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Fentanyl-induced Muscle Rigidity in Unanesthetized and Ketamine- or Thiopental-anesthetized Rats

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This study was undertaken to search for an alternative experimental model in the evaluation of fentanyl-induced muscle rigidity. Unanesthetized, spontaneously ventilating Sprague-Dawley rats, and rats anesthetized with either ketamine or thiopental whose ventilation was mechanically controlled, were studied. Intravenous administration of fentanyl (25, 50, or 100 μg/kg) caused an increase in electromyographic (EMG) activity in both unanesthetized and ketamine-anesthetized, but not in thiopental-anesthetized, animals. Muscle rigidity was more prominently manifested in the gastrocnemius muscle, when compared with the rectus abdominis muscle. Hypoxemia was exhibited during the course of rigidity by both spontaneously ventilating and ketamine-anesthetized rats, but not by thiopental-anesthetized animals. In addition, unanesthetized, spontaneously ventilating rats developed hypercarbia and respiratory acidosis. The authors suggest that, in addition to using unanesthetized animals, EMG activity in the gastrocnemius muscle of rats anesthetized with ketamine in whom ventilation is controlled may provide an alternative approach in the evaluation of fentanyl-induced muscle rigidity. (Key words: Analgesics: fentanyl. Anesthetics, intravenous: ketamine; thiopental. Complications, fentanyl: rigidity. Measurement techniques: electromyography. Muscle: rigidity.)

HIGH DOSES OF POTENT opioids, including fentanyl[1,2] and alfentanil,[3] are frequently administered in clinical practice. This anesthetic technique provides good analgesia and stable hemodynamic responses. Unfortunately, it is also commonly accompanied by muscle rigidity, especially during the induction of anesthesia.[2,4,5] This opiate-induced rigidity may in turn be associated with decrease in chest wall compliance,[6] increase in intracranial pressure secondary to elevation in central venous pressure,[7,8] and possible respiratory and acid-base disturbances.[4]

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The precise mechanism(s) that underlies opiate-induced muscle rigidity has yet to be completely elucidated. This may be due in part to the lack of a suitable animal preparation for its evaluation. A frequently employed approach,[9–15] first reported by Wand *et al.*,[9] uses the electromyographic (EMG) activity in unanesthetized, spontaneously ventilating animals as the experimental model. Inherent in this approach are possible confounding factors of hypoventilation, hypoxemia, hypercarbia, and bradycardia, all of which are commonly associated with high doses of opiates.[1,4,16] A possible solution is to control respiration during the experiment. However, an anesthetic state must be induced in the animal before ventilation can be controlled. Unfortunately, many anesthetics, such as barbiturates[7,17,18] and benzodiazepines,[19] are reported to attenuate opiate-induced rigidity.

The purpose of this study was to search for an alternative approach in the evaluation of fentanyl-induced muscle rigidity. We suggest that a combination of the advantages from both above mentioned methods may result in an acceptable experimental preparation. Using EMG activity in unanesthetized, spontaneously ventilating rats and animals anesthetized with either ketamine or thiopental whose ventilation was controlled, we thus sought answers to four basic questions. First, is rigidity related to the state of consciousness? Second, will different anesthetic agents influence rigidity differently? Third, is rigidity equally expressed in both extremity and trunk muscles? Fourth, what are the alterations in hemodynamic and blood gas parameters that may accompany fentanyl-induced muscle rigidity during consciousness and anesthesia?

Materials and Methods

SUBJECTS

Sixty-nine adult, male Sprague-Dawley rats (220–300 g) were used. They were housed three per cage with free access to food and water, and were maintained on a 12: 12 h light-dark schedule in a temperature-controlled room (23 ± 1° C). All procedures described below were carried out in accordance with institutional guidelines.

SURGICAL PREPARATIONS

Unanesthetized Rats. During pentobarbital sodium (40 mg/kg, ip) anesthesia, an arterial cannula (Clay Adams,

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PE-50) was inserted into the right femoral artery for systemic arterial pressure measurement and blood sampling. The right femoral vein was also cannulated for the injection of drugs. Both catheters were guided percutaneously to the neck of the animal, where they were filled with heparinized saline (100 U/ml) and sealed with metal plugs.

A pair of platinum needle electrodes (Grass, Type E2) was inserted intramuscularly into the bilateral rectus abdominis and left gastrocnemius muscles, respectively, and was secured to the skin of the animal by sutures and micropore tape. The distance between each pair of electrodes was about 0.5–1.0 cm. Procaine penicillin (30,000 U, im) was given at the end of surgery. Each animal was thereafter housed individually. At least 3 days were allowed for recovery before the commencement of the experimental session.

Anesthetized Rats. Animals were anesthetized with either ketamine (100–120 mg/kg, ip) or thiopental sodium (50 mg/kg, ip). The right femoral artery and vein were cannulated with heparinized saline-filled catheters (Clay Adams, PE-50). A pair of platinum needle electrodes was inserted intramuscularly into the bilateral rectus abdominis and left gastrocnemius muscles, respectively, for EMG recording.

The lungs were ventilated with ambient air *via* a tracheostomy, using a rodent ventilator (Harvard, 683). The end-tidal CO_2 was monitored with a Capnometer (Datex) and maintained between 4.0–5.0%. This corresponds to a Pa_{CO_2} of 35–45 mmHg as obtained by blood gas analysis. The rectal temperature of the animal was maintained at $37 \pm 0.5°$ C using a heating lamp. Supplemental ketamine (5 mg/kg, iv) or thiopental (2 mg/kg, iv) was administered whenever movement of the head, extremity, or tail was observed, to maintain the animal in an anesthetized state.

EMG, Systemic Arterial Pressure, and Heart Rate Recording

Raw EMG signals were bipolarly recorded from the gastrocnemius and rectus abdominis muscles and were differentially amplified by a Grass 7P3 preamplifier (bandpass: DC-3 Hz). They were also summated and integrated every 10 s, using an integrator preamplifier (Grass, 7P10). Systemic arterial pressure was measured from the cannulated femoral artery *via* a Statham pressure transducer (P23ID). Heart rate was determined by a biotachometer (Grass, 7P4) triggered by the arterial pulses.

Blood Gas Analysis

Arterial blood samples (0.25 ml) were obtained 5 min before fentanyl injection, and 5, 10, and 15 min thereafter. Blood withdrawn was replaced with an equal volume of saline to avoid hypovolemia. Pa_{O_2}, Pa_{CO_2}, *p*H, and base excess were measured using a Radiometer machine (Copenhagen, ABL 300), which was routinely calibrated daily.

Experimental Protocols

All recording session took place in a quiet room with minimal physical disturbance. The unanesthetized, spontaneously ventilating rats were placed in a cyclindrical cage that permitted restricted but unrestrained movement. The anesthetized animals remained unrestrained in a prone position.

Raw and integrated EMG signals from the gastrocnemius and rectus abdominis muscles, systemic arterial pressure, heart rate, and end-tidal CO_2 concentration (anesthetized animals only) were continuously displayed on a multi-channel Grass 7D polygraph. The effects of intravenously administered fentanyl, delivered over 15 s, on these parameters were observed for 15 min. Correct placements of EMG electrodes were verified by necropsy immediately after each experiment.

An equal volume of venous blood (0.2 ml) was slowly withdrawn prior to fentanyl injection to avoid hypervolemia. Vehicle control groups received an equal amount of saline. To avoid the confounding actions of multiple dosing and tachyphylaxis, each animal received only a single injection of fentanyl or saline.

Drugs

Drugs used in this study included fentanyl citrate (Janssen), ketamine HCl (Parke-Davis), and thiopental sodium (Lilly).

Statistics

The EMG activity from each experiment was first quantified by averaging the integrated signals recorded over each 5-min interval (30 datum points) during the observation period. These averaged values were further normalized to a percent of predrug control to compensate for interanimal variations. The effects of fentanyl or vehicle on these EMG signals from the gastrocnemius and rectus abdominis muscles, mean arterial pressure, heart rate, Pa_{O_2}, Pa_{CO_2}, *p*H, and base excess were statistically assessed using analysis of variance (ANOVA) with repeated measurements. This was followed by the Student-Newman-Keuls multiple range test for *a posteriori* analysis of individual means (fentanyl *versus* vehicle, high *versus* low dose of fentanyl) at 5, 10, and 15 min postinjection. A P value < 0.05 was taken to be statistically significant.

Results

Effects of Fentanyl in Unanesthetized Rats

Intravenous administration of fentanyl (25 μg/kg) was followed by a sustained and dramatic increase in EMG

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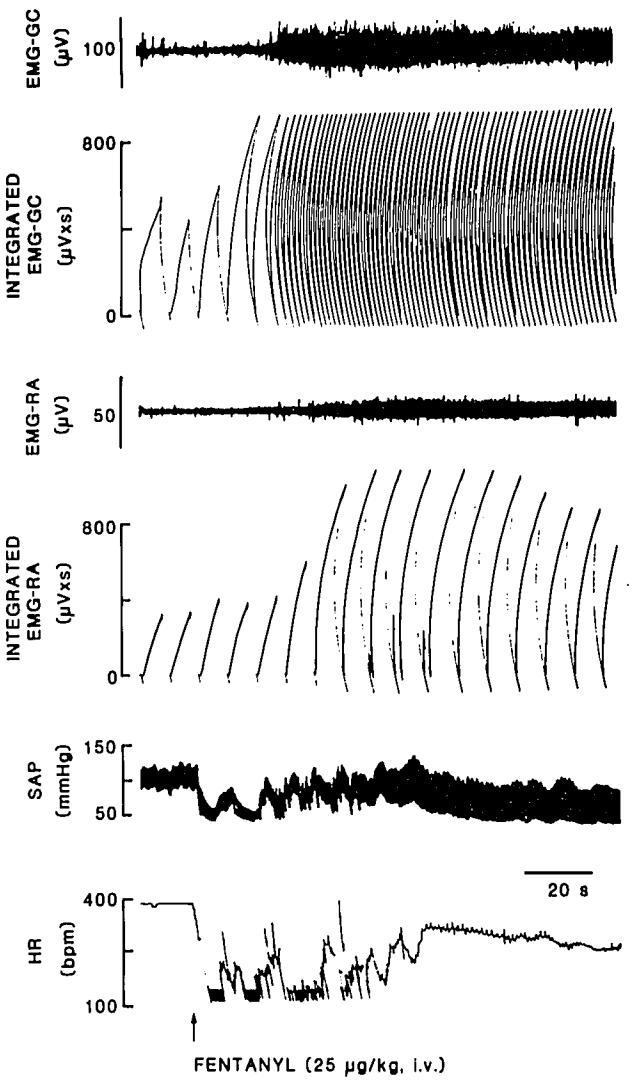

FIG. 1. Representative data from a single animal demonstrating the effects of fentanyl (25 μg/kg, iv) on electromyographic (EMG) activity of left gastrocnemius (GC) and rectus abdominis (RA) muscles, systemic arterial pressure (SAP), and heart rate (HR) in unanesthetized, spontaneously ventilating rats. The raw EMG signals were summated and integrated over 10 s for quantitative analysis.

activity from the gastrocnemius muscle (figs. 1, 2). The onset of muscle rigidity (fig. 1), defined as the time taken (from the end of injection) for the EMG signal to increase by at least 100% over the control, was almost immediate, and the peak effect occurred between 1–2 min thereafter. The enhanced activity from the rectus abdominis muscle, on the other hand, was rather transient in duration (fig. 1) and mild in intensity (fig. 2).

Accompanying the increased muscle activity were severe and prolonged hypotension and bradycardia (fig. 2), which began immediately (fig. 1) following the administration of fentanyl. There was also an apneic period that lasted 15–35 s, followed by 2–3 min of severe hypoventilation. Arterial blood gas analysis (table 1) documented the occurrence of respiratory acidosis with hypoxemia and hypercarbia.

It should be mentioned that a higher dose of fentanyl (50 μg/kg, iv) was administered in five unanesthetized, spontaneously ventilating animals. They were excluded from statistical analysis, since all of them succumbed to the abovementioned detrimental respiratory, hemodynamic, and acid-base variables, which were further intensified.

Effects of Fentanyl in Rats Anesthetized with Ketamine

Two intravenous doses (50 and 100 μg/kg) of fentanyl were used in this series. A significant ($P < 0.05$) and persistent increase in EMG activity from the gastrocnemius muscle was noted 30–60 s after the administration of fentanyl (figs. 3, 4), in a dose-dependent manner. There was,

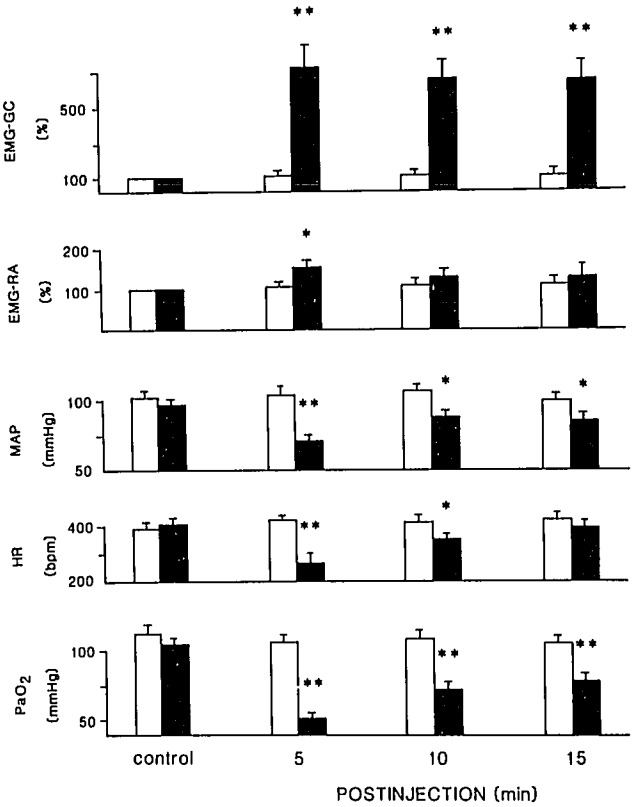

FIG. 2. Effects of intravenous administration of fentanyl (25 μg/kg, filled bar) and saline (open bar) on electromyographic (EMG) activity of left gastrocnemius and rectus abdominis muscles, mean arterial pressure (MAP), heart rate (HR), and Pa_{O_2} in unanesthetized, spontaneously ventilating rats. Values are mean ± SEM (n = 5 in each group). *$P < 0.01$, **$P < 0.005$ *versus* saline in the Student-Newman-Keuls analysis.

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TABLE 1. Arterial Blood Gas Parameters following Intravenous Administration of 25 μg/kg of Fentanyl (A) and Saline (B) in Conscious Rats. Controls were Obtained 5 Min before Fentanyl/Saline.

		Control	Postinjection		
			5 Min	10 Min	15 Min
*p*H	A	7.307 ± 0.012	7.271 ± 0.015†	7.313 ± 0.012*	7.359 ± 0.013
	B	7.410 ± 0.014	7.396 ± 0.021	7.370 ± 0.017	7.391 ± 0.021
Pa_{O_2}	A	104 ± 2	51 ± 3†	71 ± 3†	78 ± 3†
	B	112 ± 3	107 ± 3	108 ± 3	105 ± 2
Pa_{CO_2}	A	39.3 ± 0.8	57.7 ± 1.8†	48.1 ± 2.3†	44.0 ± 2.1
	B	38.8 ± 1.3	40.2 ± 1.2	40.4 ± 1.5	38.6 ± 1.6
BE	A	0.6 ± 0.4	−2.4 ± 0.5*	−3.8 ± 0.4†	−2.1 ± 0.3†
	B	0.7 ± 0.4	0.3 ± 0.1	−0.1 ± 0.4	−0.4 ± 0.3

All values are mean ± SEM (n = 5 in each group).

* $P < 0.01$, † $P < 0.005$ *vs.* saline in the Student-Newman-Keuls analysis.

on the other hand, no apparent alteration in the electric activity of the rectus abdominis muscle (figs. 3, 4). Hypotension and bradycardia were seen immediately after the injection of fentanyl. Blood gas analysis (table 2) indicated that both arterial Pa_{CO_2} and *p*H were within normal ranges. The animals did manifest hypoxemia during the course of fentanyl-induced muscle rigidity (fig. 4), even when ventilation was controlled.

EFFECTS OF FENTANYL IN RATS ANESTHETIZED WITH THIOPENTAL

Not only did both doses of fentanyl (50 and 100 μg/kg, iv) fail to cause an increase in EMG activity from the gastrocnemius and rectus abdominis muscles, there was in fact a significant ($P < 0.05$) decrease in the activity of the former muscle (fig. 5) at the higher dose. A reduction in systemic arterial pressure and heart rate still occurred, with no apparent alterations in any respiratory or acid-base parameter (table 3).

Discussion

The present study revealed that intravenous administration of fentanyl promoted an increase in EMG activity in both unanesthetized, spontaneously ventilating rats and rats anesthetized with ketamine. Furthermore, this correlate of opiate-induced muscle rigidity was preferentially manifested by the gastrocnemius muscle, when compared to the rectus abdominis muscle. Both groups of animals exhibited hypoxemia during the course of rigidity. The former, in addition, manifested respiratory acidosis and hypercarbia. Fentanyl did not, on the other hand, evoke

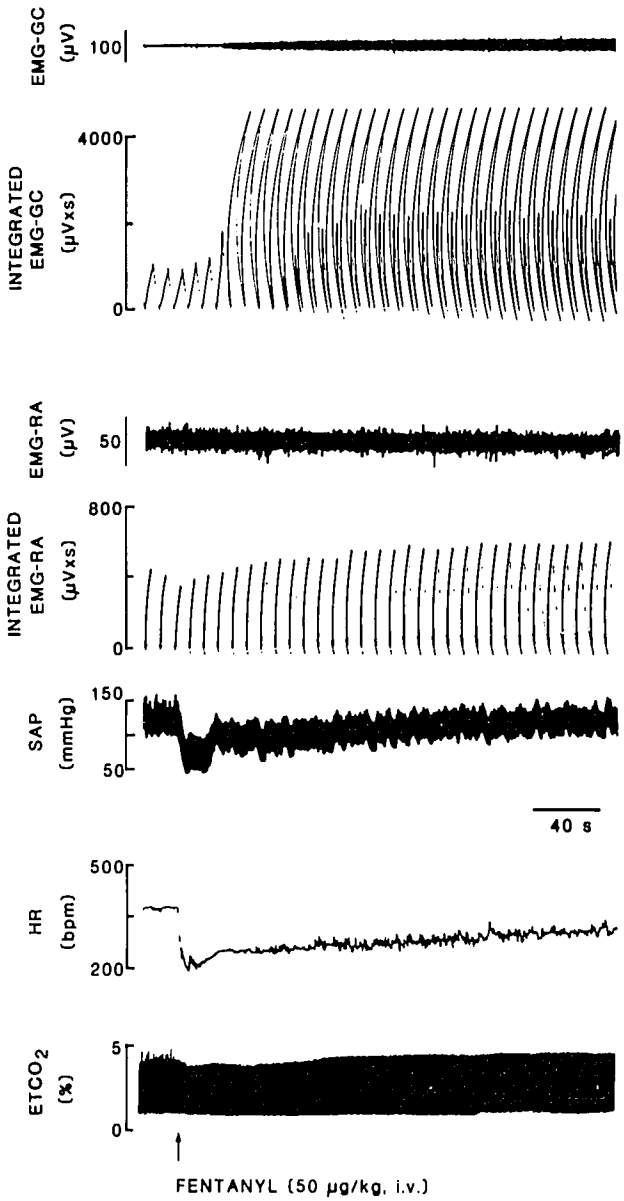

FIG. 3. Representative data from a single animal demonstrating the effects of fentanyl (50 μg/kg, iv) on electromyographic (EMG) activity of left gastrocnemius (GC) and rectus abdominis (RA) muscles, systemic arterial pressure (SAP), heart rate (HR), and end-tidal CO_2 ($ETCO_2$) in rats anesthetized with ketamine and whose lungs were mechanically ventilated.

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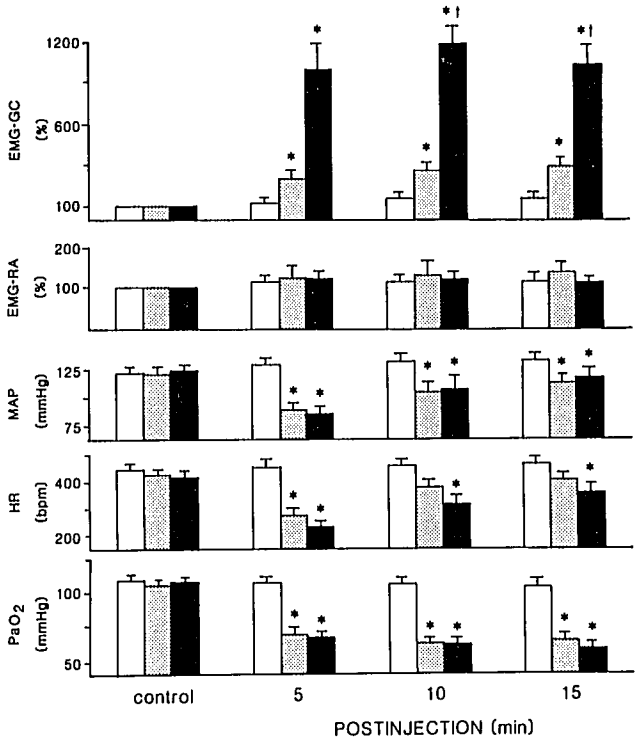

FIG. 4. Effects of intravenous administration of fentanyl at 50 (stippled bar) and 100 (filled bar) μg/kg, and saline (open bar) on electromyographic (EMG) activity of left gastrocnemius (GC) and rectus abdominis (RA) muscles, mean arterial pressure (MAP), heart rate (HR), and Pa_{O_2} in rats anesthetized with ketamine and whose lungs were mechanically ventilated. Values are mean ± SEM (n = 10 in each group). *$P < 0.01$ *versus* saline and †$P < 0.01$ *versus* 50 μg/kg of fentanyl in the Student-Newman-Keuls analysis.

any apparent EMG activation, nor alterations in Pa_{O_2}, Pa_{CO_2}, *p*H, and base excess in rats anesthetized with thiopental.

Within the limits of comparing the effects of two similar opioids in different species, our data from unanesthetized, spontaneously ventilating rats are in partial agreement with the observations by Benthuysen *et al.*[7] These authors reported that alfentanil induces in their patients marked rigidity in eight muscle groups, including the gastrocnemius and rectus abdominis muscles. Also present in their subjects were respiratory acidosis, hypoxemia, hypercarbia, and hypotension. Our results are also compatible with those from the report by Comstock *et al.*,[4] who showed that truncal rigidity and hypercarbia (Pa_{CO_2} = 52.1 ± 1.8 mmHg) were induced in 20 out of 21 patients following high-dose fentanyl (19 ± 1.9 μg/kg, iv) induction of anesthesia.

Ketamine is unique in producing an unusual trance-like state known as dissociative anesthesia.[20,21] Similar to unanesthetized rats, we observed that animals anesthetized with this agent responded to fentanyl with an increase in EMG activity, but, presumably because ventilation was controlled, failed to exhibit hypercarbia and acidosis. It might be argued that the muscular hypertonus inherent in ketamine anesthesia[20] could be a confounding factor. That this may not be the case is amply suggested by the profound enhancement in EMG activity, as opposed to the vehicle control, promoted by fentanyl. Nonetheless, an increase in oxygen consumption secondary to these heightened muscular activity may account for the hypoxemia developed in spite of controlled artificial ventilation.[7]

Kissin *et al.*[22] suggested that the interactive effects of fentanyl and thiopental may be different, depending on the endpoint of measurement. Thus, these two pharmacologic agents are synergistic with reference to the loss of righting reflex,[23] but are antagonistic in relation to purposeful movement response to tail clamping.[22] The present study provides an additional dimension to this

TABLE 2. Arterial Blood Gas Parameters following Intravenous Administration of 50 μg/kg (A), 100 μg/kg (B) of Fentanyl or Saline (C) in Rats Anesthetized with Ketamine and Whose Lungs Were Mechanically Ventilated.

		Control	Postinjection		
			5 Min	10 Min	15 Min
*p*H	A	7.384 ± 0.013	7.371 ± 0.010	7.357 ± 0.009	7.359 ± 0.010
	B	7.393 ± 0.009	7.394 ± 0.006	7.385 ± 0.012	7.390 ± 0.011
	C	7.387 ± 0.010	7.385 ± 0.008	7.381 ± 0.010	7.394 ± 0.008
Pa_{O_2}	A	116 ± 3	68 ± 3†	61 ± 2†	62 ± 3†
	B	110 ± 2	66 ± 4†	60 ± 2†	65 ± 3†
	C	108 ± 2	106 ± 2	105 ± 1	103 ± 1
Pa_{CO_2}	A	39.2 ± 1.3	39.2 ± 1.6	40.6 ± 1.7	41.9 ± 1.3
	B	41.1 ± 1.6	38.5 ± 2.4	38.0 ± 1.4	37.6 ± 1.2
	C	39.1 ± 1.0	39.5 ± 0.9	38.4 ± 0.7	38.6 ± 0.6
BE	A	−1.1 ± 0.4	−2.3 ± 0.5	−2.5 ± 0.4*	−2.2 ± 0.3*
	B	0.2 ± 0.4	−1.4 ± 0.5	−2.6 ± 0.5*	−2.1 ± 0.5*
	C	−0.7 ± 0.4	−0.9 ± 0.2	−0.7 ± 0.3	−0.9 ± 0.3

Controls were obtained 5 min before fentanyl/saline. All values are mean ± SEM (n = 10 in each group).

* $P < 0.01$, † $P < 0.005$ *vs.* saline in the Student-Newman-Keuls analysis.

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fentanyl-thiopental interaction. The barbiturate attenuated (and even reduced) the muscular rigidity induced by the narcotic agent. From the standpoint of clinical practice, it appears that thiopental may be a suitable adjunct to fentanyl anesthesia, since it removes a major side-effect of the opiate.[5,18,19] On the other hand, it will be a poor choice of anesthetic agent because it eliminates the key experimental index in animals in which fentanyl-induced muscle rigidity is being studied.

As pointed out by many authors,[7,18,19,24] we are aware that some general anesthetics may influence the occurrence of opiate-induced rigidity. We also noted that the magnitude of rigidity elicited by fentanyl (50 μg/kg, iv) in rats anesthetized with ketamine was less than that seen in the unanesthetized animals receiving only 25 μg/kg of the opiate. One may therefore argue that ketamine would not be an ideal anesthetic in an animal in which rigidity was being studied. This seeming deficit, however, must be weighed against the advantages of ketamine anesthesia. First, fentanyl still produces an elevation in EMG activity in animals anesthetized with ketamine that is significantly different from vehicle control, without the detrimental effects of hypercarbia and respiratory acidosis that were present in unanesthetized, spontaneously ventilating rats. Second, ketamine has the benefit of being synergistic with fentanyl in their drug actions. Radioligand binding and behavioral studies[25–27] indicate that this dissociative anesthetic may interact synergistically with the opiate receptors, possibly the mu-subtype, in the elicitation of catalepsy and analgesia. Thus, it appears that EMG activity in the gastrocnemius muscle of rats anesthetized with ketamine in whom ventilation is controlled may provide an alternative approach in the investigation of opiate-induced rigidity.

The primary purpose of our study was to search for an alternative experimental approach in the evaluation of fentanyl-induced muscle rigidity. To be acceptable, this animal model must demonstrate EMG activation by fentanyl that is at least qualitatively similar to that elicited in conscious animals, without, however, the undesirable effects of hypercarbia and respiratory acidosis. It appears that EMG activity in gastrocnemius muscle of rats anes-

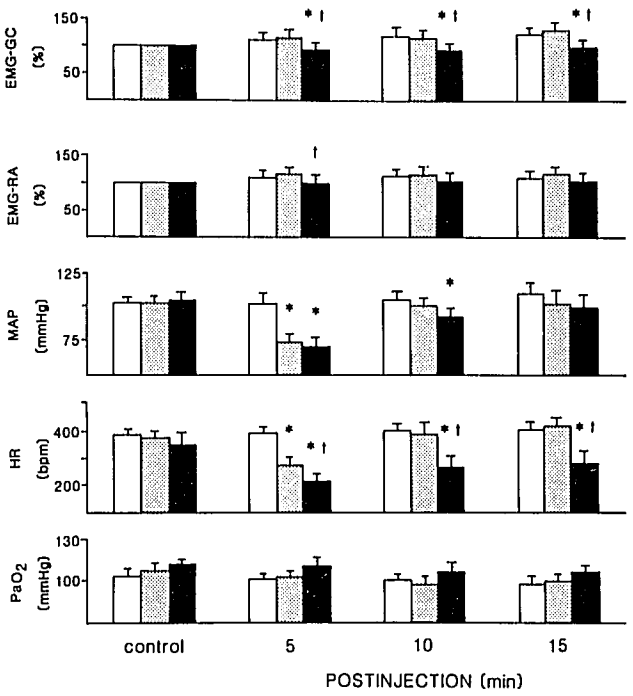

FIG. 5. Effects of intravenous administration of fentanyl at 50 (stippled bar) and 100 (filled bar) μg/kg, and saline (open bar) on electromyographic (EMG) activity of left gastrocnemius (GC) and rectus abdominis (RA) muscles, mean arterial pressure (MAP), heart rate (HR), and Pa_{O_2} in rats anesthetized with thiopental and whose lungs were mechanically ventilated. Values are mean ± SEM (n = 8 in each group). *$P < 0.05$ *versus* saline and †$P < 0.05$ *versus* 50 μg/kg of fentanyl in the Student-Newman-Keuls analysis.

TABLE 3. Arterial Blood Gas Parameters following Intravenous Administration of 50 μg/kg (A), 100 μg/kg (B) of Fentanyl and Saline (C) in Rats Anesthetized with Thiopental Whose Lungs Were Mechanically Ventilated.

			Postinjection		
		Control	5 Min	10 Min	15 Min
*p*H	A	7.395 ± 0.011	7.384 ± 0.012	7.378 ± 0.007	7.391 ± 0.011
	B	7.407 ± 0.016	7.391 ± 0.035	7.405 ± 0.027	7.402 ± 0.023
	C	7.372 ± 0.002	7.372 ± 0.006	7.379 ± 0.008	7.374 ± 0.014
Pa_{O_2}	A	101 ± 2	93 ± 3	97 ± 4	102 ± 3
	B	105 ± 1	95 ± 2	96 ± 3	99 ± 3
	C	104 ± 2	101 ± 3	97 ± 5	108 ± 1
Pa_{CO_2}	A	37.6 ± 0.9	39.5 ± 1.3	41.3 ± 1.2	41.4 ± 2.0
	B	37.2 ± 1.5	38.8 ± 2.2	38.9 ± 2.3	41.0 ± 2.6
	C	38.6 ± 1.1	38.3 ± 0.9	37.4 ± 0.8	37.5 ± 0.9
BE	A	−0.4 ± 0.3	−1.2 ± 0.5	−1.6 ± 0.3	−1.6 ± 0.2
	B	−0.6 ± 0.5	−0.4 ± 0.6	−1.0 ± 0.6	−0.5 ± 0.8
	C	0.3 ± 0.2	−0.7 ± 0.3	−0.8 ± 0.1	−1.1 ± 0.2

Controls were obtained 5 min before fentanyl/saline. All values are mean ± SEM (n = 8 in each group).

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thetized with ketamine and in whom ventilation is controlled may satisfy all these stipulations. Based on this experimental model, we recently identified[28] that the pontine nucleus, locus coeruleus, and noradrenergic neurotransmission are critically involved in fentanyl-induced muscle rigidity in the rat.

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