

## Ketanserin Pretreatment Reverses Alfentanil-induced Muscle Rigidity

Matthew B. Weinger, M.D.,\* Elizabeth J. Cline, B.S.,† N. Ty Smith, M.D.,‡ George F. Koob, Ph.D.§

Systemic pretreatment with ketanserin, a relatively specific type-2 serotonin receptor antagonist, significantly attenuated the muscle rigidity produced in rats by the potent short-acting opiate agonist alfentanil. Following placement of subcutaneous electrodes in each animal's left gastrocnemius muscle, rigidity was assessed by analyzing root-mean-square electromyographic activity. Intraperitoneal ketanserin administration at doses of 0.63 and 2.5 mg/kg prevented the alfentanil-induced increase in electromyographic activity compared with animals pretreated with saline. Chlordiazepoxide at doses up to 10 mg/kg failed to significantly influence the rigidity produced by alfentanil. Despite the absence of rigidity, animals that received ketanserin (greater than 0.31 mg/kg i.p.) followed by alfentanil were motionless, flaccid, and less responsive to external stimuli than were animals receiving alfentanil alone. Rats that received ketanserin and alfentanil exhibited less rearing and exploratory behavior at the end of the 60-min recording period than did animals that received ketanserin alone. These results, in combination with previous work, suggest that muscle rigidity, a clinically relevant side-effect of parenteral narcotic administration, may be partly mediated *via* serotonergic pathways. Pretreatment with type-2 serotonin antagonists may be clinically useful in attenuating opiate-induced rigidity, although further studies will be necessary to assess the interaction of possibly enhanced CNS, cardiovascular, and respiratory depression. (Key words: Analgesics: alfentanil. Anesthetics, intravenous: alfentanil. Antagonists, serotonergic: ketanserin. Complications: rigidity. Hypnotics, benzodiazepines: chlordiazepoxide. Measurement techniques: electromyography. Muscle: rigidity.)

IT HAS LONG BEEN RECOGNIZED that the administration of high doses of opiate agonists to rats produces a catatonic state characterized by akinesia and profound muscle hypertonus.<sup>1</sup> Clinically, a similar muscle rigidity is an important side-effect of the use of potent short-acting opiates during general anesthesia.<sup>2</sup> Limited data in humans<sup>3</sup> suggest that pretreatment with thiopental

or diazepam significantly but incompletely attenuates the rigidity commonly associated with anesthetic induction using alfentanil, a new synthetic fentanyl analog.<sup>4</sup> The benzodiazepines and barbiturates have also both been reported to be effective at attenuating opiate-induced rigidity in rodents.<sup>5</sup> This is consistent with studies that support a GABAergic mechanism for morphine-induced rigidity.<sup>6</sup> Rackham,<sup>7</sup> however, was unable to demonstrate a significant decrease in opiate-induced rigidity in rodents after pretreatment with high doses of either diazepam or pentobarbital. While the mechanisms of opiate rigidity may not be identical in rats and humans, studies using a rodent model could help identify potentially useful clinical interventions to prevent rigidity.

Recent work by Blasco *et al.*<sup>8,9</sup> has shown that the area around the nucleus raphe pontis (NRP) in the rat appears to play an important role in the expression of opiate-induced rigidity. Like the other raphe nuclei, the NRP is known to contain serotonergic neurons, which have both ascending and descending projections.<sup>10</sup> At least two serotonin receptor sub-types have been identified in the brain (types 1 and 2), and are hypothesized to mediate different central serotonergic actions.<sup>11</sup> For example, it has been shown that type-2, but not type-1, serotonin receptors play a role in rodent motor behavior.<sup>12,13</sup> The purpose of this study was to compare the effects of pretreatment with ketanserin, a relatively specific type-2 serotonin (5-HT<sub>2</sub>) receptor antagonist,<sup>14</sup> with those of the benzodiazepine chlordiazepoxide on alfentanil-induced muscle rigidity in rats.

### Materials and Methods

#### SUBJECTS

The subjects were 82 male albino Wistar rats (Charles River, Wilmington, MA) weighing 200–260 gm. They were housed three per cage with food and water available continuously in a temperature-controlled room. A 12-h light, 12-h dark schedule was maintained, with the light period between 7:00 AM and 7:00 PM. Physiological recording and behavioral testing was always done in the morning from 8:00 AM to 12:00 noon. Rats were handled prior to experimental days to minimize potential effects of stress on the results. The conduct of this study met the guidelines established by our institutional animal resources committee.

\* Assistant Professor of Anesthesiology, University of California, San Diego, School of Medicine.

† Student, Scripps Clinic and Research Foundation.

‡ Professor in Residence, University of California, San Diego.

§ Associate Member, Scripps Clinic and Research Foundation.

Received from the Department of Anesthesiology, University of California, San Diego, School of Medicine and the Veterans Administration Medical Center, San Diego, California; and the Division of Preclinical Neuroscience and Endocrinology, Scripps Clinic and Research Foundation, La Jolla, California. Accepted for publication April 10, 1987. Supported in part by NIDA grant #04043 and Janssen Pharmaceutica. Presented in part at the annual meeting of the American Society of Anesthesiologists in Las Vegas, Nevada, on October 21, 1986.

Address reprint requests to Dr. Weinger: Department of Anesthesiology, V-125, Veterans Administration Hospital, 3350 La Jolla Village Drive, San Diego, California 92161.

INJECTION AND RECORDING PROCEDURES

All animals were pretreated with either ketanserin [KET], chlordiazepoxide [CDP], or saline [SAL] by intraperitoneal injection [ip]. They were then immediately placed in barred cylindrical holding cages which allowed free movement of the extremities as well as easy access to injection and recording sites. Two monopolar (10 mm × 100 μm diameter) platinum recording electrodes (Grass® E2) were then placed percutaneously in the left gastrocnemius muscle, while a third (ground) electrode was inserted subcutaneously in the right hindlimb. Leads were secured with cellophane tape in a manner which allowed unimpeded joint mobility. Two caged animals at a time were placed inside a sound-proof box (Coulbourn®). A cardboard partition was put between the cages, and an electric fan was run continuously to provide white noise. Initial EMG readings were obtained within 2–3 min of pretreatment injection in every animal. EMG activity was assessed for a 15-min baseline period, with readings recorded at 5, 10, and 15 min after the initial pretreatment injection. Actual muscle potentials were differentially amplified 200 times, and band-pass filtered from 10 Hz to 3 KHz (Grass® P511K). The resulting signal, viewed on an oscilloscope (Tektronics® 7633), was then converted with an RMS voltage rectifier ( $t_{1/2} = 3$  s) to produce a time-varying analog deflection on a 200 mV meter (Triplet® 820-M), from which data were obtained. At the end of this 15-min baseline, each rat was injected *in situ* subcutaneously [s.c.] in the mid-back region with either saline or alfentanil. Readings were obtained at 1 and 5 min post-injection, and then at 5-min intervals throughout the remainder of the 60-min observation period. During data collection, care was taken to elimi-

nate the effects of transient movement artifacts, thereby permitting an assessment of tonic rather than phasic muscle activity.

EXPERIMENTAL GROUPS

Drugs used were ketanserin tartrate (Janssen® Pharmaceutica, Piscataway, New Jersey), chlordiazepoxide hydrochloride (Hoffman-La Roche, Nutley, New Jersey), and alfentanil hydrochloride [ALF] (Janssen®). All drugs, obtained as powders, were prepared fresh daily by dissolving in sterile 0.9% saline. All injections were given in a milliliter volume equal to each animal's weight in kilograms (1 ml/kg concentration). The ALF dose used throughout the study was 0.5 mg/kg, because this dose yielded consistent, prolonged rigidity in previous dose-response studies.<sup>8,9</sup>

One group (n = 18) received CDP (2.5, 5.0, or 10.0 mg/kg i.p.) as pretreatment 15 min before subcutaneous ALF injection. The corresponding control group (n = 6) received CDP (10 mg/kg i.p.) and saline s.c. ["CDP control"]. A second experimental group (n = 35) received KET (0.31, 0.63, 1.25, and 2.5 mg/kg i.p.) as pretreatment before ALF injection. "KET controls" (n = 8) received ketanserin (1.25 mg/kg i.p.) followed by saline subcutaneously. Two additional control groups were studied; the "ALF control" group (n = 9) received saline i.p. as pretreatment and then ALF s.c. to produce a baseline for alfentanil-induced rigidity; the "SAL control" group (n = 6) received saline i.p. followed by saline s.c. One KET pretreatment group (5.0 mg/kg, n = 6) was added at the end of the study to further characterize the dose-related effect of KET on alfentanil rigidity. See table 1 for a summary of the experimental groups.

TABLE 1. Summary of the Behavioral Data Obtained for the Animals in the Different Control and Pretreatment Groups

Group	Pretreatment Drug Dose (mg/kg)	ALF or SAL	n*	Rearing† (# Per 5 Min)	Exploration (# Circles of Perimetry Per 5 Min)	Grooming	
						+	-
ALF control	0	ALF	4	7.3 ± 4.0	2.88 ± 1.53	3	1
KET control	1.25	SAL	4	10 ± 2.0‡	2.25 ± 0.14§	4	0
KET pre Rx	0.31	ALF	3	4.7 ± 3.7	0.67 ± 0.67	2	1
	0.63	ALF	4	0.5 ± 0.3	0.00 ± 0.00	3	1
	1.25	ALF	6	2.5 ± 0.7	0.42 ± 0.15	4	2
	2.5	ALF	4	5.0 ± 1.5	0.63 ± 0.32	3	1
	5.0	ALF	0				
CDP control	10.0	SAL	6	6.8 ± 3.0	1.33 ± 0.54	1	5¶
CDP pre Rx	2.5	ALF	6	3.7 ± 1.6	1.00 ± 0.34	4	2
	5.0	ALF	8	4.9 ± 2.0	0.94 ± 0.36	7	1
	10.0	ALF	6	4.2 ± 1.5	1.08 ± 0.24	0	6¶
SAL control	0	SAL	6	14 ± 5.7	2.5 ± 1.1	3	3

\* Note that the numbers of animals that were studied for rigidity were larger than the numbers listed in this table for animals that were behaviorally observed.

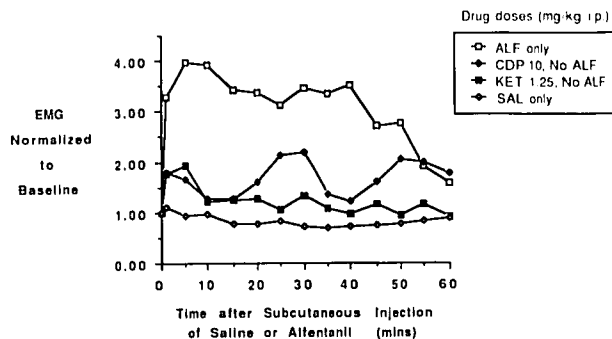
† All data expressed as mean ± SEM.

‡ P < 0.05 compared with all animals treated with KET and ALF (grouped together with a mean of 3.0 ± 0.8).

§ P < 0.01 compared with all animals treated with KET and ALF (grouped together with a mean of 0.41 ± 0.14).

¶ P < 0.01 compared with ALF control group animals.

A.



B.

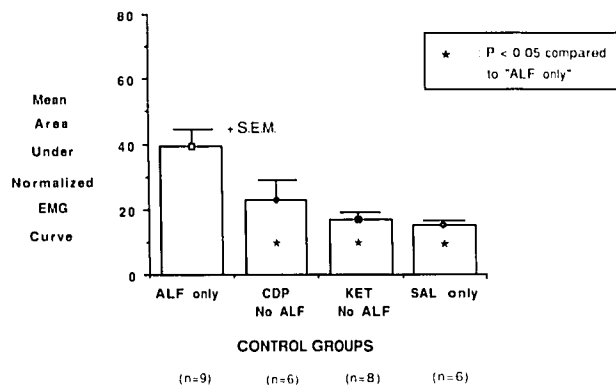


FIG. 1. A comparison of the four control groups used in this study. The upper graph (A) gives the actual EMG values over time (normalized to baseline values) for the four groups. The lower graph (B) presents the mean area under the normalized EMG curve for each group. The mean area under the EMG curve for the ALF control group was significantly greater than the mean area under the EMG curves for the other three control groups ( $P < 0.05$ ). See table 1 for a summary of the treatment regimens administered to each group.

### BEHAVIORAL OBSERVATIONS

During the EMG observation period, behavioral changes in the animals, such as increased activity or noise sensitivity (including startle responses), were noted. Following completion of the 60-min data gathering period, rats were assessed for catatonia. The front limbs of the animal were placed on a bar suspended 10 cm above the tabletop, and the time (in seconds) for the animal to remove either limb was recorded. Rats showing greater than a 60-s latency were assigned a value of 60 s. Following the test for catatonia, each rat was placed in a novel environment, a 52 cm by 70 cm open-ended box, and open field activity was recorded for 5 min. Specific attention was paid to the number of times each animal groomed, reared, and explored the complete perimeter of the open field. Note that formal be-

havioral testing was performed on all of the animals in the CDP pretreatment groups, but on only about one-half of the animals in the KET pretreatment groups.

### DATA ANALYSIS

Data from the 60-min observation period for each animal was normalized by that rat's baseline EMG activity. This was accomplished by obtaining the average of the three baseline readings for each animal and dividing this value into all subsequent values. The mean area under the EMG curve for each treatment observation was then calculated, and a two-factor analysis of variance (ANOVA) was performed. Statistical significance between groups was determined using a Newman-Keuls test. The significance of differences between the various dose groups on the catatonia test, as well as in the mean amount of rearing and active exploration during the open field test, were evaluated in a similar fashion. The presence or absence of grooming during the open field test was determined for each animal, and an "Information Statistic" based on contingency table analysis between groups was then performed.<sup>15</sup>

### Results

#### EMG

The mean baseline readings for those animals receiving 10 mg/kg (i.p.) of CDP were significantly lower than for those receiving saline pretreatment ( $5.4 \pm 0.8 \mu\text{V}$  versus  $8.8 \pm 0.6 \mu\text{V}$  [mean  $\pm$  SEM],  $P < 0.05$ ). There were no other statistical differences in the baseline values between groups (overall mean  $7.8 \pm 0.3 \mu\text{V}$ ).

#### CONTROL GROUPS

The administration of systemic alfentanil following saline pretreatment produced akinesia and electromyographically documented muscle rigidity (fig. 1A, "ALF only" group). Akinesia generally occurred within 30 s of intraperitoneal injection. The first electromyographic evidence of rigidity was seen within 1–2 min, and the peak effects occurred between 5 and 10 min after alfentanil injection. The mean area under the normalized EMG curve ( $41.3 \pm 3.7$ , fig. 1B) is consistent with previous results obtained in our laboratory with naive animals (unpublished data).<sup>8</sup> If left undisturbed, our rats remained rigid and akinetic for 35–50 min after alfentanil injection. However, external auditory stimulation almost always produced the "explosive motor responses" typically described after opiate administration and thought to be a component of the "death-feign reflex".<sup>16</sup>

Relatively low doses of naloxone (1 mg/kg) will, within 1–2 min after subcutaneous injection, routinely antagonize all of the locomotor and behavioral effects of alfentanil at any time up to an hour after opiate administration (unpublished observations). This suggests that the changes in EMG activity and behavior observed in this study are due to an action at an opioid receptor.

Animals that received ketanserin (1.25 mg/kg) followed by saline instead of alfentanil (KET control group) appeared mildly sedated throughout the experimental period. The mean area under the EMG curve (fig. 1) for this group was indistinguishable from that of saline control animals, and was significantly less than the ALF control group ( $P < 0.01$ ). Despite a higher overall mean and standard error, rats that received chlordiazepoxide (10 mg/kg) followed by saline (CDP control group) had EMG readings over time which were not significantly different from the ketanserin or saline control animals.

#### EXPERIMENTAL GROUPS

Pretreatment with ketanserin at doses of 0.31 and 1.25 mg/kg (see Discussion) did not significantly attenuate alfentanil-induced rigidity (fig. 2). Animals pretreated with ketanserin at doses of 0.63 and 2.5 mg/kg exhibited markedly decreased EMG evidence of rigidity ( $P < 0.05$  compared to ALF controls). Both of these doses of ketanserin (0.63 and 2.5 mg/kg) reduced EMG values to a level statistically indistinguishable from that of animals that did not receive alfentanil (KET and SAL controls). Rats that received ketanserin at doses greater than 0.31 mg/kg followed by alfentanil generally (20/27 animals) exhibited a profound flaccid akinesia, in the apparent absence of rigidity. Especially at higher ketanserin doses, the akinesia often persisted past the 60-min recording period. These animals had an obtunded startle reflex and did not respond to external auditory stimuli with "explosive motor behavior." We subsequently studied an additional group of six animals in which alfentanil administration was preceded by a pretreatment ketanserin dose of 5.0 mg/kg. This group also was profoundly flaccid, but unresponsive, and showed even lower levels of EMG activity ( $19.65 \pm 3.76$ ).

Pretreatment with chlordiazepoxide (fig. 3) had no statistically significant attenuating effects on muscle rigidity. Animals that received chlordiazepoxide and alfentanil exhibited a greater degree of individual variability in their electromyographic response to alfentanil administration, as reflected by the larger standard errors. There was, in fact, a tendency for chlordiazepoxide to augment the excess tonic muscle activity produced by alfentanil, particularly at the 5 mg/kg dose.

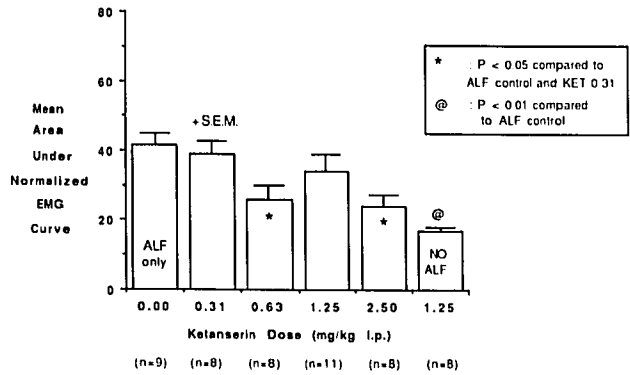


FIG. 2. The effects of ketanserin pretreatment on alfentanil-induced muscle rigidity. Pretreatment groups composed of animals receiving ketanserin in doses ranging from 0.31–2.5 mg/kg i.p. followed by alfentanil are compared with ALF and KET control groups. Note that, at doses of 0.63 and 2.5 mg/kg, ketanserin pretreatment significantly ( $P < 0.05$ ) reduces muscle rigidity (compared with ALF control or KET 0.31 mg/kg i.p. groups). The EMG activity of the 0.63 and 2.5 mg/kg groups is not significantly different from the activity of the KET control group (which did not receive alfentanil). As described in figure 1, the EMG activity of the ALF control group was significantly different from the activity of the KET control group ( $P < 0.01$ ).

#### BEHAVIOR

Behavioral testing at the end of the 60-min recording period (75 min after initial drug pretreatment) revealed that ketanserin alone had no significant effect on catatonia (as measured by a bar test) or free field behavior when these animals were compared with SAL control animals. There was no statistical difference between any group in the catatonia test, perhaps partly due to the tremendous amount of inter-subject variability (mean latency for all groups:  $8.9 \pm 2.0$  s).

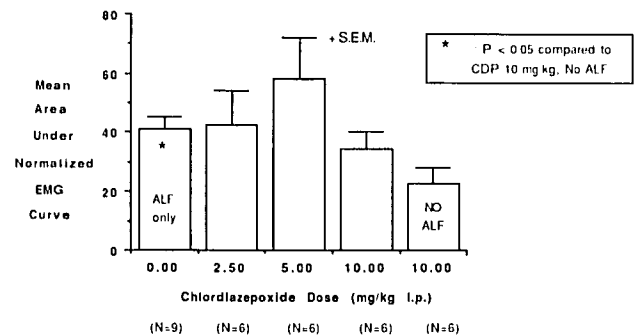


FIG. 3. The effects of chlordiazepoxide pretreatment on alfentanil-induced muscle rigidity. Pretreatment groups were composed of animals receiving chlordiazepoxide in doses ranging from 2.5–10 mg/kg i.p. followed by alfentanil. There were no significant differences in the mean area under the EMG curve for the CDP pretreatment groups compared with either ALF or CDP control groups. As described in figure 1, the EMG activity of the ALF control group was significantly different from the activity of the CDP control group ( $P < 0.05$ ).

KET control animals had significantly more rearing behavior than those receiving KET followed by alfentanil ( $10 \pm 2$  versus  $3 \pm 1$ ,  $P < 0.05$ ) (table 1). The combination of KET and ALF markedly decreased exploratory behavior at 60 min compared with KET controls ( $0.41 \pm 0.14$  versus  $2.25 \pm 0.14$ ,  $P < 0.01$ ) and approached significance when compared with ALF controls ( $2.88 \pm 1.53$ ,  $P < 0.10$ ). Animals that received KET and ALF most commonly moved to one corner of the experimental field and huddled without moving for the entire 5-min duration of the open field test. There was no loss of righting reflex, significant ataxia, or statistical differences in grooming behavior.

At the end of the 60-min recording period, the chlordiazepoxide control animals appeared mildly sedated, but were not catatonic. Grooming behavior was observed in only one of the 12 animals that received CDP 10 mg/kg, a significant difference from ALF control animals (three out of four animals studied,  $P < 0.01$ ). While rearing and exploratory behavior was less than that of SAL or ALF control groups, these differences did not attain statistical significance.

### Discussion

Systemic pretreatment with ketanserin (at doses of 0.63 and 2.5, but not 1.25, mg/kg i.p.), a relatively specific 5-HT-2 antagonist, significantly attenuated the muscle rigidity produced by the subcutaneous administration of the potent opiate agonist alfentanil. In contrast, the benzodiazepine chlordiazepoxide had no attenuating effect on rigidity over a meaningful range of doses. These results complement those from a large number of previous studies, all performed on rodents, which have attempted to elucidate the neuropharmacological etiology of opiate-induced rigidity.<sup>1,6,8,9</sup>

Work in our laboratory<sup>8,9,17</sup> has revealed that the area of the brainstem raphe nuclei may play an important role in opiate-induced rigidity. Direct injections of an opiate antagonist into the nucleus raphe pontis are significantly more effective at attenuating alfentanil rigidity than are injections into the caudate nucleus. Nearly all of the serotonergic projections in the brain originate in the raphe nuclei, a cluster of midline nuclei located in the mesencephalon, pons, and medulla.<sup>10</sup> Fiber tracts from the dorsal raphe project primarily to the basal ganglia, while the median raphe sends 5-HT efferents principally to the limbic system.<sup>18</sup> Most descending efferent serotonergic pathways originate in the medullary raphe nuclei.<sup>10</sup> The NRP has been shown to have ascending,<sup>19</sup> descending, and cerebellar efferents.<sup>10</sup>

A number of previous studies have suggested that serotonergic pathways mediate locomotor behaviors,

including opiate-induced akinesia and rigidity. Myoclonus induced by central 5-HT activation can be reversed by type-2 specific (including ketanserin 1-100 mg/kg),<sup>12</sup> but not by type-1 specific<sup>13</sup> serotonin antagonists. Balsara *et al.*<sup>20</sup> demonstrated that the activation of central 5-HT systems has a facilitatory effect on morphine-induced catatonia. Costall *et al.*<sup>21</sup> showed that the administration of the serotonin antagonist cyproheptadine diminished the catatonia produced by direct injections of morphine into the rat brain. Depletion of brain serotonin by intraventricular pretreatment with 5,7-dihydroxytryptamine prevented the increased hindlimb muscle tone produced by the injection of  $\beta$ -endorphin into the periaqueductal gray.<sup>22</sup> Fenfluramine, an indirect 5-HT agonist, potentiated the catatonia produced by morphine injected directly into the nucleus raphe pontis.<sup>23</sup> Many of these studies used the increased latency of paw removal on a bar test as an indicator of opiate-induced catatonia. Since the akinesia and rigidity following opiate administration may be neuroanatomically distinct phenomena,<sup>24</sup> it is difficult to fully appreciate from these studies the role serotonergic pathways play in muscle rigidity. The results of the present study suggest that type-2 serotonergic receptors do indeed mediate opiate-induced rigidity. It remains to be determined if 5-HT neurons act as part of a feedback system from the raphe nuclei, *via* ascending fibers, to the thalamus and basal ganglia, or if they are a component of the final common motor pathway to the spinal cord.

It is unclear why the 1.25 mg/kg dose of ketanserin was significantly less effective at attenuating alfentanil-induced muscle rigidity than either lower (0.63 mg/kg) or higher (2.5 mg/kg) doses. Additional animals were added to the 1.25-mg/kg group in an attempt to reduce the role intra-subject variability could have played in our results. It is possible that pretreatment with the lower dose results in a specific antagonism of serotonin-mediated motor activity, while higher doses produce other central or peripheral effects which non-specifically attenuate opiate-induced rigidity. The fact that animals pretreated with an even higher dose of ketanserin (5.0 mg/kg) had very little evidence of rigidity after alfentanil supports this hypothesis. Ketanserin is a potent and specific antagonist of serotonergic effects in a variety of pharmacologic tests at doses ranging from an ED<sub>50</sub> of 0.06 mg/kg for tryptamine-induced cyanosis to an ED<sub>50</sub> of 1.35 mg/kg for the reversal of tryptamine tremors.<sup>14</sup> Future research will be necessary to determine if ketanserin's beneficial effects on opiate rigidity are due to specific 5-HT-2 antagonism at a particular site in the CNS. Ketanserin does exhibit antihistaminergic (H-1) and alpha-1 blocking properties at higher doses (ED<sub>50</sub> > 2.5 mg/kg).<sup>14</sup> The design of the present study can not exclude the possibility that nonserotoner-

gic properties are involved in ketanserin's effects, particularly at the higher doses.

The benzodiazepines have been shown to have specific muscle relaxant properties,<sup>25</sup> and are clinically employed as muscle relaxant agents in a variety of spastic and dystonic motor conditions.<sup>26</sup> It is still debated whether their site of action is spinal, supraspinal, or both. Previous work has been controversial as to whether benzodiazepine pretreatment attenuates opiate rigidity. While some studies have demonstrated a beneficial effect,<sup>5,27</sup> others have failed to show such an effect.<sup>7</sup> The failure of chlordiazepoxide to significantly reverse alfentanil-induced rigidity in the present study, while consistent with previous findings,<sup>27</sup> could be explained by several factors. When administered alone, doses of chlordiazepoxide as low as 5 mg/kg induce significant anti-conflict effects in rats.<sup>28</sup> Thus, the lower doses of chlordiazepoxide may behaviorally disinhibit an animal, resulting in increased motor activity. A dose of 10 mg/kg may not produce sufficient generalized sedation to nonspecifically reduce motor activity following alfentanil. However, the significant decrease in baseline values for animals in the CDP control group (CDP 10 mg/kg), as well as the decrease in grooming behavior after CDP 10 mg/kg (followed by ALF), suggests that these animals were, in fact, as sedated as those in the higher dose KET groups.

Because respiratory parameters were not measured, the possibility can not be excluded that differences in drug-induced hypoventilation between the treatment groups contributed to differences in the degree of rigidity. All of our animals maintained spontaneous ventilation (at rates of 50–100 breaths/min) throughout the study period. In humans, the effects of pretreatment with diazepam (2.5–10.0 mg)<sup>3</sup> or midazolam (1.25–5.0 mg) (unpublished data) on alfentanil-induced rigidity did not correlate with PaCO<sub>2</sub> or PaO<sub>2</sub> during several minutes of apnea. Studies are presently underway to assess the effects of ketanserin pretreatment on alfentanil-induced respiratory depression in spontaneously ventilating rats.

Ketanserin is a potent antihypertensive agent.<sup>29,30</sup> It remains controversial whether its site of action is central or peripheral and exactly what role 5-HT receptor blockade plays in its hypotensive effect.<sup>31</sup> It is possible that, in the present study, CNS or muscle hypoperfusion, particular at higher pretreatment doses, contributed to the etiology of ketanserin's attenuation of alfentanil-induced rigidity. However, severe brain ischemia generally results in decerebrate rigidity rather than flaccidity.<sup>32</sup> Future studies will be necessary to evaluate this potential factor.

Serotonergic neurons originating in the raphe nuclei are known to be important in the processing of noci-

ceptive signals. A decrease in central serotonergic activity has been associated with hyperalgesia and diminished antinociceptive drug action (See review by Messing and Lytle<sup>33</sup>). Thus, there was some concern that ketanserin might exhibit anti-analgesic properties during clinical usage. Serotonin also plays a role in sleep and arousal.<sup>34</sup> The behavioral results in the present study, as well as work by others,<sup>35</sup> suggest that central 5-HT receptor blockade may be associated with significant CNS depression, especially with concurrent opiate administration. Nevertheless, investigators using intravenous ketanserin as a perioperative antihypertensive agent<sup>29,30</sup> or to block the adverse hemodynamic consequences of serotonin release following arterial embolization of carcinoid tumors<sup>36,37</sup> did not comment on any noticeable alterations in anesthetic or analgesic requirements.

Ketanserin pretreatment attenuates alfentanil-induced muscle rigidity, whereas equally sedating doses of chlordiazepoxide do not. The results of the present study lend additional support to the proposition that muscle rigidity, a clinically relevant side-effect of parenteral narcotic administration, may be mediated by central serotonergic activity. Future research will determine whether central or peripheral nonserotonergic activity contribute to ketanserin's complex dose-response relationship. Further study may be indicated to evaluate whether pretreatment with ketanserin (or another of this potentially useful class of compounds) will safely prevent opiate-induced muscle rigidity in a clinical setting without producing undesirable side-effects.

The technical assistance of Mr. Norm Head was greatly appreciated.

## References

1. Wand P, Kuschinsky K, Sontag KH: Morphine-induced muscular rigidity in rats. *Eur J Pharmacol* 24:189–193, 1973
2. Benthuyzen JL, Smith NT, Sanford TJ, Head N, Dec-Silver H: Physiology of alfentanil-induced rigidity. *ANESTHESIOLOGY* 64:440–446, 1986
3. Blasco TA, Smith NT, Sanford TJ, Benthuyzen J, Dec-Silver H, Head N: A clinical study of the effects of various pretreatment agents on alfentanil-induced rigidity: EMG data (abstract). *ANESTHESIOLOGY* 63:A380, 1985
4. Cookson RF, Niemegeers CJ, Vanden Bussche G: The development of alfentanil. *Br J Anaesth* 55:147S–155S, 1983
5. Turski L, Havemann U, Kuschinsky K: Reversal of the muscle relaxant effect of diazepam by the specific benzodiazepine antagonist Ro-15-1788: An electromyographic study in the morphine model of muscular rigidity in rats. *Life Sci* 33(Suppl 1): 755–758, 1983
6. Turski L, Havemann U, Kuschinsky K: GABAergic mechanisms in mediating rigidity, catalepsy, and postural asymmetry in rats: difference between dorsal and ventral striatum. *Brain Res* 322:49–57, 1984
7. Rackham A: Opiate-induced muscle rigidity in the rat: Effects of centrally acting agents. *Neuropharmacology* 19:855–859, 1980

8. Blasco TA, Lee DE, Amalric M, Swerdlow NR, Smith NT, Koob GF: The role of the nucleus raphe pontis and the caudate nucleus in alfentanil rigidity in the rat. *Brain Res* 386:280-286, 1986
9. Amalric M, Blasco TA, Smith NT, Lee DE, Swerdlow NR, Koob GF: Catatonia produced by alfentanil is reversed by methyl-naloxonium microinjections into the brain. *Brain Res* 386:287-295, 1986
10. Steinbusch HWM: Serotonin-immunoreactive neurons and their projections in the CNS, *Handbook of Chemical Neuroanatomy: Classical Neurotransmitters and Transmitter Receptors in the CNS, Part II*. Edited by Bjorklund A, Hokfelt T, Kuhar MJ. New York, Elsevier Science Publishers, 1984, pp 68-96
11. Leysen J: Serotonin receptor binding sites: Is there pharmacological and clinical significance? *Med Biol* 61:139-143, 1983
12. Pranzatelli MR, Snodgrass SR: Antimyoclonic properties of S<sub>2</sub> serotonin receptor antagonists in the rat. *Neuropharmacology* 25:5-12, 1986
13. Pranzatelli MR, Snodgrass SR: Serotonin lesion myoclonic syndromes: II. Analysis of individual syndrome elements, locomotor activity, and behavioral correlations. *Brain Res* 364:67-76, 1986
14. Janssen PAJ: Pharmacology of potent and selective S<sub>2</sub>-serotonergic antagonists. *J Cardiovasc Pharmacol* 7(Suppl 7):S2-11, 1985
15. Fray PJ, Sahakian BJ, Robbins TW, Koob GF, Iversen SD: An observational method for quantifying the behavioural effects of dopamine agonists: Contrasting effects of d-amphetamine and apomorphine. *Psychopharmacology (Berlin)* 69:253-259, 1980
16. De Ryck M, Schallert T, Teitelbaum P: Morphine versus haloperidol catalepsy in the rat: A behavioral analysis of postural support mechanisms. *Brain Res* 201:143-172, 1980
17. Weinger MB, Cline EJ, Smith NT, Koob GF: Ketanserin pretreatment prevents alfentanil-induced muscular rigidity in the rat (abstract). *ANESTHESIOLOGY* 65:A344, 1986
18. Geyer MA, Puerto A, Dawsey WJ, Knapp S, Bullard WP, Mandell AJ: Histologic and enzymatic studies of the mesolimbic and mesostriatal serotonergic pathways. *Brain Res* 106:241-256, 1976
19. Bjorklund A, Nobin A, Stenevi V: The use of neurotoxic dihydroxytryptamines as a tool for morphological studies and localized lesioning of central indoleamine neurons. *Z Zellforsch* 145:479-501, 1979
20. Balsara JJ, Jadhav JH, Muley MP, Chandorkar AG: Effect of drugs influencing central 5-hydroxytryptaminergic mechanisms on morphine-induced catalepsy in the rat. *J Pharm Pharmacol* 31:255-257, 1979
21. Costall B, Fortune DH, Naylor RJ: The induction of catalepsy and hyperactivity by morphine administered directly into the nucleus accumbens of rats. *Eur J Pharmacol* 49:49-64, 1978
22. Widdowson PS, Griffiths EC, Slater, P: The effects of opioids in the periaqueductal gray region of rat brain on hind-limb muscle tone. *Neuropeptides* 7:251-258, 1986
23. Broekkamp CL, LePichon M, Lloyd KG: Akinesia after locally applied morphine near the nucleus raphe pontis of the rat. *Neurosci Lett* 50:313-318, 1984
24. Winkler M, Havemann U, Kuschinsky K: Unilateral injection of morphine into the nucleus accumbens induces akinesia and catalepsy, but no spontaneous muscular rigidity in rats. *Naunyn-Schmiedeberg's Arch Pharmacol* 318:143-147, 1982
25. Biscoe TJ, Fry JP: Some pharmacologic studies on the spastic mouse. *Br J Pharmacol* 75:23-35, 1982
26. Young RR, Delwaide PJ: Drug therapy: Spasticity. *N Engl J Med* 304:96-99, 1981
27. Novack GD, Zwolshen JM: Predictive value of muscle relaxant models in rats and cats. *J Pharmacol Methods* 10:175-183, 1983
28. Koob GF, Thatcher-Britton K, Britton DR, Roberts DC, Bloom FE: Destruction of the locus coeruleus or the dorsal NE bundle does not alter the release of punished responding by ethanol or chlordiazepoxide. *Physiol Behav* 33:479-485, 1984
29. Van der Starre PJA, Scheijgrond HW, Reneman RS, Kolling JB: The use of ketanserin, a 5-hydroxytryptamine receptor antagonist, for treatment of postoperative hypertension following coronary artery bypass surgery. *Anesth Analg* 62:63-69, 1983
30. Van den Broeke JJ, Karliczek GF, Brenken U, Schokkenbroek R, Homan van der Heide JN: Is prevention of hypertension after open heart surgery possible by blocking 5-HT-2 receptors with ketanserin? *Acta Anaesthesiol Belg* 2:115-120, 1982
31. Vanhoutte PM, Ball SG, Berdeaux A, Cohen ML, Hedner T, McCall R, Ramage AG, Reimann IH, Richer C, Saxena PR, Schalekamp M, Struyker-Boudier HAJ, Symoens J, Van Nueten JM, Van Zwieten PA: Mechanism of action of ketanserin in hypertension. *Trends Pharm Sci* 7:58-59, 1986
32. Fukuda H, Ito T, Hashimoto S, Kudo Y: Rigidity in rats due to anemic decerebration and the effect of chlorpromazine. *Jpn J Pharmacol* 24:810-813, 1974
33. Messing RB, Lytle LD: Serotonin-containing neurons: Their possible role in pain and analgesia. *Pain* 4:1-21, 1977
34. Kelly DD: Sleep and dreaming, *Principles of Neural Science*, 2nd edition. Edited by Kandel ER, Schwartz JH. New York, Elsevier, 1985, pp 648-658
35. Bailey PL, Port JD, Pace NL, Stanley TH, Kimbal J: The ED<sub>50</sub> of carfentanil for elk immobilization with and without the tranquilizer R51703. *J Wildlife Manage* 49:931-934, 1985
36. Houghton K, Carter JA: Perioperative management of carcinoid syndrome using ketanserin. *Anaesthesia* 41:596-599, 1986
37. Casthely PA, Jablons M, Griep RB, Ergin MA, Goodman K: Ketanserin in the preoperative and intraoperative management of a patient with carcinoid tumor undergoing tricuspid valve replacement. *Anesth Analg* 65:809-811, 1986