it might be argued that alfentanil 175 μg/kg produced such severe muscle rigidity that no pretreatment drug could reasonably be expected to be protective, the benzodiazepines were in fact effective. One might expect greater protective effects of pretreatment drugs with lower doses of alfentanil. It also should be noted that other doses of drugs and other times prior to induction could produce different results.

Opioids may produce muscle rigidity by acting at opioid receptors in the caudate nucleus and substantia nigra, resulting in an inhibition of GABA activity within the striatal pathway.[24–27] It has since been shown that GABAergic pathways linking the substantia nigra to the ventromedial thalamus[28,29] and the ventral tegmental area of the superior colliculus[30] can play a role in the production of muscle rigidity. More recent studies have emphasized the role of periventricular and pontine structures in the expression of opiate rigidity.[31]

The central actions of thiopental, diazepam, and midazolam are associated to a significant extent with GABA facilitation.[15,32] It is, therefore, tempting to speculate that the mechanism of the beneficial effects of these drugs on rigidity is due to a common enhancement of GABAergic activity. Our study did not establish this mechanism. These drugs also are sedative-hypnotics, and some investigators have suggested that loss of consciousness, rather than any specific neurotransmitter action, may produce protection from opioid rigidity.[18] However, there are no objective data to support this theory, and, in fact, animal data tend to refute it. Drugs with minimal sedative properties have significant ameliorating effects on opioid rigidity.[20] In addition, the two patients described here who received midazolam 5 mg 5 minutes before alfentanil were deeply anesthetized yet still became quite rigid. All the patients appeared to be asleep after alfentanil, independent of the magnitude of their rigidity.

Although diazepam and midazolam appeared to provide the most protection against opioid-induced rigidity, some patients in both groups manifested significant rigidity. These findings confirm that the "ideal" preinduction drug, which would provide complete protection from rigidity without side effects, is still lacking. However, recent work using rodent models of opioid rigidity have identified a new class of drugs that might prove efficacious in preventing opioid rigidity in humans. The selective alpha-2-adrenoceptor agonist dexmedetomidine profoundly antagonizes opioid rigidity in rats[33,34] via a central adrenoreceptor-mediated effect.[34–36] Dexmedetomidine is a potent anesthetic[37] in its own right, producing significant analgesia, sedation, and bradycardia with minimal respiratory depression.*,[37] The possibility that the combination of potent alpha-2 agonists and opioids will produce an intense anesthetic and analgesic state accompanied by muscle flaccidity instead of rigidity may represent an important advance in anesthesiology.

There appear to be a number of interesting pathways for future clinical and laboratory research in this area. One approach might be the use of selected combinations of pretreatment drugs. It is hoped that such combinations will both improve protection from rigidity and minimize cardiovascular side effects. In addition, it is apparent that a more complete knowledge of the neurochemical pathways of opioid rigidity is necessary to guide future efforts.

In summary, small doses of the nondepolarizing muscle relaxants atracurium and metocurine failed to attenuate alfentanil-induced rigidity. The barbiturate thiopental provided protection against truncal but not extremity rigidity. The benzodiazepines diazepam and midazolam were the most effective pretreatment drugs studied. For the present, benzodiazepine pretreatment may be the best clinical option for ameliorating opioid-induced rigidity in humans.

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