Dexmedetomidine, A Selective α₂-Agonist, Does Not Potentiate the Cardiorespiratory Depression of Alfentanil in the Rat

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The authors examined the cardiovascular and respiratory effects of the highly selective α₂-adrenergic agonist dexmedetomidine, both alone and in combination with the synthetic opiate alfentanil. Spontaneously ventilating rats (n = 28) were pretreated with dexmedetomidine, 10 or 30 μg/kg, dexmedetomidine, 30 μg/kg in combination with the central-acting α₂-agonist idazoxan, 10 mg/kg; or vehicle. Fifteen minutes later all rats received alfentanil, 500 μg/kg. Pretreatment with dexmedetomidine reduced heart rate in a dose-related fashion. Administration of alfentanil also caused a significant reduction in heart rate. However, following alfentanil, the dexmedetomidine-treated animals did not have significantly greater bradycardia than control animals. An increase in blood pressure was observed in those animals receiving the larger dose of dexmedetomidine, but this difference disappeared following injection of alfentanil. The addition of idazoxan to the pretreatment regimen prevented the changes seen with dexmedetomidine. Pretreatment with dexmedetomidine produced no significant changes in arterial pH or PaO₂. In all groups, administration of alfentanil resulted in a decrease in arterial pH that ultimately became a mixed respiratory and metabolic acidosis. The acidosis promptly resolved following injection of naloxone (1 mg/kg). It appears that dexmedetomidine, at the doses given, has little or no effect on respiration. Dexmedetomidine decreases heart rate but does not add to bradycardia following alfentanil. There is a hypertensive effect seen at the higher dose of dexmedetomidine, but this effect disappears when the drug is given in conjunction with alfentanil. These data show that addition of the α₂-agonist dexmedetomidine will not worsen the cardiovascular and respiratory depression associated with high-dose opiates in the spontaneously ventilating rat. (Key words: Analgesics; alfentanil. Blood pressure: drug effects. Heart: pulse rate. Sympathetic nervous system: α-adrenergic agonists. Sympathetic nervous system: α-adrenergic antagonists. Ventilation.)

There is growing interest in the potential of α₂-agonists as anesthetic adjuvants. These agents have been shown to reduce the MAC of volatile anesthetic agents in rats and dogs. A decrease in isoflurane and sevoflurane requirements has been demonstrated in patients pretreated with clonidine, a less-specific α₂-agonist. α₂-agonists possess substantial antinociceptive and sedative effects; these properties are not inhibited by the opiate antagonist naloxone. Selective competitive antagonists are available that reverse the actions of these drugs. Recent work has also shown that pretreatment with α₂-agonists prevents opiate-induced rigidity in rats. These properties have led some investigators to advocate their clinical use as anesthetic adjuvants.

Dexmedetomidine (DMED), an imidazole compound, is a novel α₂-adrenergic agonist that has an approximately eight-times higher selectivity for α₂ receptors than clonidine. Initially developed as a veterinary sedative, dexmedetomidine appears to exert its effects, at least in part, through central postsynaptic adrenergic receptors. Data in animals have demonstrated that dexmedetomidine can be a complete anesthetic. Some studies have suggested, however, that dexmedetomidine may increase systemic vascular resistance and decrease cardiac output. On the other hand, dexmedetomidine is only a mild respiratory depressant.

Dexmedetomidine's pharmacologic profile suggests that its initial clinical use will be as an anesthetic adjuvant, especially in association with an opiate-based anesthetic technique. Opiates produce bradycardia, hypotension, and depression of central respiratory drive. Because dexmedetomidine may have some of these same actions, it is important to investigate the effects of the combination of dexmedetomidine and opiates in an animal model before clinical studies are undertaken. The present study was designed to examine the cardiorespiratory response to dexmedetomidine in combination with the potent opiate agonist alfentanil in spontaneously ventilating rats.

Materials and Methods

Twenty-six male albino Wistar rats (Harlan Laboratories, Chicago, IL) weighing 300–375 g were studied over a 3-month period. Animals were housed in groups of three in a temperature-controlled room and maintained on a 12-h light/dark cycle. Free access to food and water was permitted. Animals were acclimated to the experimental apparatus for 1-h periods 3–4 times during the 4 days prior to the experiment to minimize the effects of stress due to restraint. All animals were used only once. The experimental protocol was approved by the Animal Care Committee of the San Diego VA Medical Center.

On the day of testing, animals were anesthetized with 2.5% halothane in oxygen through a nose cone. Rectal temperature was continuously monitored and maintained.

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Received from the Department of Anesthesiology, University of California, San Diego School of Medicine, and the Anesthesiology Service of the San Diego VA Medical Center, San Diego, California. Accepted for publication December 13, 1989. Supported in part by the American Society of Anesthesiology, the Parker B. Francis Foundation, and a grant from the Department of Veterans Affairs. Dr. Weinger is a Parker B. Francis Investigator in Anesthesiology.

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at 37.5 ± 1° C by use of a heating pad. The right femoral artery was exposed through a skin incision and cannulated with polyethylene tubing (PE-50). One milliliter of heparinized saline (50 IU/ml) was injected intra-arterially to prevent clotting. The catheter was threaded subcutaneously around to the back where it was externalized and secured with 4-0 silk. The femoral incision was closed and lidocaine 0.5% was injected at the sites of incision and exteriorization. Two monopolar platinum electrodes (Grass E2, Grass Instruments, Quincy, MA) were placed percutaneously in the left gastrocnemius muscle, and a third electrode was placed in the right hindlimb to permit recording of hindlimb electromyographic (EMG) activity. Leads were secured with cellophane tape in a manner so as not to restrict joint mobility. The arterial catheter was connected to a pressure transducer (Electromedics MD-5) for mean blood pressure (MBP) measurements. Heart rate (HR) was determined by a tachograph from the blood pressure waveform. EMG activity was calculated from the differential signal of the gastrocnemius muscle, which was fed through a band-pass filter (10 Hz–3 kHz) and converted to a root-mean-square (RMS) voltage. MBP, HR, and EMG signals were continuously displayed on a physiologic recorder (Grass Instruments 79C). Periodic arterial blood samples (200 µl/sample) were drawn through a side port in the arterial catheter and analyzed for pH, Pao2, and Paco2 (Instrumentation Laboratories IL-1306, Lexington, MA). Volume was replaced with heparinized saline. Hematocrit was determined on each arterial blood sample to detect hemodilution. The halothane anesthetic never lasted more than 1 h.

Rats were randomly assigned to one of four pretreatment groups (table 1). Animals received either vehicle (n = 8); dexmedetomidine (Farmos Group Ltd, Turku, Finland), 10 µg/kg (n = 6); dexmedetomidine, 30 µg/kg (n = 6); or the combination of dexmedetomidine, 30 µg/kg, with the α2-antagonist idazoxan (Reckitt and Coleman, Kingston-upon-Hull, England), 10 mg/kg (n = 6). Drugs were obtained as powders, reconstituted in a 0.9% physiologic saline vehicle, and injected intraperitoneally in a volume of 1 ml/kg. The investigator was blinded as to treatment group. Each animal was used in only one experiment.

For the experiment, the rats were placed in barred, cylindrical holding cages that allowed for free movement of the extremities. Experiments were conducted in a soundproof chamber (Coulbourn Instruments, Lehigh Valley, PA). Following cessation of halothane anesthesia, animals were allowed a 60–90-min recovery period breathing room air. Baseline data (MBP, HR, EMG) were collected for 15 min, at the end of which time a baseline arterial blood gas determination (pH, Pao2, Paco2) was made. The pretreatment drug was injected intraperitoneally and the animals monitored for 15 min. Blood gases were obtained at 5- and 15-min intervals postinjection. Alfentanil (Jansen Pharmaceutica, Piscataway, NJ), 500 µg/kg in saline vehicle, was then injected subcutaneously. Animals were observed for the next 30 min, with blood gases obtained at intervals of 5, 15, and 30 min postinjection. Finally, the opiate antagonist naloxone (DuPont Pharmaceuticals, Wilmington, DE), 1 mg/kg subcutaneously, was administered and the animals observed for an additional 5 min before a final arterial sample for blood gas analysis was obtained.

Data for HR, MBP, EMG, arterial pH, Pao2, and Paco2 were collected for each experimental animal. While hemodynamic and EMG data were continuously recorded, data at 5-min intervals were chosen for statistical analysis. Statistical differences between treatment groups were determined using two-way analysis of variance (ANOVA). Newman-Keuls a posteriori tests were performed to determine differences among treatment groups at individual time points as well as differences over time within individual treatment groups. Values of P < 0.05 were considered significant. Data are expressed as mean ± SEM unless indicated otherwise.

Results

There were no significant differences among groups with respect to baseline arterial blood gases or cardiovascular parameters. Rats pretreated with dexmedetomidine alone were noticably more sedated than saline controls and failed to vocalize when receiving subcutaneous injections. In contrast, animals receiving dexmedetomidine plus idazoxan were more irritable than either control animals or those receiving dexmedetomidine alone. Hematocrit remained within 5% of initial values in all animals during the study (table 1).

<table>
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<th>Table 1. Treatment Group Assignments (n = 26)*</th>
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* Data expressed as mean ± SD.

† Initial and final values, respectively.
HEMODYNAMIC EFFECTS

Pretreatment with the larger dose of dexmedetomidine resulted in a significant ($P < 0.05$) decrease in heart rate compared with other groups (fig. 1). The heart rate data was then subjected to further analysis. A mean baseline (prior to study drug treatment) heart rate was calculated, and subsequent values were normalized by dividing by the mean baseline value. After this normalization process, which corrected for variations in baseline among groups, a significant decrease in heart rate was also seen at the lower dose of dexmedetomidine ($P < 0.05$) when compared with controls. The higher dose of dexmedetomidine produced an increase in blood pressure ($P < 0.05$), while the lower dose had no effect (fig. 2). Coadministration of idazoxan with dexmedetomidine inhibited the bradycardia and hypertension seen with dexmedetomidine alone. Injection of alfentanil produced a decrease in both heart rate and blood pressure in all animals; importantly, however, there were no significant differences in these parameters among groups by 15 min after alfentanil injection. The bradycardia seen in the dexmedetomidine, 30 $\mu$g/kg, group was not significantly augmented by injection of alfentanil. Naloxone rapidly returned hemodynamic values to baseline, with bradycardia and hypertension persisting in those animals pretreated with the higher dose of dexmedetomidine.

Respiratory Effects

Administration of dexmedetomidine produced no significant changes in room air arterial $pH$ or $P_{CO_2}$ (figs. 3 and 4). Dexmedetomidine alone had no effect on $P_{O_2}$, but animals receiving the combination of dexmedetomidine and idazoxan had slightly elevated $P_{O_2}$ values following pretreatment (fig. 5). Injection of alfentanil resulted in a significant decline in arterial $pH$ and $P_{O_2}$ in all animals, with a concurrent rise in $P_{CO_2}$. The acidosis was initially respiratory in nature but, by the end of the 30-min period, a metabolic component was also present.

Rats pretreated with the higher dose of dexmedetomidine, however, were significantly less acidic following alfentanil than animals receiving other pretreatments ($P < 0.05$). The lower arterial $pH$ values were accompanied by somewhat lower $P_{CO_2}$ values in the DMED group. Administration of naloxone resulted in return of $P_{CO_2}$ to baseline values in all groups; there remained a persistent
Acidosis in all animals except those pretreated with dexmedetomidine, 30 μg/kg. PaO₂ was increased from baseline in all groups following injection of naloxone.

**Figure 3.** Effect of dexmedetomidine on arterial pH. Pretreatment with dexmedetomidine (10 μg/kg) [DMED 10; □], dexmedetomidine (30 μg/kg) [DMED 30; △], dexmedetomidine (50 μg/kg) plus idazoxan (10 mg/kg) [DMED + Idz; □], or saline vehicle [ □] had no effect on pH. Alfentanil 500 μg/kg (ALF) produced a significant decrease from baseline in all groups (P < 0.05), with animals receiving the largest dose of dexmedetomidine significantly less acidic at each time point (P < 0.05). Naloxone 1 mg/kg (NAL) reversed this effect, with all groups exhibiting a residual acidosis (P < 0.05) except those pretreated with DMED 30. In this figure, the X axis gives the time points at which arterial pH values were obtained. These include a baseline time point (Baseline), two time points 5 and 15 min after drug pretreatment (Pre + 5 and Pre + 15), three points after alfentanil injection (ALF + 5, ALF + 15, and ALF + 30), and a final point 5 min after naloxone injection (NAL + 5). Data are plotted as mean ± SEM.

**Figure 4.** Effect of dexmedetomidine on PaO₂. Pretreatment with dexmedetomidine (10 μg/kg) [DMED 10; □], dexmedetomidine (30 μg/kg) [DMED 30; △], dexmedetomidine (20 μg/kg) plus idazoxan (10 mg/kg) [DMED + Idz; □], or saline vehicle [ □] had no effect on arterial PaO₂ (mean ± SEM). Alfentanil 500 μg/kg (ALF) resulted in significant respiratory depression in all groups (P < 0.05 compared with baseline). Animals pretreated with the higher dose of dexmedetomidine were significantly less hypercapnic than controls at 15 and 30 min after alfentanil (P < 0.05). Naloxone 1 mg/kg (NAL) returned PaO₂ values to baseline in all groups. As in figure 3, the X axis gives the time points at which arterial values were obtained.

**Figure 5.** Effect of dexmedetomidine on arterial PaO₂. Pretreatment with dexmedetomidine at both the 10 μg/kg [DMED 10; □] and the 30 μg/kg [DMED 30; △] dose had no effect on room air arterial PaO₂ as compared with saline controls [ □]. In contrast, rats pretreated with dexmedetomidine (30 μg/kg) and idazoxan (10 mg/kg) [DMED + Idz; □] exhibited an elevated PaO₂ at 15 min following pretreatment (P < 0.05). Alfentanil 500 μg/kg (ALF) produced a significant hypoxemia in all animals (P < 0.05 compared with baseline). Those animals pretreated with DMED 30 or DMED + Idz were significantly less hypoxic than other groups at 5 min following alfentanil injection (P < 0.05), but this difference did not persist thereafter. Naloxone 1 mg/kg (NAL) reversed the hypoxemia and produced a significant increase in PaO₂ in all groups above baseline values (P < 0.05). As in figure 3, the X axis gives the time points at which arterial values were obtained.

**Muscle Rigidity**

Alfentanil-induced muscle rigidity, as measured by hindlimb EMG activity, was attenuated by pretreatment with dexmedetomidine in a dose-related fashion. The mean (± SEM) area under the EMG activity-versus-time curve for the 30-min period between alfentanil and naloxone injections decreased progressively with increasing doses of DMED (saline: 56.0 ± 5.7; DMED 10 μg/kg: 33.1 ± 12.2; DMED 30 μg/kg: 15.7 ± 5.9). The higher dose of DMED completely inhibited muscle rigidity compared with saline controls (P < 0.05). Coadministration of idazoxan prevented dexmedetomidine’s rigidity-blocking effects, and actually resulted in a slight increase in muscle tone after alfentanil compared with controls (65.2 ± 13.5).

**Discussion**

In this study it was demonstrated that: 1) dexmedetomidine had little or no effect on arterial blood gases in spontaneously ventilating rats; 2) dexmedetomidine produced a decrease in heart rate; 3) the higher dose of dexmedetomidine was associated with an increase in systemic blood pressure; 4) pretreatment with dexmedetomidine lessened the acidosis seen following alfentanil administration; and 5) the addition of dexmedetomidine did not significantly worsen the decrease in heart rate and blood
pressure seen after a high dose of alfentanil in the rat. The prevention of dexmedetomidine’s effects by the coadministration of the highly selective α₂-antagonist idroxazan is consistent with a competitive α₂-adrenoceptor-mediated process.

Clinical studies using clonidine have suggested that α₂-agonists can safely reduce anesthetic requirements and improve perioperative hemodynamic stability.4,5,21 Use of α₂-agonists in conjunction with conventional anesthetics may enhance sedation and analgesia without producing respiratory depression, muscle rigidity, or prolonged recovery periods. Because α₂-agonists inhibit opiate-induced rigidity, it is natural that these agents be used as adjuvants with high-dose opiate anesthesia. Before these agents can be put into routine clinical use, however, it is important to characterize their effects on cardiovascular and respiratory function, both alone and in combination with other anesthetics. The results of the present study suggest that dexmedetomidine could be a safe adjuvant to opiate anesthetics.

Previous observations of the effects of dexmedetomidine on the respiratory and cardiovascular systems have been made on anesthetized animals, and this confounding variable mitigates against the direct assessment of the respiratory effects of the anesthetic versus those of the α₂-agonist. In this study, animals were permitted a minimum of 1 h of breathing room air to recover from halothane anesthesia; this period was chosen because it has been used previously in studies on blood gas values in rats.22 Baseline blood gas data were consistent with those reported in the literature for unanesthetized animals.23 On the other hand, similar data are unavailable to rule out the unlikely possibility that some residual cardiovascular effects of halothane might have influenced the results of the present study.

Data from this study and others have shown that dexmedetomidine produces a dose-dependent decrease in heart rate. The failure of high-dose alfentanil to significantly augment the bradycardia seen with high-dose dexmedetomidine suggests a ceiling effect to this drug combination. Opiates appear to produce bradycardia by attenuation of sympathetic outflow and by increased vagal tone.24-26 While the precise etiology of the bradycardic effects of the α₂-agonists has yet to be determined, similar mechanisms to those invoked by the opiates could be involved. Because neither class of drug appears to be a direct myocardial depressant,15,27 it is possible that their cardiovascular effects are mediated by similar or parallel central mechanisms. If both drug classes produce bradycardia primarily by decreased central sympathetic outflow, then this would explain the limit to the magnitude of their negative chronotropic effects whether given individually or in combination.

At the higher dose of dexmedetomidine, an increase in blood pressure accompanies the decrease in heart rate. This hypertensive effect has been reported previously,16 and is felt to be due to the activation of peripheral post-synaptic α₂-adrenoceptors in vascular smooth muscle.28 Studies with the α₂-agonist ST-91 have shown it to increase mean arterial pressure in spontaneously ventilating ewes.29 Both clonidine and ST-91 produce hypertension in spinaly transected rats,30 supporting a peripheral mode of action.

As expected, a profound acidosis developed in the experimental animals following the administration of alfentanil. The acidosis was initially respiratory but, by the end of the 30-min period, a metabolic component was also present, suggesting tissue hypoperfusion. The antagonism of the alfentanil-induced respiratory depression with naloxone did not completely restore to normal the acid/base balance in control animals. The presence of normal blood gas values in these animals prior to alfentanil administration seems to exclude the possibility of residual halothane-induced respiratory depression. Perhaps more than 5 min is required to eliminate the reservoir of tissue CO₂ after a prolonged episode of hypercarbia and hypoperfusion. Interestingly, pretreatment with dexmedetomidine lessened the degree of acidosis seen following alfentanil, and the arterial pH values in these animals, in fact, returned completely to baseline following administration of naloxone. This effect may be due to an improvement in chest wall compliance (owing to inhibition of opiate-induced rigidity), or to improved tissue perfusion, or both.

The elevation in Pₐₒ₂ seen following pretreatment with idoxazan plus dexmedetomidine was surprising. Because α₂-agonists have been shown to produce hypoxemia by a peripheral effect,29 it is possible that the dose of idoxazan used in the present study was larger than necessary and resulted in antagonism of endogenous peripheral α₂ activity. Alternatively, the Pₒ₂ sparing effect may stem from the unmasking of dexmedetomidine's minimal α₁ properties in the presence of the highly selective α₂-antagonist. The dose of idoxazan used in this study was higher than previously reported to produce complete blockade of α₂ receptors.11,29 The increased irritability noted in those animals receiving idoxazan is consistent with either hypothesis. However, the increase in arterial Pₒ₂ after alfentanil in this group argues against hyperventilation as a major contributing factor for the Pₒ₂ sparing effect. Parallel studies using idoxazan alone as a pretreatment regimen were not performed.

The recovery of Pₒ₂ to above baseline values in all of the groups following naloxone reversal deserves comment. It is possible that this relative hypoxia was due to hyperventilation in hypercarbic animals in whom opiate
anesthesia has been rapidly antagonized. Further studies would be necessary to support this hypothesis.

Our data appear to confirm that dexmedetomidine has little or no effect on respiration. Pretreatment with dexmedetomidine did not affect resting arterial pH or PaCO₂ in the spontaneously ventilating animal, and also did not worsen the alfentanil-induced respiratory depression. In fact, pretreatment with dexmedetomidine at 30 μg/kg decreased the acidosis and hypercapnia seen following administration of alfentanil. Previous studies of the effects of α₂ agonists on respiration using clonidine have either found no effect or hypoxia unaccompanied by changes in arterial pH or PaCO₂. Bloor et al. found minimal, if any, increase in PaCO₂ following administration of dexmedetomidine to spontaneously ventilating dogs under isoflurane anesthesia. Our findings support these studies and suggest that dexmedetomidine may even be protective when given with opiates anesthetics, perhaps due to decreased CO₂ production or improved chest wall compliance.

In this study we examined the effect of dexmedetomidine on ventilatory dynamics by measuring serial arterial blood gases in rats spontaneously breathing room air. More revealing information concerning respiratory drive is generally obtained by determining the ventilatory response to graded levels of inspired CO₂. It is possible that dexmedetomidine alters the slope of the minute ventilation-CO₂ curve, as suggested by Bloor et al. in studies of dexmedetomidine and isoflurane; the design of the present study did not permit detection of these more subtle levels of ventilatory depression.

The results of this study suggest that, in contrast to other anesthetic adjuvants such as the benzodiazepines, the α₂-agonist dexmedetomidine does not further compromise cardiovascular or respiratory status in the presence of high-dose opiates. This finding can now be added to other animal and human data that suggest that dexmedetomidine produces sedation, lessens anesthetic requirements, and inhibits opiate-induced muscle rigidity. In total, the growing pharmacologic evidence supports dexmedetomidine use as an adjuvant in clinical opiate anesthesia.

The authors wish to thank Drs. Mervyn Maze and John Drummond for editorial assistance, Ms. Joan Azar for help in the preparation of the manuscript, and Ms. Natalia Riosco-Terry for technical assistance. Dexmedetomidine was generously provided by Dr. Riso Laminimstaust of Farmos Group Ltd; alfentanil was a gift of Janssen Pharmaceutical. Specialized temperature probes were kindly furnished by Mon-ı-Therm Corporation.

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