Sedative, analgesic, and cardiovascular effects of levomedetomidine alone and in combination with dexmedetomidine in dogs

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Objective—To determine whether a high dose of levomedetomidine had any pharmacologic activity or would antagonize the sedative and analgesic effects of dexmedetomidine in dogs.

Animals—6 healthy Beagles.

Procedure—Each dog received the following treatments on separate days: a low dose of levomedetomidine (10 µg/kg), IV, as a bolus, followed by continuous infusion at a dose of 25 µg/kg/h; a high dose of levomedetomidine (80 µg/kg), IV, as a bolus, followed by continuous infusion at a dose of 200 µg/kg/h; and a dose of isotonic saline (0.9% NaCl) solution, IV, as a bolus, followed by continuous infusion (control). For all 3 treatments, the infusion was continued for 120 minutes. After 60 minutes, a single dose of dexmedetomidine (10 µg/kg) was administered IV. Sedation and analgesia were scored subjectively, and heart rate, blood pressure, respiratory rate, arterial blood gas partial pressures, and rectal temperatures were monitored.

Results—Administration of levomedetomidine did not cause any behavioral changes. However, administration of the higher dose of levomedetomidine enhanced the bradycardia and reduced the sedative and analgesic effects associated with administration of dexmedetomidine.

Conclusions and Clinical Relevance—Results suggest that administration of dexmedetomidine alone may have some cardiovascular benefits over administration of medetomidine, which contains both dexmedetomidine and levomedetomidine. Further studies are needed to confirm the clinical importance of the effects of levomedetomidine in dogs. (Am J Vet Res 2001;62:616–621)

Medetomidine, a potent and selective α2-adrenoceptor agonist that contains equal parts of 2 optical enantiomers, dexmedetomidine and levomedetomidine, is widely used for sedation in small animals. Dexmedetomidine is undergoing extensive clinical studies for use during the perioperative period in humans.1,3 Levomedetomidine, on the other hand, is generally considered to be an inactive ingredient in medetomidine.

In vitro studies have demonstrated that levomedetomidine may act as a weak partial α2-adrenoceptor agonist10 or as an inverse α2-adrenoceptor agonist (negative antagonist), depending on the test system and constitutive activity of the receptors.11 It is also capable of binding to and activating α1-adrenoceptors, although it is weaker than dexmedetomidine in this respect.7 The α2-to-α1 adrenoceptor selectivity ratio reported for dexmedetomidine is 1,300, whereas that of levomedetomidine is only 23,7 and it has been suggested that activation of central α1-adrenoceptors functionally antagonizes hypnotic responses to an α2-adrenoceptor agonist.12 Thus levomedetomidine and dexmedetomidine may have opposite effects in vivo.

In vivo studies of the effects of levomedetomidine are scarce. Cardiovascular and respiratory changes associated with levomedetomidine administration have not been reported, and the behavioral alterations that have been reported are difficult to interpret. In addition, previous studies used batches of levomedetomidine that may have contained some dexmedetomidine10,11 or did not mention how purity of the drug was determined.12-16 Levomedetomidine has been shown to prolong sleeping time in rats sedated with hexobarbital,14,15 but this was likely a result of kinetic interaction and not of any sedative effects levomedetomidine has on its own.14 In rats, levomedetomidine was without hypnotic effects even at doses of 30 mg/kg of body weight,16 whereas in another study, a dose of 10 mg/kg provoked arousal.14 Moreover, in mice, levomedetomidine (100 and 300 µg/kg) increased cerebellar cyclic guanosine 3’,5’-monophosphate (cGMP) content, whereas dexmedetomidine decreased cerebellar cGMP content at doses that typically cause sedation.17 The cerebellar cGMP concentration is generally increased by drugs that cause stimulation and decreased by drugs that cause sedation.17

In dogs, low doses (≤ 10 µg/kg) of levomedetomidine did not result in the typical responses caused by dexmedetomidine.12,13 In a previous study,16 involving conscious dogs, analgesia caused by dexmedetomidine (20 µg/kg) lasted longer than analgesia caused by medetomidine (40 µg/kg), although level of sedation and changes in cardiovascular parameters did not differ. A bolus dose of levomedetomidine (10 µg/kg or 20 µg/kg, 100% optical purity) did not cause any apparent sedation, analgesia, or cardiovascular changes; however, vague signs of abnormal behavior (fatigue or arousal) were noticed after administration of levomedetomidine in some dogs.
The present study was undertaken to further clarify the action of levomedetomidine in dogs, whether given alone or with dexmedetomidine. In particular, the purpose of the study reported here was to determine whether a high dose of levomedetomidine was capable of stimulating or sedating dogs or would antagonize the sedative and analgesic effects of dexmedetomidine.

Materials and Methods

Animals—Six purpose-bred healthy laboratory Beagles (3 sexually intact females and 3 castrated males) were used in the study. Dogs were approximately 1 year old and weighed between 13 and 17 kg. They were housed together in a large pen and received outdoor exercise in a yard for several hours daily. Regular dog food was given once daily, and water was freely available. All procedures were performed during the daytime, and on study days, the dogs were fed only after the experiments were completed. The dogs were accustomed to handling, instrumentation, the study room, and the researchers. The study protocol was approved by the Faculty of Veterinary Medicine's Animal Care and Use Committee.

Treatments—Each dog received the following treatments on separate days: administration of a low dose of levomedetomidine hydrochloride (10 µg/kg), IV, as a bolus, followed by continuous infusion at a dose of 25 µg/kg/h; administration of a high dose of levomedetomidine (80 µg/kg), IV, as a bolus, followed by continuous infusion at a dose of 200 µg/kg/h; and administration of 0.9% NaCl solution, IV, as a bolus, followed by continuous infusion (control). For all 3 treatments, the infusion rate was 1.25 ml/kg/h, and the infusion was continued for 120 minutes. During times that the dogs received levomedetomidine, steady-state serum concentrations were assumed to have been achieved after 60 minutes because of the bolus given initially. At 60 minutes, a single dose of dexmedetomidine hydrochloride (10 µg/kg) was administered IV. Treatments were separated by a minimum of 2 weeks and were administered in random order. Investigators were blinded to the treatment given.

Levomedetomidine solutions were made by dissolving purified (100% optical purity) powder in isotonic saline solution. Dexmedetomidine was obtained in ampoules containing purified (100% optical purity) powder in isotonic saline solution. Samples for catecholamine analysis (0, 60, and 120 minutes) were collected into tubes containing EDTA and set on melting ice. Plasma was immediately separated by refrigerated centrifugation and frozen at −80°C (later accidentally removed to −20°C for 2 weeks) and analyzed in duplicate by means of capillary gas chromatography with mass spectrometry detection. The detection limit was 0.05 ng/ml. Samples for catecholamine analysis (0, 60, and 120 minutes) were collected into tubes containing EDTA and set on melting ice. Plasma was immediately separated by refrigerated centrifugation and frozen at −80°C (later accidentally removed to −20°C for 2 weeks) and analyzed in duplicate by means of high-performance liquid chromatography. The detection limit was 0.05 nmol/l.

Statistical analyses—Data for the first (0 to 60 minutes) and second (60 to 120 minutes) parts of each treatment were analyzed separately. Numerical variables, including overall degree of sedation, were analyzed by use of repeated-measures ANOVA to check for the main effects of treatment and for interactions between treatment and time. If differences were detected, separate 2-tailed paired t-tests were calculated for each time point. Categorical variables were analyzed by use of the nonparametric Friedman test for each time point. Values of P < 0.05 were considered significant. Data are expressed as mean ± SD.

Results

Sedative and analgesic results—Dogs were not sedated during the first hour of treatment. A few dogs (3 during treatment with the high dose of levomedetomidine, 1 during treatment with the low dose of lev-
omeditomidine, and 1 during the control treatment) seemed slightly tired and sometimes lay down, but at 60 minutes all dogs were alert and standing. No signs of arousal, trembling, nausea, or any other abnormal behavior could be detected.

After administration of dexmedetomidine, all dogs were sedated and became laterally or sternally recumbent. At 70 minutes, total sedation score was significantly ($P = 0.025$) lower when dogs were treated with the high dose of levomedetomidine than when they received the control treatment (Fig 1). Sedation scores were not significantly different among treatments at other times; however, overall degree of sedation was significantly higher when dexmedetomidine was given alone (control treatment) than when given in combination with a high dose of levomedetomidine ($P = 0.002$) or a low dose of levomedetomidine ($P = 0.027$). At 70 minutes, relaxation of the jaw muscles was significantly less when dogs were given the high dose of levomedetomidine than when they were given the control treatment ($P = 0.046$). At 120 minutes, response to a loud noise was best when dogs were given the high dose of levomedetomidine, compared with response when dogs were given the control treatment ($P = 0.046$) or a low dose of levomedetomidine ($P = 0.025$). At 70 and 80 minutes, degree of analgesia was weakest when dogs were given the high dose of levomedetomidine, compared with the control treatment ($P = 0.025$) and the low dose of levomedetomidine ($P = 0.046$; Fig 2).

Cardiorespiratory effects—At 60 minutes, mean HR was significantly lower with the high dose of levomedetomidine (mean ± SD, 67 ± 11 beats/min) than with the low dose of levomedetomidine (89 ± 12 beats/min; $P = 0.005$) or the control treatment (88 ± 10 beats/min; $P = 0.008$), and the change from baseline value with the high dose of levomedetomidine was significantly different from the change from baseline value with the low dose of levomedetomidine ($P = 0.005$). After administration of levomedetomidine, HR decreased with all the treatments. However, HR with the high dose of levomedetomidine was significantly lower than HR with the control treatment ($P = 0.043$) or the low dose of levomedetomidine ($P = 0.011$) during most time points (Fig 3).

No ECG abnormalities were detected at 0 or 60 minutes. After administration of dexmedetomidine, frequent episodes of first-degree atrioventricular block with accentuated sinus arrhythmia were detected in all dogs, regardless of treatment, during the next hour. A few episodes of second-degree atrioventricular block were seen in 1 dog at 75 and 90 minutes, regardless of which treatment was given (although most of these were seen with the control treatment), and in another dog with the control treatment at 75 minutes.

At 60 minutes, DBP was significantly higher with the high dose of levomedetomidine than with the low dose of levomedetomidine ($P = 0.018$) or the control treatment.
treatment \( (P = 0.014; \text{Fig 4}) \), but SBP and MBP were not significantly different among treatments. After administration of dexmedetomidine, blood pressure increased transiently and then gradually decreased to baseline values, with no differences among treatments from 70 to 120 minutes.

Respiratory rate, rectal temperature, and results of blood gas analyses did not change during the first hour. After administration of dexmedetomidine, RR, rectal temperature, pH, and PaO2 decreased, and PaCO2 increased. Lowest mean pH after administration of dexmedetomidine was 7.34 ± 0.02 (range, 7.30 to 7.39), lowest mean PaO2 was 94 ± 9 mm Hg (range, 80 to 110 mm Hg), and highest mean PaCO2 was 40 ± 2.2 mm Hg (range, 33 to 44 mm Hg).

Plasma catecholamine concentrations—Plasma epinephrine (Fig 5) and norepinephrine (Fig 6) concentrations decreased during the initial 60 minutes and decreased further after dexmedetomidine administration. However, significant differences among treatments were not detected at any time.

Table 1—Mean ± SD plasma levomedetomidine and dexmedetomidine concentrations (ng/ml) in dogs given a low or high dose of levomedetomidine and in control dogs, with and without dexmedetomidine.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Control</th>
<th>LLEVO</th>
<th>HLEVO</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>0.6 ± 1.0</td>
<td>24.2 ± 3.9</td>
<td>171.9 ± 40.3</td>
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<td>90</td>
<td>3.8 ± 0.5</td>
<td>20.5 ± 3.3</td>
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<tr>
<td>105</td>
<td>2.9 ± 0.5</td>
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<td>189.3 ± 33.9</td>
</tr>
<tr>
<td>120</td>
<td>2.1 ± 0.3</td>
<td>19.8 ± 1.4</td>
<td>183.6 ± 35.1</td>
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</tbody>
</table>

Dogs were given a low dose of levomedetomidine (10 µg/kg), IV, as a bolus, followed by continuous infusion at a dose of 25 µg/kg/h (LLEVO; \( n = 6 \)); a high dose of levomedetomidine (80 µg/kg), IV, as a bolus, followed by continuous infusion at a dose of 200 µg/kg/h (HLEVO; \( n = 6 \)); or a dose of isotonic saline solution, IV, as a bolus, followed by continuous infusion (Control, \( n = 5 \)). At 60 minutes, a single dose of dexmedetomidine (10 µg/kg) was administered IV to all dogs.

Plasma levomedetomidine and dexmedetomidine concentrations—With the control treatment, dexmedetomidine concentration gradually decreased from 6.6 ± 1.0 to 2.1 ± 0.3 ng/ml. When levomedetomidine was administered, administration of dexmedetomidine resulted in an abrupt increase in the combined levomedetomidine-dexmedetomidine concentration, which did not decrease during the subsequent 60 minutes (Table 1).

Other effects—Short periods of apnea, slight cyanosis, and muscular twitching were detected in some dogs after dexmedetomidine administration, with no differences among treatments. One of the dogs vomited after administration of dexmedetomidine with the low and with the high dose of levomedetomidine but not after administration of dexmedetomidine alone.

Discussion—Results of the present study indicated that administration of levomedetomidine to conscious dogs did not cause any behavioral changes. Because the dogs were calm before any drugs were given, it was difficult
to determine whether levomedetomidine had any sedative properties. A few dogs did seem drowsy at some times during the first 60 minutes of each treatment, but these dogs were readily aroused and alert if something unexpected happened in their environment, so the drowsy appearance could perhaps be attributed to boredom. Previous studies\(^2,4,13\) have reported some degree of stimulation following administration of levomedetomidine, but the dose of levomedetomidine in the present study may not have been high enough to induce arousal.

In the present study, administration of a high dose of levomedetomidine reduced the sedative and analgesic effects caused by administration of dexmedetomidine. However, analgesic effects of dexmedetomidine in a conjunct with a low dose of levomedetomidine (i.e., a clinical dose) were similar to effects obtained when dexmedetomidine was given alone. It was anticipated that the antagonizing effects of a high dose of levomedetomidine would continue throughout the study, because levomedetomidine was given as a continuous infusion. However, it was predominantly the initial sedation and analgesia that were reduced. It is possible that the high dose of levomedetomidine slowed the elimination of dexmedetomidine, prolonging its effects. Levomedetomidine has been reported to inhibit hepatic metabolism of some other anesthetic agents.\(^10,22\)

With deep sedation, analgesic effects may be difficult to distinguish from sedative effects. We decided to test analgesia by observing the withdrawal reflex in response to toe web pinching. The test is easy to perform and interpret and does not cause tissue damage. Withdrawal reflexes are spinal mediated and may not involve actual pain perception. However, dexmedetomidine-induced analgesia is also mainly spinal mediated.\(^3,23\) Despite their suspected spinal origin, withdrawal reflex tests are widely used and generally considered valid when \(\alpha_2\)-adrenoceptor agonist-mediated analgesia is evaluated.\(^15,20\)

The cardiovascular changes seen with the high dose of levomedetomidine in the present study were unexpected and, to our knowledge, have not been reported previously. Because HR and arterial blood pressures were not measured during the first hour, possible changes in these variables soon after administration of the initial bolus remain unclear. However, at 60 minutes, HR was significantly lower and DBP was significantly higher with the low dose of levomedetomidine alone (control treatment) and the concentration after 60 minutes of levomedetomidine infusion. This finding can most likely be explained by the effect on metabolism induced by the cardiovascular changes provoked by dexmedetomidine. Thus, with high doses of medetomidine, the plasma levomedetomidine concentration and even the effect of levomedetomidine may be unexpectedly elevated.

Our findings imply that high doses of levomedetomidine on their own may have some typical partial \(\alpha_2\)-adrenoceptor agonist properties. However, the combined effect with dexmedetomidine can be unpre-
dictable. Inverse agonist action may occur when a full \(\alpha_2\)-adrenoceptor agonist changes the activity of the receptors or competitive antagonism is induced by levomedetomidine.

In conclusion, levomedetomidine did not cause any behavioral changes in conscious dogs even at the higher dose. The higher dose did, however, enhance bradycardia and reduce the sedative and analgesic effects associated with dexmedetomidine. Accordingly, administration of dexmedetomidine alone may have some cardiovascular benefits over administration of medetomidine, which contains both dexmedetomidine and levomedetomidine, but further studies are needed to confirm the clinical importance of this assumption.

References