■ CLINICAL INVESTIGATIONS

Fentanyl-induced Rigidity and Unconsciousness in Human Volunteers

Incidence, Duration, and Plasma Concentrations

James B. Streisand, M.D.,* Peter L. Bailey, M.D.,* Leon LeMaire, M.D.,† Michael A. Ashburn, M.D.,‡ Stephen D. Tarver, M.D.,§ John Varvel, M.D.,¶ Theodore H. Stanley, M.D.**

Background: Muscle rigidity frequently accompanies induction of anesthesia with opioids. The authors sought to determine whether unconsciousness and amnesia occur when humans develop rigidity and apnea after intravenous fentanyl (without other concomitant anesthetics).

Methods: The incidence and duration of rigidity and level of consciousness were evaluated and associated plasma concentrations of fentanyl were measured in 12 healthy adult male volunteers given only intravenous fentanyl. Fentanyl was infused at a rate of 150 μg/min until a total of 15 μg/kg had been administered. Arterial blood samples for fentanyl assay were drawn and responsiveness, heart rate (HR), and systolic and diastolic arterial blood pressures were determined at frequent intervals during and after infusion. If rigidity was accompanied by an Sp_{O_2} < 90%, positive pressure ventilation with 100% O_2 with a mask was instituted until spontaneous ventilation resumed.

Results: The incidence of muscular rigidity was 50% (6/12). All subjects who developed rigidity were apneic, unresponsive, and had no recall of commands to breathe or of positive pressure ventilation. Subjects not developing rigidity remained awake and responsive. No subject developing rigidity required neuromuscular blockade to allow positive pressure ventilation

and adequate oxygenation (Sp_{O_2} > 90%). When rigidity occurred, it started 3 ± 0.9 (range 1–4) min after the peak plasma fentanyl concentration and lasted for 11.5 ± 5.8 (range 7–23) min. Rigidity started at a plasma fentanyl concentration of 21.5 ± 4.4 (range 16–28) ng/ml and ended at 6.9 ± 1.5 (range 5.2–8.7) ng/ml. Baseline HR was less in the subjects who subsequently developed rigidity (56.7 ± 7.8 *vs.* 67.2 ± 7.8, P = 0.04). No differences in fentanyl plasma concentrations or predicted effect site concentrations for rigidity were detected between subjects who developed rigidity and those who did not.

Conclusions: These findings support the hypothesis that unconsciousness occurs in the unstimulated subject during fentanyl-induced apnea and rigidity. (Key words: Anesthetics, intravenous: fentanyl. Central nervous system: unconsciousness. Complications: rigidity.)

* Associate Professor of Anesthesiology, University of Utah.

† Visiting Research Fellow, University of Utah.

‡ Assistant Professor of Anesthesiology, University of Utah.

§ Research Fellow, University of Utah.

¶ Staff Anesthesiologist, St. Elizabeth Community Health Center, Lincoln, Nebraska.

** Professor of Anesthesiology, University of Utah

THE development of muscle rigidity frequently accompanies induction of anesthesia with opioids.[1,2] When muscle rigidity occurs, neuromuscular blocking agents are usually administered to permit controlled ventilation and the continuation of anesthesia.[3] Because muscle relaxation impairs somatic signs of inadequate anesthesia, the patient's level of consciousness is difficult to assess. This is of particular concern when opioids are the sole anesthetic because of the possibility that rigidity occurs before loss of consciousness[4] or that opioids do not reliably produce unconsciousness.[5] Therefore, clinicians frequently administer a sedative-hypnotic to ensure unconsciousness after anesthetic induction with high doses of opioids. Unfortunately, many sedative-hypnotic and amnestic agents may compromise the hemodynamic stability sought with opioid-based techniques.[2,6,7]

In this study, we observed whether unconsciousness accompanies opioid-induced rigidity in human volunteers receiving only intravenous fentanyl. In addition, we noted the incidence and duration of rigidity and its relationship with arterial plasma concentrations and predicted effect-site concentrations of fentanyl.

Methods

Approval for the study was obtained from the Human Institutional Review Board of the University of Utah Health Sciences Center and informed oral and written consent was obtained from 12 healthy adult male volunteers. The data reported here were obtained when determining the intravenous fentanyl kinetics of subjects participating in a study establishing the bioavailability of Oral Transmucosal Fentanyl Citrate.[8] Subjects were nonsmokers, 23–31 yr of age, who weighed within 15% of ideal body weight (height and weight tables, Metropolitan Life, Inc.); they had no history of drug or ethanol abuse and were not taking any pain medications.

All subjects fasted overnight before the study session. An 18-G catheter was inserted into a peripheral vein for fentanyl infusion and maintenance fluid administration (lactated Ringer's solution at the rate of 1.5 ml·kg^{-1}·h^{-1}) and a 20-G catheter was inserted into the radial artery for blood sampling. An automatic noninvasive blood pressure cuff (Dinamap®), an ECG (Tektronix®), and a finger pulse oximeter (Nellcor®) were placed on each subject.

While administering supplemental oxygen *via* nasal cannula (3 L/min), intravenous fentanyl was infused at a rate of 150 μg/min until 15 μg/kg had been given (6–8 min, depending on the weight of each subject). Arterial samples (4 ml) for fentanyl assay were drawn at baseline, every 2 min during the infusion, and at 1, 2, 3, 4, 6, 8, 10, 15, 30, 45, and 60 min, and then every 2 h for 24 h after infusion. All blood samples were injected into preheparinized glass tubes and immediately placed on ice. Plasma was separated from red cells with a refrigerated centrifuge, placed in polypropylene tubes, and frozen at −20° C until analyzed for fentanyl. Plasma concentrations of fentanyl were determined by radioimmunoassay using the modified technique described by Schüttler and White.[9] The assay was sensitive to 0.2 ng/ml with a coefficient of variation of 10% at 0.2 ng/ml, 4% at 0.8 ng/ml, and 2% at 1.7 ng/ml.

A subject was considered to have developed rigidity if all of the following postural changes developed after fentanyl administration: flexion of the upper extremities, extension of the lower extremities, flexion of the head with rigidity of the neck musculature, increased abdominal wall tone, and decreased chest wall compliance associated with positive pressure ventilation.

Each subject's hemoglobin oxygen saturation was monitored continuously with a finger pulse oximeter (Sp$_{O_2}$). Respiratory rate (by visual inspection), systolic and diastolic arterial blood pressures, and heart rate (HR) were measured and recorded at baseline and just before obtaining each arterial blood sample. If spontaneous ventilation became inadequate (SpO$_2$ < 90% or respirations < 8 breaths/min), subjects were encouraged by verbal command to take a deep breath. If subjects did not respond to command and apnea (no respiratory effort for 15 s) or rigidity occurred, positive pressure ventilation with oxygen via bag and mask was instituted until spontaneous ventilation resumed.

The subjects were considered unconscious if they could not respond to the commands: "open your eyes," "squeeze my hand," and "how do you feel?" The presence and duration of rigidity and lack of responsiveness (unconsciousness) were documented every minute during and after fentanyl administration until spontaneous ventilation and responsiveness returned. When subjects were awake and alert, they were questioned regarding recall of commands to breathe, positive pressure ventilation and rigidity.

Pharmacokinetic and Pharmacodynamic Analysis

Each subject's fentanyl concentration versus time profile following intravenous administration of fentanyl was fit to a triexponential equation using an extended least squares nonlinear regression program, MAKEMODL.†† The data points were weighted by the reciprocal of the square of the predicted plasma concentrations. The parameters from this fit were then used in portions of the pharmacodynamic modeling described below.

The peak and time of occurrence of peak plasma fentanyl concentration (C$_{MAX}$ and T$_{MAX}$, respectively) were noted from the individual plasma fentanyl concentration versus time curves.

For each subject who developed rigidity after receiving the fentanyl infusion, there is an observed time of onset of rigidity and an observed time when the rigidity subsides. Under the assumption that fentanyl-induced rigidity is the result of the action of fentanyl at some site within the body (effect site), we may deduce that the fentanyl concentration at the effect site at the onset

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†† MAKEMODL is an extended least-squares nonlinear regression and modeling program for the IBM PC/PS2® and compatibles. It was created by N. Holford and is distributed by Biosoft, Milltown, New Jersey.

of rigidity should be equal to the effect site concentration when rigidity subsides. A computer program was written by one of the authors (JRV) to determine the unique value for K_{eo}, for each of the rigid subjects, satisfying this condition. K_{eo} is a first-order rate constant that characterizes the rate of equilibration between the blood and effect site. The half-time for this equilibration, $t_{1/2}K_{eo}$, is $0.693/K_{eo}$. Using the pharmacokinetic parameters determined by the triexponential fit (see above) and a value for K_{eo}, fentanyl concentrations at the effect site were calculated. This pharmacokinetic-pharmacodynamic modeling has been described in detail by Holford and Sheiner.[10]

Peak effect site fentanyl concentrations as well as the effect site concentrations at which rigidity occurred were calculated for each of the subjects who developed rigidity. Peak effect site concentrations were calculated for each of the nonrigid subjects using the average K_{eo} from the rigid subjects.

Statistical comparisons were made between rigid and nonrigid groups using an unpaired t test. Significance was reached if $P < 0.05$. Unless otherwise stated, results are presented as mean values ± standard deviations.

Results

The incidence of fentanyl-induced muscular rigidity was 50% (6/12). All subjects who developed rigidity were apneic, unresponsive to commands and lacked recall of positive pressure ventilation or rigidity. Conversely, subjects who did not develop rigidity remained conscious and responded to commands throughout the study session. Rigidity subsided just prior to the return of consciousness in all subjects. Although all volunteers developing rigidity needed positive pressure ventilation, none required neuromuscular blockade to maintain $SpO_2 > 90\%$. All of the subjects who didn't develop rigidity required only verbal prompts to breathe (usually at the end of the fentanyl infusion) to prevent apnea and oxygen desaturation.

Figure 1 compares the mean HR of the subjects who developed rigidity and those subjects who did not. Baseline HR of the subjects who subsequently developed rigidity were statistically less than the baseline HR of subjects without rigidity (56.7 ± 7.8 versus 67.2 ± 7.8, $P = 0.04$). Given this initial difference, there were no differences between groups in HR over time. No differences were detected between groups in base-
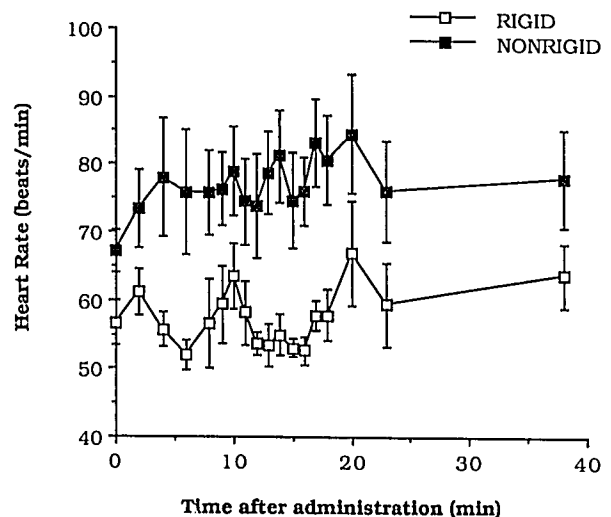

Fig. 1. Heart rate (mean ± SD) before and after administration of fentanyl, 15 μg/kg. The baseline HR of subjects developing rigidity was statistically less than the baseline HR ($P = 0.04$) of subjects who did not.

line systolic (131 ± 7 vs. 136 ± 8 mmHg) or diastolic (74 ± 7 vs. 73 ± 9 mmHg) blood pressures. Furthermore, there were no significant changes from baseline in HR or systolic arterial or diastolic arterial blood pressures after fentanyl infusion in both groups.

Individual plasma fentanyl concentration versus time curves for the six subjects developing rigidity are illustrated in figure 2. Rigidity started 3 ± 0.9 (range 1–4) min after C_{MAX} and lasted for 11.5 ± 5.8 (range 7–23) min. Rigidity started at a plasma fentanyl concentration of 21.5 ± 4.4 (range 16–28) ng/ml and ended at 6.9 ± 1.5 (range 5.2–8.7) ng/ml, 20.8 ± 6.0 (range 16–32) min after the start of the fentanyl infusion.

Table 1 shows the pharmacokinetic and pharmacodynamic values for the individual subjects. The table is divided into the group who became rigid and the group who did not become rigid after the fentanyl infusion. There was no difference in C_{MAX} or T_{MAX} in the subjects who developed rigidity and subjects who did not develop rigidity (35.2 ± 4.4 vs. 32.2 ± 6.6 ng/ml and 6.3 ± 0.8 vs. 6.0 ± 1.3, respectively). The combined pharmacokinetic–pharmacodynamic model for the rigidity effect site yielded an average K_{eo} of 0.054 ± 0.016 1/min and a $t_{1/2}K_{eo}$ of 12.8 ± 3.7 min. The peak rigidity effect-site fentanyl concentration in the subjects developing it was equal to that of the subjects in whom rigidity did not develop (10.4 ± 1.4 vs. 10.4 ± 1.6 ng/ml).
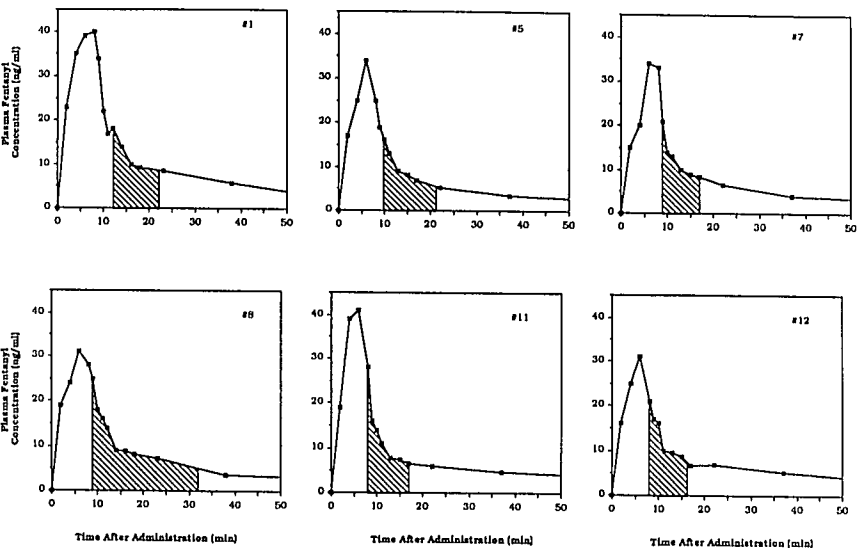
Fig. 2. Plasma fentanyl concentration *versus* time curves for the six subjects who developed rigidity after the fentanyl infusion (15 μg/kg). The cross-hatched areas show the onset and duration of rigidity episodes.

Discussion

Increases in muscle tone and rigidity occur frequently during induction of anesthesia with large doses of fentanyl, sufentanil, and alfentanil. Controversy exists regarding the ability of opioids to produce unconsciousness. In this study, unconsciousness occurred simultaneously with opioid-induced rigidity. All subjects who lost consciousness (lack of responsiveness and recall) did so in association with rigidity. Those subjects who did not become rigid remained awake and responsive during the entire study.

Only a few studies have evaluated the effect of opioids on rigidity and consciousness in humans receiving no other adjuvant medications. Even detailed studies designed to evaluate opioid-induced rigidity employed amnestic drugs that confound the interpretation of observed effects.[11] For example, while Benthuysen et al. did report that unconsciousness and unresponsiveness occurred with alfentanil-induced rigidity, it is not clear to what extent lorazepam, given the night before the study, contributed to this finding.[11] Furthermore, in previous studies, the assessment of unconsciousness

Table 1. Pharmacokinetic and Pharmacodynamic Characteristics of Fentanyl in Adult Male Volunteers

Subjects	C_{MAX} (ng/ml)	T_{MAX} (min)	C_{E-MAX} (min)	$C_{E-RIGID}$ (ng/ml)	K_{eo} (L/min)
Rigid					
1	31	8	11.0	10.7	0.038
5	41	6	8.6	8.1	0.044
7	31	6	11.7	10.9	0.071
8	34	6	9.3	7.9	0.043
11	34	6	11.7	10.7	0.054
12	40	6	10.2	9.6	0.076
Mean ± SD	35.2 ± 4.4	6.3 ± 0.8	10.4 ± 1.3	9.7 ± 0.6	0.054 ± 0.016
Nonrigid					
2	39	6	11.2	ND	ND
3	34	6	11.5	ND	ND
4	36	6	9.4	ND	ND
6	25	4	8.4	ND	ND
9	36	8	12.5	ND	ND
10	23	6	9.4	ND	ND
Mean ± SD	32.2 ± 6.6	6.0 ± 1.3	10.4 ± 1.6	ND	ND

C_{MAX} = peak plasma concentration; T_{MAX} = time of occurrence of C_{MAX}; C_{E-MAX} = peak effect site concentration; $C_{E-RIGID}$ = effect site concentration at rigidity; K_{eo} = equilibration rate between plasma and effect site; ND = not done.

during rigidity was particularly difficult because patients were questioned about recall hours later, after other anesthetic agents had been administered and their anesthetic completed.[3,12]

Other investigators suggest that rigidity can occur without loss of consciousness. Freund administered iv morphine, 2 mg/kg, to nine volunteers and demonstrated that, although consciousness was not lost, abdominal muscle activity was increased.[13] Grell et al. reported that, after an average of 7.3 µg/kg of fentanyl, 11 of 12 patients developed rigidity that neither produced unconsciousness nor impaired spontaneous ventilation (however, in one patient in whom rigidity was associated with apnea, unconsciousness did occur).[14] Waller et al. found that patients could open their eyes to command and initiate a breath despite the presence of chest wall rigidity during anesthetic induction with fentanyl.[4] In the studies of both Grell et al. and Waller et al., fentanyl was administered at slower rates than in our study (30 and 50 µg/min vs. 150 µg/min) and chest wall rigidity occurred at lower doses (7.3 and 8 µg/kg vs. 15 µg/kg). It appears that a mild form of rigidity (e.g., decreased chest wall compliance) can be detected with maintenance of consciousness and spontaneous ventilation. In contrast, in our investigation, rigidity included marked flexion of the upper extremities, extension of the lower extremities, flexion of the chin onto the chest with stiff neck musculature, and reduced chest wall compliance.

The $T_{1/2}k_{eo}$ from our study, 12.8 min, was twice that determined by Scott et al., who used EEG slowing to measure fentanyl effect. This shows that, with respect to fentanyl, the effect site for rigidity equilibrates with the plasma more slowly than does the effect site for EEG slowing. Because the EEG reflects neuronal activity in the cerebral cortex, our findings are consistent with animal models that suggest that rigidity is not a cerebral cortical event.[15]

This is the first study to demonstrate that fentanyl-induced unconsciousness and rigidity is a self-limited phenomenon. The onset of rigidity occurred an average of 3 min after peak fentanyl plasma concentrations. This is consistent with the 5-min lag between fentanyl concentrations and CNS effect on EEG spectral edge.[16] Although the rates of administration were similar (150 µg/min) in this study and that of Scott et al., we administered nearly twice as much fentanyl as did Scott et al.; thus, the explanation for the more rapid onset of effect and shorter lag time, despite the longer $T_{1/2}k_{eo}$ that we determined for rigidity effect. Rigidity in our subjects lasted an average of 11.5 min, but persisted up to 23 min in one subject. Redistribution of fentanyl out of the brain with accompanying lower plasma concentrations of fentanyl probably accounted for the termination of rigidity.

It is interesting that fentanyl, 15 µg/kg, given at a rate of 150 µg/min produced rigidity in exactly one-half of the subjects. Why some subjects developed rigidity while others did not, despite similar fentanyl dosing regimens and resultant plasma and effect site concentrations, is unclear. Subjects with rigidity had lower initial HR than did nonrigid subjects. One could speculate that subjects with higher vagal tone (or less sympathetic tone) are pharmacodynamically more sensitive to opioid-induced effects, such as muscle rigidity.

Our study could be criticized for the lack of quantitation of muscle rigidity (such as with electromyography). However, anesthesiologists who are quite familiar with this phenomenon carefully observed, at all times, the subjects who developed rigidity. In addition, although hemoglobin oxygen saturation was maintained at greater than 90% in all subjects, P_{CO_2} was not controlled. The conceivable differences in hypercarbia between volunteers may have influenced fentanyl ionization and cerebral blood flow; thus, the transport of fentanyl into the brain and incidence and duration of rigidity. Finally, all of the clinical signs of rigidity developed over approximately 1 min, rather than all at once. Also, the rigid state subsided over approximately 1 min. Thus, the accuracy of the K_{eo} determination is somewhat flawed by the inability to cleanly define the onset and offset of rigidity.

In summary, we found that fentanyl, 15 µg/kg, administered at a rate of 150 µg/kg, resulted in rigidity, apnea, and unconsciousness in 50% of our young adult volunteer subjects. The onset of rigidity and unconsciousness was associated with plasma fentanyl concentrations consistent with drug action.[17] The duration of rigidity was self-limited and probably due to drug redistribution and decreased plasma fentanyl concentrations. No subject recalled commands or positive pressure ventilation during rigidity episodes. Although a more extensive study would be required for unequivocal conclusions, we hypothesize that opioid-induced rigidity associated with apnea indicates unconsciousness.

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