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Nitrous Oxide Produces a Biphasic Effect on Opiate-Induced Muscle Rigidity in the Rat

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CHANG, N. J., M. B. WEINGER AND J. B. DYCK. *Nitrous oxide produces a biphasic effect on opiate-induced muscle rigidity in the rat.* PHARMACOL BIOCHEM BEHAV **50**(3) 351-358, 1995.—Muscle rigidity is a side effect of potent opiate agonists like alfentanil. Older clinical studies suggested that nitrous oxide (N_2O) augments opiate rigidity, but this has never been rigorously examined in an animal model. Sixty-two Wistar rats were placed in a Plexiglas box through which fresh gas flowed at 4 l/min. Muscle rigidity was assessed using gastrocnemius electromyographic (EMG) activity. Rats were exposed to either 60% N_2O in O_2 or 100% O_2, EMG was measured for 10 min, alfentanil (0, 50, 175, or 350 μg/kg) was administered intravenously, and data were collected for 45 min. Alfentanil produced a dose-dependent increase in EMG activity in both O_2 and N_2O groups ($p < 0.001$). At 1 min postalfentanil, N_2O caused significantly *more* rigidity than 100% O_2 ($p < 0.001$). However, beginning at 5 min, N_2O *attenuated* both the magnitude and the duration of rigidity. Study of a separate group of animals breathing 30% O_2 demonstrated that N_2O's attenuating effect on alfentanil rigidity was *not* due to reduced inspired oxygen concentration. These results are described by a theoretical model of the pharmacodynamic interactions of alfentanil and nitrous oxide.

Opiates Alfentanil Nitrous oxide Muscle rigidity Skeletal muscle Electromyography

MUSCLE rigidity is a potentially troublesome side effect of potent selective opiate agonists such as alfentanil (ALF). Clinical studies, which are now more than 10 years old, suggested that nitrous oxide (N_2O), commonly used with high-dose opiate techniques, augmented both morphine-induced (7,24) and fentanyl-induced (21,24) muscle rigidity. However, in these studies, the effects of N_2O on opiate rigidity were only examined over a relatively brief time period. In addition, these studies used nonquantitative (24) or indirect (21) measures of muscle tone. Nevertheless, as a result of these studies, the augmentation of opiate rigidity by N_2O is stated as an unequivocal fact by current textbooks of anesthesia (1,18). However, in preliminary animal experiments, N_2O failed to produce the magnitude of increase in opiate rigidity reported by these earlier clinical investigations. Therefore, a study was undertaken, using a well-established spontaneously ventilating rat model (30,31), to investigate the effect of N_2O on ALF-induced muscle rigidity.

METHOD

Following approval by our Animal Care Committee, 62 male albino Wistar rats (Harlan Sprague-Dawley, Chicago, IL) weighing 322 ± 6 g (range 265-435 gm) were studied. The animals were housed two-three per cage in a temperature-controlled room, with free access to food and water. Each rat was handled before the experiment to minimize the potential effects of stress on the results. The animals were also acclimated to the experimental apparatus, a cylindrical holding device, in three 1-h sessions prior to the experiment. All experiments were performed during the animals' light cycle (1000-1700 h). In these studies, animals were randomly assigned to treatment groups and the observer was blind to the treatment administered.

Under halothane anesthesia and sterile conditions, each animal was surgically implanted with a venous catheter. The right internal jugular vein was exposed through a skin incision and cannulated with polyethylene tubing (PE-50). Heparinized saline (1 ml, 50 IU/ml) was injected IV to prevent clotting. The catheter was threaded SC around to the back where it was externalized and secured with a suture ligature. The incisions were closed and lidocaine 0.5% was injected in the surgical sites. The animals were then allowed 3 days of recovery.

On the day of the experiment, each rat was placed in a

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cylindrical holding device, which allowed free movement of the extremities and easy access to injection and recording sites. Hindlimb electromyographic (EMG) activity was used as the assay of muscle tone in these normal, awake rats (30,31). Two monopolar (10 mm × 100 μm diameter) platinum recording electrodes (Grass E2) were placed percutaneously into the left gastrocnemius muscle, and a third (ground) electrode was inserted subcutaneously (SC) into the right leg. Leads were secured with cellophane tape in such a way as to permit unimpeded joint mobility.

Muscle potentials were differentially amplified and bandpass filtered from 10 Hz to 3 kHz (Grass P511K). The resulting signal was displayed on an oscilloscope and continuously recorded on a strip-chart recorder. The resulting signals, viewed on an oscilloscope, were converted with an RMS voltage rectifier ($t_1 2$ = 3 s) to produce time-varying analog deflections on 200-mV meters reflecting RMS voltage.

Each rat, inside the holding cage, was then placed in a 2-l Plexiglas (Harvard) induction box through which 100% medical grade oxygen flowed at a rate of 4 l/min via a calibrated (Foregger) flowmeter. After a 10-min baseline, rats were exposed to either 60% N_2O in O_2 or 100% O_2, delivered at the same 4 l/min flow rate. Respiratory gases were scavenged via a regulated suction system. EMG data were then collected for 10 min. ALF (Janssen Pharmaceutica, Piscataway, NJ), obtained as a powder, was dissolved in 0.9% sterile physiological saline and injected IV as a bolus dose of either 0, 50, 175, or 350 μg/kg in a volume of 0.5 ml/kg. Data were collected at 1 min post-ALF and then at 5-min intervals thereafter for 45 min. A separate group of animals (n = 7) was exposed to 30% O_2 in nitrogen and then given ALF 350 μg/kg.

Statistical differences between treatment groups were determined using three-way analysis of variance (ANOVA) with two between-subjects factors (N_2O dose and ALF dose) and one within-subject factor (time). Appropriate two-way ANOVAs were then performed to investigate selected drug effects (ALF or N_2O over time). Newman-Keuls a posteriori tests were used to determine the significant differences between groups over time (33). All data were expressed as mean ± SEM and a value of $p < 0.05$ was considered statistically significant.

Pharmacokinetic/Pharmacodynamic Modeling

In the absence of measured plasma ALF concentrations, a simulation was undertaken using previously determined ALF rat pharmacokinetic parameters (3). Given CL_1 of 7.263 ml/min, CL_2 of 29.81 ml/min, V_1 of 8.085 ml, and V_2 of 95.15 ml, the expected ALF concentration vs. time profile following any of the three different bolus doses of ALF was calculated. The effect measurements (μV RMS) for all time points prior to the administration of ALF were averaged and represented the baseline effect measure at time zero in the absence of ALF. First-order transfer between the central volume of distribution and the site of drug effect was used to model the concentration of ALF in the effect site (Fig. 1) (22).

The concentration of ALF in the effect site was assumed to be related to the measured effect through the sigmoid E_{max} equation:

$$Effect = \frac{E_{max} * C_e^{gamma}}{C_e^{gamma} + C_{e50}^{gamma}}$$

where E_0 is the baseline effect; E_{max} is the maximum possible effect. C_{e50} is the concentration of ALF at 50% of maximal effect. Gamma is a dimensionless term influencing the sigmoidicity of the relationship (and is functionally equivalent to the Hill coefficient). Least-squares nonlinear regression with a weighting factor of 1 was used to estimate the parameters E_{max}, C_{e50}, gamma, and ke_0. Pharmacokinetic linearity was assumed.

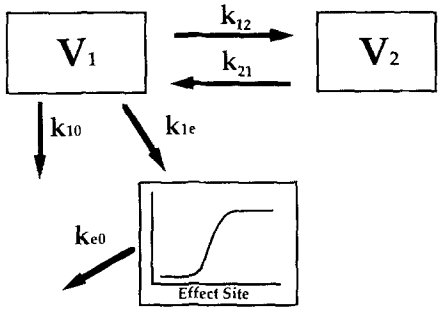

FIG. 1. A two-compartment pharmacokinetic model with parameters from the literature was used to simulate the ALF concentration vs. time profile. First-order rate constants link the simulated plasma concentration to a sigmoid E_{max} pharmacodynamic model.

RESULTS

When administered to animals breathing 100% oxygen, IV ALF produced a dose-dependent increase in EMG activity, $F(3, 49) = 11.9$, $p < 0.0001$. Although ALF 175 μg/kg resulted in significant rigidity for only 15 min (compared with either baseline values in the same group or at the same time points in the saline group), significant rigidity persisted for up to 25 min in the group given ALF 350 μg/kg (Fig. 2, top graph). EMG activity was significantly higher for 25 min after ALF administration in the 350-μg/kg dose group compared with the 175-μg/kg group.

Intravenous ALF also produced significant muscle rigidity in animals breathing 60% N_2O, $F(3, 49) = 7.7$, $p < 0.001$ (Fig. 2, bottom graph). However, the contour of the ALF dose-time curves was different from that seen in animals breathing 100% O_2 (compare the top and bottom graphs in Fig. 2). Rats in the N_2O + ALF 175-μg/kg group also had significant rigidity for only 10 min (compared with either baseline or the saline group), whereas rats receiving O_2 demonstrated more prolonged rigidity. However, during the first 5 min after ALF, the increased EMG activity in the ALF 175-μg/kg group was similar to that seen in the higher (350-μg/kg) ALF group. Beginning at 15 min after ALF, the rats in the 175-μg/kg group were virtually indistinguishable from rats receiving saline. In contrast, in the N_2O + ALF 350-μg/kg group, significant rigidity persisted for 15 min after ALF. Interestingly, it was only at the 15-min time point that the EMG activity in the 350-μg/kg dose was significantly greater than that in the 175-μg/kg group ($p < 0.05$).

At the 175-μg/kg dose of ALF, N_2O significantly augmented ALF-induced rigidity at 1 min, $F(1, 142) = 19.3$, $p < 0.001$, but there were no significant effects of N_2O at any other time point. In contrast, at the 350-μg/kg ALF dose, whereas N_2O significantly *augmented* ALF's effects at 1 min, $F(1, 144) = 6.4$, $p < 0.015$, it significantly *diminished* the ALF-induced rigidity at 5 min ($F = 8.8$, $p < 0.005$) and 10 min ($F = 5.5$, $p < 0.03$).

It was possible that the effects seen in the 60% N_2O group

could have been due to differences in inspired oxygen tensions between the two study groups (100% O_2 vs. 60% N_2O in O_2). Therefore, an additional group of animals (n = 7) was studied in which ALF 350 μg/kg was administered during the inhalation of 30% oxygen in nitrogen. Rats breathing 100% O_2 or 60% N_2O had significantly greater EMG activity compared with baseline for 25 and 15 min, respectively, whereas increased EMG activity in rats breathing 70% N_2 persisted for 20 min (Fig. 3). The EMG activity at 1 min was significantly higher in the 70% N_2 in 30% O_2 group than in the 100% O_2 or 60% N_2O groups. In contrast, EMG activity in both the 100% O_2 and 70% N_2 groups was significantly greater than in the 60% N_2O group between 5 and 15 min post-ALF.

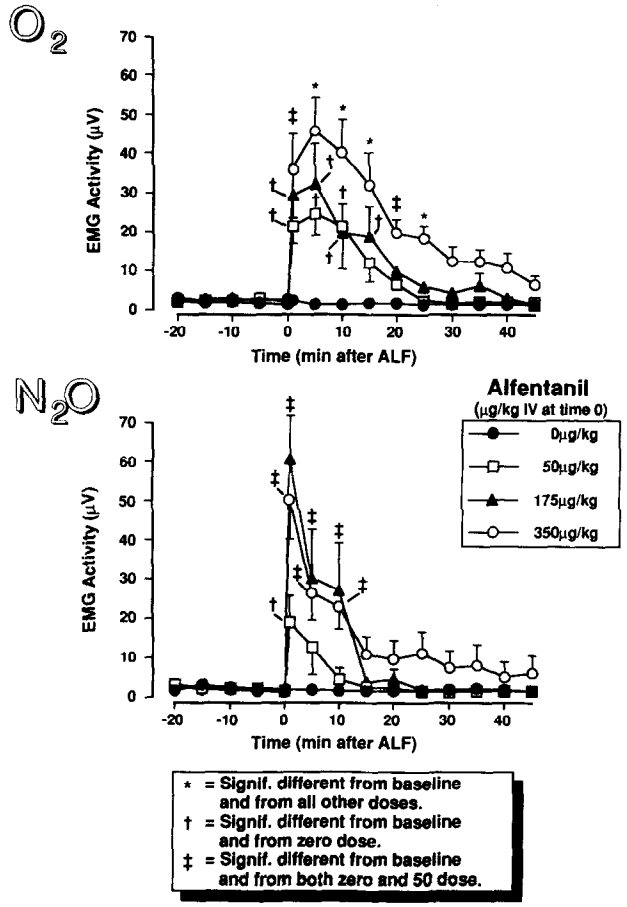

FIG. 2. EMG activity (ordinate) is plotted against time in minutes before or after alfentanil (ALF) administration (abscissa) for groups of rats breathing 100% oxygen (top graph) or 60% nitrous oxide in oxygen (bottom graph). One of three doses [0 (●), 50 (□), 175 (▲), and 350 (○) μg/kg] of ALF was administered IV in each condition. For 100% oxygen, ALF 175μg/kg resulted in significant rigidity for only 15 min [compared with either baseline values in the same group (*$p < 0.05$) or at the same time points in the 0-dose group (†$p < 0.05$)]. Significant rigidity persisted for up to 25 min in the 350-μg/kg group. EMG activity was generally significantly higher in the 350-μg/kg group compared with the 175-μg/kg group between 5–15 min and 25 min after ALF (*$p < 0.05$). In rats breathing 60% nitrous oxide (bottom graph), the ALF 175-μg/kg group (▲) had significant rigidity for only 10 min [compared with either baseline values in the same group (*$p < 0.05$) or with the same time points in the 0-dose (●) group (‡$p < 0.05$)]. Significant rigidity persisted for up to 15 min in the 350-μg/kg (○) group. In contrast to the oxygen-treated animals, EMG activity was no longer significantly higher than baseline in the 350-μg/kg group by 20 min and in the 175-μg/kg group by 15 min time. Thus, N_2O attenuated ALF-induced rigidity, particularly at the highest ALF dose studied.

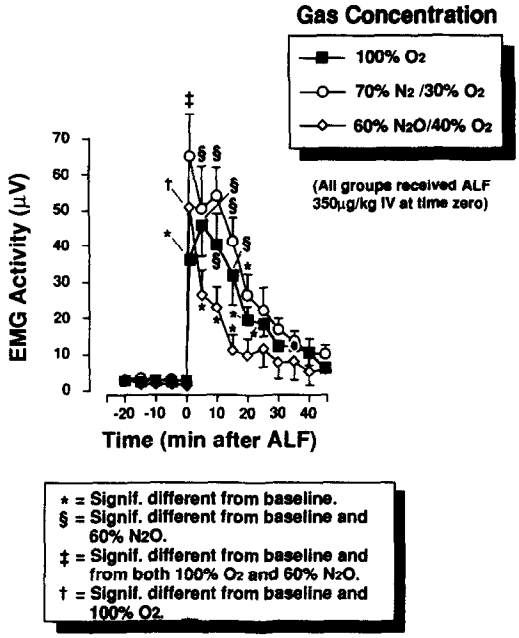

FIG. 3. The EMG activity is plotted against time before or after alfentanil (350 μg/kg) administration for groups of rats breathing 100% O_2, 60% N_2O, or 70% N_2 in O_2. The depression of alfentanil-induced muscle rigidity by 60% N_2O when compared with 100% O_2 does not appear to be due to reduced inspired oxygen concentration because the 70% N_2/30% O_2 group was not similarly affected.

Pharmacokinetic/Pharmacodynamic Model

Baseline measurements of rigidity were uniform across the various groups (mean ± SD of 2.126 ± 0.001; no significant differences between groups). Therefore, E_0 was held constant and not estimated during the nonlinear regression. The concentration-effect data for all rats receiving 100% O_2 were pooled, as were the data from all rats receiving 60% N_2O. The pharmacodynamic parameters calculated through nonlinear regression of the concentration-effect data for the pooled 100% O_2 and 60% N_2O groups are shown in Table 1. Figure 4 graphically depicts the relationship between ALF concentration and the magnitude of rigidity in the presence of 100% O_2 and 60% N_2O. The concentration-effect relationship clearly shows the influence of the larger gamma in the presence of N_2O as an increase in sigmoidicity. The greater sigmoidicity in the ALF concentration-effect relationship in the presence of N_2O will decrease the measured rigidity at low ALF effect site concentrations while accentuating the rigidity at higher concentrations.

The effects predicted by the fitted parameters of this model provide a reasonable description of the measured effects (Fig. 5). Despite pooling of the three different ALF doses for 100% O_2 and 60% N_2O, the fitted model captures the contour of the measured effect over time. Rigidity in the presence of N_2O is initially greater than that with O_2 but at later time points is decreased.

TABLE 1
PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

	All Rats		ALF 350-μg/kg Groups		
	100% O_2	60% N_2O	70% N_2	100% O_2	60% N_2O
E_{max}	79.7	63.7	88.8	100	89.4
Gamma	0.98	1.894	1.8395	1.67	2.87
C_{e50}	992	761	529	821	1111
ke_0	0.315	1.60	0.201	0.1637	0.422

The substitution of 60% N_2O for 100% O_2 clearly has the potential to produce greater hypoxia, especially in the presence of opioids known to depress respiration. If hypoxia associated with 60% N_2O had substantially altered the concentration-effect relationship, it would be expected that a reduction to 30% inspired O_2 in N_2 would have produced even more dramatic results. Comparison of the pharmacodynamic parameters describing the concentration-effect relationship for rats breathing different oxygen concentrations suggests that the increased sigmoidicity of the relationship secondary to N_2O cannot be readily explained by a reduction in inspired oxygen concentration (Table 1, Fig. 6).

DISCUSSION

These data show that N_2O transiently (< 5 min) augmented the increased rat hindlimb muscle tone produced by IV ALF. However, beginning at 5 min after ALF administration, N_2O significantly attenuated the magnitude and the duration of opiate rigidity, particularly at the highest dose of ALF studied (350 μg/kg). Although the initial augmentation of ALF rigidity is consistent with prior clinical studies (7,21,24), N_2O's subsequent attenuation of opiate rigidity has not been described previously. The greater transient increase in EMG activity in the 70% N_2 group suggests that the initial augmentation of ALF rigidity by N_2O may not be a specific effect of N_2O per se but rather may be a consequence of the reduced inspired oxygen concentration.

Sokoll et al. were the first to suggest that N_2O augmented opiate-induced muscle rigidity (24). Thirty volunteers were given one of four opiates (morphine 0.4 mg/kg, meperidine 4 mg/kg, fentanyl 5 μg/kg, and pentazocine 2 mg/kg) and the H-reflex as well as abdominal EMG and subjective measures of muscle tone were assessed. They found that the addition of 70% N_2O increased abdominal EMG activity, augmented abdominal muscle tone, and impaired the ability to ventilate the subjects by mask. Unfortunately, EMG activity was not quantitated and the data were apparently not subjected to statistical analysis.

Using a similar experimental design, a subsequent study used nine volunteers whose $PaCO_2$ was controlled (7). Morphine 2 mg/kg produced a statistically significant increase in integrated abdominal EMG muscle activity. The addition of 70% N_2O produced a "board-like" abdomen and a marked increase in abdominal EMG activity that was eightfold higher within 3 min of N_2O exposure. Six of the subjects were unable

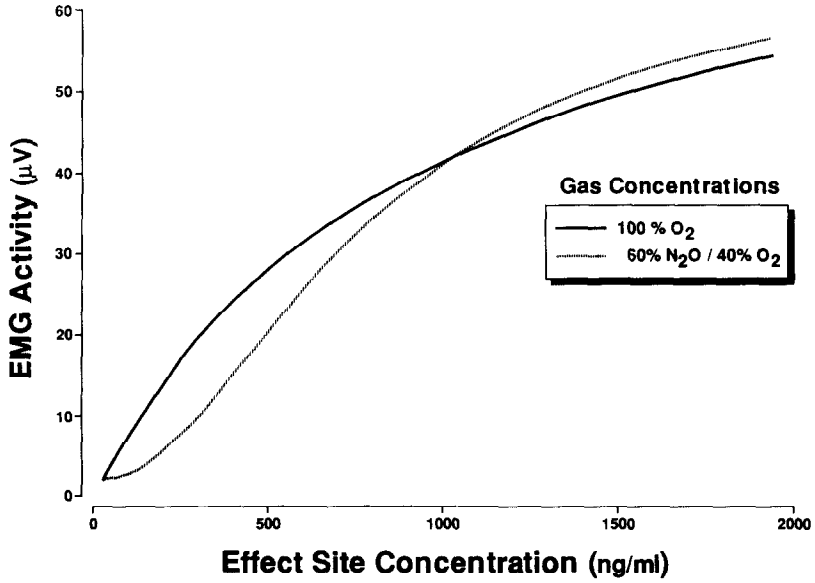

FIG. 4. A model of EMG activity vs. calculated effect site ALF concentration is presented for all rats receiving 100% O_2 compared with all rats receving 60% N_2O in 40% O_2. The increased sigmoidicity in the 60% N_2O group can explain the differences seen between the two groups in the effect-time relationships shown in Figs. 2 and 5.

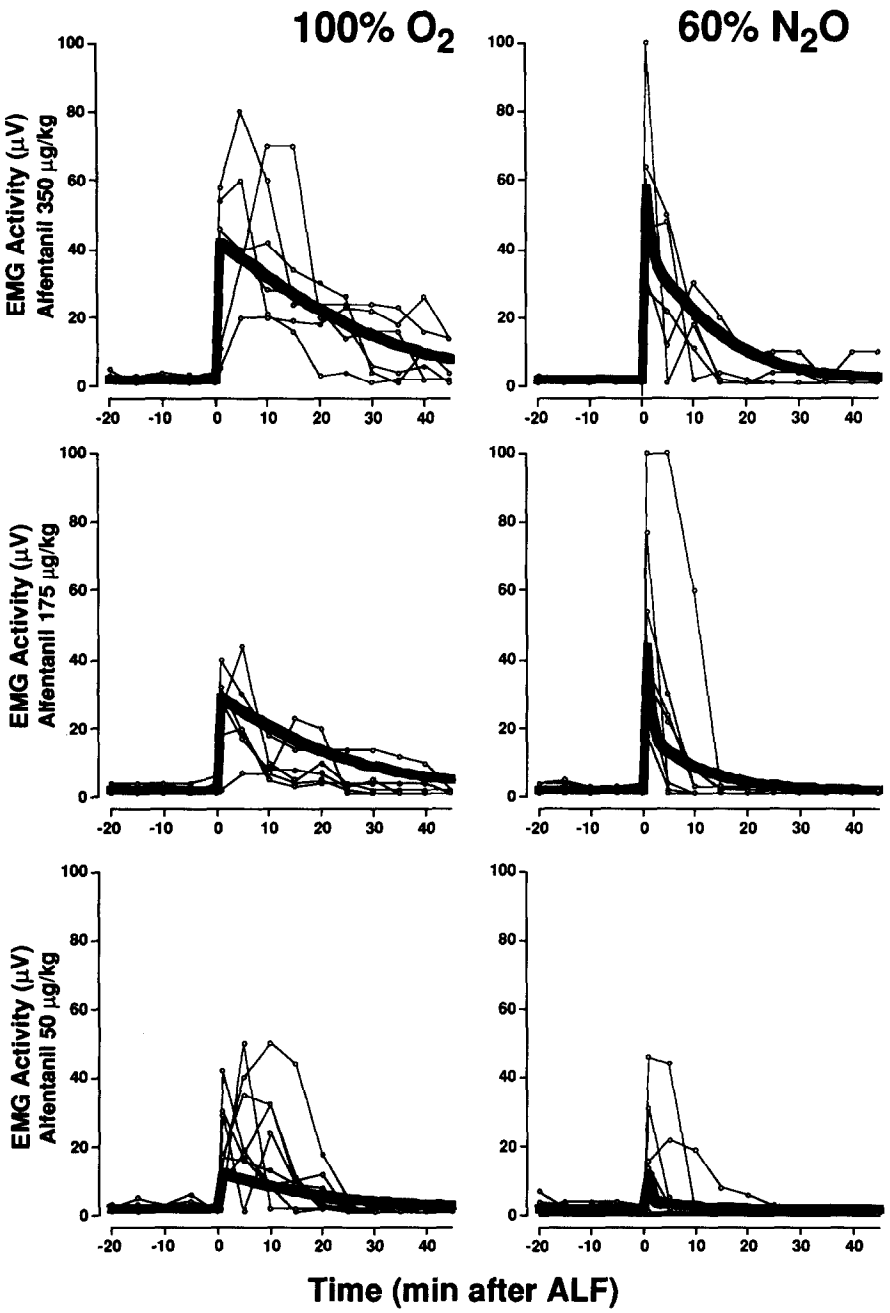

FIG. 5. The EMG activity (ordinate) vs. time following alfentanil for individual animals in each treatment group is presented. The top, middle, and bottom row of curves corrspond to 350, 175, and 50 μg/kg of alfentanil, respectively. The left and right columns correspond to 100% O_2 and 60% N_2O in 40% O_2, respectively. The open circles (○) are experimental EMG values. The bold lines represent the simulated effect-time curves generated using the fitted parameters shown in Table 1.

to be ventilated adequately, were given succinylcholine, intubated, and upon recovery, still exhibited significant muscle rigidity. Ten years later, the pulmonary compliance of five tracheostomized patients given fentanyl 30 μg/kg was measured (21). Fentanyl produced a 16 ± 2% decrease in compliance (altered plateau pressure during mechanical ventilation). Five minutes after the addition of 60% N_2O, compliance was reduced further to 38 ± 4% below preoperative baseline.

The above studies were performed in human volunteers and employed different indices of muscle tone than the present study. Although it is tempting to explain the disparity between these previous results and the present ones on the basis of species differences, other studies of the pharmacology of opiate-induced muscle rigidity in the rat (27) have shown remarkable homology with similar studies performed on human volunteers (2,20). On the other hand, the effects of N_2O on

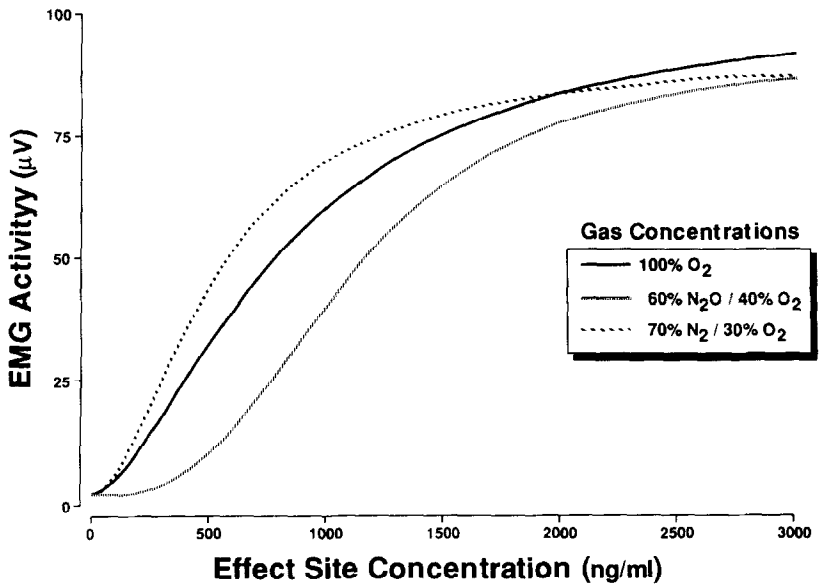

FIG. 6. EMG activity vs. effect site alfentanil concentration for rats receiving 350 μg/kg ALF IV and inspiring either 100% O_2, 60% N_2O in 40% O_2, or 70% N_2 in 30% O_2. See text for details. Note that because only rats in the ALF 350-μg/kg dose groups are depicted, this graph cannot be compared directly with Fig. 4.

opiate-related increases in locomotor activity have been shown to exhibit significant variability even within different strains of mice (11).

In previous clinical studies, muscle tone was assessed in abdominal muscles or by overall chest wall compliance. In contrast, in the present study, tonic muscle activity in the extremities was measured. There are data to suggest that the human response to high-dose opiates may be different in different muscle groups [(20), unpublished]. For example, in human volunteers given ALF 175 μg/kg, thiopental (1 mg/kg) pretreatment attenuated intercostal muscle rigidity (as measured by EMG) but had minimal effects on abdominal and peripheral muscle tone. Thus, it remains unclear whether the differences between the present results and those of earlier clinical studies are due to differences in the species studied, muscle tone measurement methodology, study design, or other factors.

In the present study, ALF was given IV, in contrast to the SC route of administration used in previous animal studies in this laboratory (27,28,30,31,35). Intravenous administration was employed to decrease between-subject variability in the absorption profile that might occur following SC or IP drug administration. Although there is an extremely rapid onset of rigidity after both IV (<1 min) and SC (<3 min) ALF administration, the duration of rigidity after IV administration was appreciably shortened compared with that seen after SC administration. For example, ALF, 150 and 300 μg/kg SC, produced significant rigidity for 30 min and greater than 60 min, respectively (35), compared with the 10 and 30 min observed after ALF 175 and 350 μg/kg (both breathing 100% oxygen), respectively, in the present study. This is consistent with a more rapid decline in ALF plasma concentrations following an IV bolus.

Comparison of EMG recordings following a single bolus dose of ALF in the presence or absence of N_2O would suggest that nitrous oxide accentuates the rigidity immediately following an IV bolus and subsequently attenuates muscle rigidity. This time-dependent alteration in measured effect could be explained on the basis of either a pharmacokinetic or a pharmacodynamic alteration induced by the inhalation of N_2O. Nitrous oxide has not been reported to alter the pharmacokinetics of other medications. N_2O does not affect fentanyl pharmacokinetics in humans (15). There is no a priori reason why a pharmacokinetic alteration would have been induced by N_2O in this study. Theoretically, a reduction in the central volume of distribution with a simultaneous increase in the clearance of ALF would produce higher concentrations immediately following a bolus with a more rapid decline in plasma concentrations at later time points. If this unprecedented pharmacokinetic mechanism was invoked as an explanation for the results of this study, one would expect a consistent initial accentuation of measured muscle activity in the presence of N_2O regardless of ALF dose. However, comparison of rigidity in the 50-μg/kg ALF groups shows approximately the same amount of initial rigidity with or without N_2O (Fig. 4). This is not consistent with an N_2O-induced pharmacokinetic alteration.

Because nitrous oxide is active on the central nervous system, it seems more plausible that N_2O has a pharmacodynamic interaction with ALF. If this explanation is pursued, the initial accentuation of muscle activity following a bolus dose of ALF in the presence of N_2O would be due primarily to a shorter ke0. This allows the concentration in the site of drug effect to more closely mirror the plasma, thereby rising rapidly to a higher concentration. The depression of muscle activity at later time points with nitrous oxide compared with 100% oxygen is due primarily to an accentuation of the sigmoidicity of the concentration-effect relationship.

Although this model appears to describe the effects of N_2O on ALF-induced muscle rigidity in the spontaneously ventilating rat, alternative explanations are possible. Increased concentrations of endogenous opioids in the brain that may result from N_2O exposure (25) may act as a type of "priming" analogous to the concept of the priming principle applied to the administration of neuromuscular antagonists (23). The sigmoid shape of the concentration-effect relationship would

predict very little to no measurable effect from this small initial endogenous opioid dose. However, the concentration in the site of drug effect would be advanced closer to the steep portion of the sigmoid curve. Thus, a subsequent bolus of opioid would push the effect rapidly up the steep portion of the curve, increasing the rapidity of drug effect compared with the same ALF dose administered in the absence of N_2O. In this circumstance, one might expect the model to behave as if there was a priming infusion of "undetected" opiate running throughout the experiment that would result in a leftward shift in the concentration-effect relationship. Our proposed model is not entirely consistent with this prediction because, in the highest ALF dose group, the C_{e50} showed a modest *right*ward shift with the addition of N_2O. Other possible effects of N_2O on ALF could include alterations in opioid receptor efficacy or changes in blood or brain solubility. Additional experiments in which ALF plasma levels are measured in animals breathing similar concentrations of N_2O vs. nitrogen in oxygen will be required to validate any hypothetical pharmacokinetic/pharmacodynamic model. An additional point is that because nitrogen is inert it is possible, although unlikely, that the results obtained may be due to a physiological effect of N_2.

Possible Underlying Mechanisms

It is possible that N_2O-mediated alterations in endogenous opioid (5,17,19) or opioid receptor activity (9) are responsible for N_2O's effects on ALF rigidity. Based on animal data, it has been speculated that N_2O produces analgesia by either augmenting release of endogenous opioids (5,17,19) or, perhaps, by acting directly on brain opioid receptors (4,9). The initial augmentation of opiate rigidity by N_2O is consistent with its ability to stimulate locomotor activity (10) and, in humans, to produce increased muscle activity when used alone at higher doses (16). On the other hand, the initial augmentation of opiate rigidity was also seen in the 70% N_2 group. However, relative hypoxemia can produce a stress response that is accompanied by a release of endogenous opioids.

Ketamine, like N_2O, is an anesthetic agent that has been shown to bind to opioid receptors (6) and to produce increases in muscle tone following anesthetic doses (32). In contrast to the transient augmentation of opiate rigidity with N_2O, ketamine pretreatment partially attenuated fentanyl-induced muscle rigidity in the mechanically ventilated rat (13).

It is possible that N_2O's subsequent attenuation of ALF rigidity may be due to more generalized CNS depressant effects. It has been suggested that most anesthetic medications, in sufficient dosage, will attenuate opiate-induced muscle rigidity due to generalized depression of CNS neuronal function rather than via some specific mechanism (27). A number of CNS depressants have been shown to blunt opiate rigidity, including barbiturates (7,13,20,26), benzodiazepines (20,27), ketamine (13), α_2 agonists (12,14,30), and the serotonergic antagonist ketanserin (27). Whereas in pilot studies, IV propofol (up to 3 mg/kg) failed to antagonize ALF rigidity in the rat (unpublished observations), propofol has been shown to attenuate ALF rigidity in humans (34).

Because respiratory variables were not measured in this study, it is possible that differences in ventilation between the treatment groups contributed to differences in the degree of muscle rigidity. All of the animals maintained spontaneous ventilation (at rates of 50–100 breaths/min) throughout the experiment. It should also be noted that the ameliorating effects of pretreatment with benzodiazepines in humans (20,29) on ALF-induced rigidity did not correlate with $PaCO_2$ or PaO_2 during several minutes of apnea (2). It is also possible that CNS hypoperfusion due to the combined drug effects contributed to the etiology of N_2O's attenuation of ALF-induced rigidity. However, severe brain ischemia generally results in increased muscle tone rather than flaccidity (8). Nevertheless, additional studies may be required to determine whether the interaction of N_2O and high-dose opiates on muscle tone is affected by concomitant alterations in ventilation or cardiovascular function.

In summary, using a well-established spontaneously ventilating rat model of ALF-induced muscle rigidity, nitrous oxide produced a transient (< 5 min) augmentation of opiate rigidity. However, beginning at 5 min post-ALF, N_2O significantly *attenuated* both the magnitude and the duration of ALF rigidity. These results may be explained on the basis of a pharmacodynamic effect of N_2O on ALF. Further studies will elucidate the neuropharmacological and clinical implications of these findings.

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