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Effects of intrathecally administered dexmedetomidine, MPV-2426 and tizanidine on EMG in rats

P. TALKE[1], M. XU[3], M. PALOHEIMO[2] and E. KALSO[2]
[1]*Departments of Anesthesia and Perioperative Medicine, University of California, San Francisco, CA,* [2]*Anesthesia and Intensive Care, Helsinki University Hospital,* [3]*Pharmacology and Toxicology, Institute of Biomedicine, Helsinki University, Helsinki, Finland*

Background: When administered intrathecally, alpha-2 adrenergic agonists produce spinally mediated antinociception, but also rapidly redistribute to supraspinal sites. This investigation the compared EMG effects of intrathecally administered dexmedetomidine, MPV-2426 (fadolmidine), and tizanidine in Sprague-Dawley rats, which has not been previously described.
Methods: We studied electromyographic (EMG) responses of the head and gastrocnemius muscles, antinociception using the tail-flick test, and sedation by using observer assessment. Saline, dexmedetomidine (0.5 μg, 2.5 μg and 12.5 μg), MPV-2426 (2 μg, 10 μg and 50 μg) and tizanidine (2 μg, 10 μg and 50 μg) were administered intrathecally.
Results: Tizanidine 50 μg, MPV-2426 10 μg and 50 μg, and dexmedetomidine 2.5 μg and 12.5 μg, decreased EMG activity ($P < 0.005$). Dexmedetomidine 12.5 μg, MPV-2426 50 μg, and tizanidine 10 μg and 50 μg increased tail-flick latencies ($P < 0.01$). Dexmedetomidine alone significantly increased the magnitude of observer-assessed sedation ($P < 0.0001$).
Conclusion: We conclude that in rats, intrathecally administered dexmedetomidine, MPV-2426 and tizanidine have dose-dependent effects on EMG. At antinociceptive doses, the EMG effects of these three alpha-2 adrenergic agonists differ (dexmedetomidine > MPV-2426 > tizanidine).

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ALPHA-2 adrenergic agonists produce antinociception, an effect that appears to be mediated primarily at the level of the spinal cord (1–6). This suggests that alpha-2 adrenergic agonists may be useful for intrathecal pain management, but these agents are not without risks. For example, when administered intrathecally, clonidine and dexmedetomidine produce spinally mediated antinociception, but both also rapidly redistribute to supraspinal sites, producing unwanted effects such as sedation and hypotension (7, 8). Similarly, epidural delivery of clonidine is useful in managing cancer-related neuropathic pain, but also incurs sedative and hemodynamic effects (9). To exploit the therapeutic potential of these agents therefore requires development of an intrathecally administered alpha-2 adrenergic agonist with antinociceptive but minimal or negligible supraspinally mediated side-effects. Two alpha-2 adrenergic agonists show some promise.

MPV-2426 (fadolmidine) is a new, full, non-subtype-selective agonist at the alpha-2 adrenoceptor that has been shown to have antinociceptive and antiallodynic effects in animal models (4, 10–13). With intrathecal administration, MPV-2426 appears to produce antinociception equipotent to that of dexmedetomidine while being less rapidly distributed to supraspinal sites (11, 14). Tizanidine, another alpha-2 adrenergic agonist, seems to produce antinociceptive effects similar to those of clonidine, with minimal hemodynamic side-effects and limited distribution to the central nervous system (1, 15, 16). Effects of intrathecally administered dexmedetomidine, MPV-2426 and tizanidine on supraspinally mediated electromyogram (EMG) activity in rats *in vivo* have not been described. We therefore tested the hypothesis that intrathecally administered MPV-2426 and tizanidine have a less supraspinally mediated effect compared with dexmedetomidine. As alpha-2 agonists reduce EMG activity after intraventricular administration (17–19), but have no direct effects on neuromuscular activity (1, 11, 12, 17, 20), we used gastrocnemius EMG as a measurement of the supraspinal actions of alpha-2 agonists. In addition we compared the antinociceptive and sedative effects of dexmedetomidine, MPV-2426 and tizanidine.

Methods

With approval from the Animal Care and Use Committee of the University of Helsinki, this study was performed in 62 Sprague-Dawley rats (weighing 280–380 g) that were housed individually in clear Plexiglas® (Plexiglas©, Philadelphia, USA) containers maintained in a temperature-controlled (25 ± 1 °C) room throughout study. Animals were given free access to food and water.

Animal preparation

To permit placement of an intrathecal cannula, the rats were anesthetized by a subcutaneous injection of midazolam 5.0 mg kg^{-1} (Dormicum®, Roche, Basel, Switzerland) and Hypnorm® 1.0 ml kg^{-1} (fentanyl 0.2 mg ml^{-1}, and fluanisone 10 mg ml^{-1}; Janssen Pharmaceutica, Beerse, Belgium). A polyethylene catheter (PE-10; Meadox Surgimed A/S, Stenlose, Denmark) was then inserted 80 mm caudal into the lumbar subarachnoid space through the cisterna magna, fixed with a suture to the paravertebral muscles, and externalized through the skin at the neck region (21). At least 7 days of recovery were allowed before the study was started.

Animals were habituated to handling and test equipment before the study. Only those demonstrating normal behavior and motor function, followed by complete bilateral paralysis of the hind limbs in response to an intrathecal injection of a test dose of 10 µl of 5% hyperbaric lidocaine (Lidocain Pond®, Medipolar, Oulu, Finland), were included. Each animal was studied up to four times, with 3 days of respite between successive experiments.

Study drug protocol

Dexmedetomidine hydrochloride (Orion Corporation, Turku, Finland), MPV-2426 (Orion Corporation, Turku, Finland) and tizanidine hydrochloride (Novartis, Basel, Switzerland) were studied. The alpha-2 adrenergic antagonist atipamezole (Orion Corporation, Turku, Finland) was used to reverse the action of each agonist. All drugs were dissolved in sterile physiologic saline in concentrations that allowed intrathecal injections in volumes of 10 µl, and all were administered manually as a single injection followed by a flush of physiologic saline 10 µl. Study drugs were administered via the intrathecal catheter while the rats were awake and restrained within their containers. Investigators were blinded to both the drugs and doses, unless otherwise specified.

To identify the effects of dexmedetomidine, MPV-2426 and tizanidine on gastrocnemius EMG, antinociception and sedation, we used a four-way crossover, randomized (within groups), double-blind (drug and dose) design. For this experiment, there were three groups of six rats each. On four separate days, each rat received an intrathecal injection of either placebo (saline), dexmedetomidine [0.5 µg (2.1 nM), 2.5 µg (10.5 nM) and 12.5 µg (53 nM)], MPV-2426 [2 µg (0.8 nM), 10 µg (3.9 nM) and 50 µg (19 nM)], or tizanidine [2 µg (0.7 nM), 10 µg (3.5 nM) and 50 µg (17 nM)] at dose ranges determined by preliminary data. Gastrocnemius EMG was measured continuously throughout the study. Antinociception was assessed by the tail-flick (TF) test just before and 15 min after study drug administration. Sedation was measured using observer assessment immediately before study drug administration, and 15 min after study drug administration, during the second TF test.

To demonstrate that the effects of the intrathecally administered alpha-2 agonists were not mediated only at the site of drug administration, we simultaneously determined the effects of dexmedetomidine on head and gastrocnemius EMG response in six rats that received an intrathecal injection of dexmedetomidine (12.5 µg). Antinociception was assessed by the TF test just before and 15 min after study drug administration. Immediately after the second TF test, each rat was given an intrathecal injection of atipamezole 40 µg. In an additional experiment, to demonstrate that the action of lidocaine is limited by the site of administration, two rats were given an intrathecal injection of lidocaine hydrochloride, 500 µg, and head and gastrocnemius EMG activity was recorded continuously before, during and following drug administration, until the EMG values returned to baseline.

To determine the effects of the three agonists on spontaneous locomotion, four groups of six rats each were randomized to receive an intrathecal injection of either placebo (saline), dexmedetomidine (12.5 µg), MPV-2426 (50 µg) or tizanidine (50 µg). Dosages were determined from those showing antinociceptive and sedative effects in the first stage of study. Spontaneous locomotion was tested for a 15-min time period, starting immediately after drug administration.

Measurements

Gastrocnemius EMG responses were obtained via needle electrodes (Xomed, Jacksonville, FL) inserted bilaterally into the gastrocnemius and subcutaneously into the base of the tail (reference electrode). In a subset of animals, EMG responses from the animal's mimic muscles of the head were also obtained via electrodes (Xomed) inserted through the skin medial to the rat's ears. All electrodes were inserted on the

day of the experiment, while the animals were awake, and removed after each experiment. Electrodes were secured to the animal's hair using glue (Instant Krazy Glue®, Elmer's Products, Inc., Columbus, OH). The EMG signals were amplified and digitized with mean integrated amplitudes recorded on a computer every 10 s by an Anesthesia and Brain Activity Monitor (ABM, Datex, Helsinki, Finland). Electromyographic energy was expressed in arbitrary integrated units. The EMG activity data were reduced to 1-min median values. Data from predetermined time periods were used for analysis and expressed as percent change from baseline EMG activity (22).

Thermal nociceptive thresholds were assessed using the TF test, TF latencies being established using an Ugo Basile (Comerio, Italy) apparatus. Measurements of TF latency were obtained in triplicate at least 1 min apart, using an 8.0-s cut-off time to minimize tissue damage. Results are expressed as a percentage of the maximum possible effect (MPE%) calculated using the following formula:

$$\text{MPE\%} = (\text{postdrug latency} - \text{predrug latency}) / (8.0\text{s} - \text{predrug latency}) \times 100\%$$

Continuous investigator observation of the animals allowed the authors to score sedation at predetermined times using the following scale: 1 = normal behavior, alert, awake; 2 = slightly sedated; 3 = moderately sedated but responsive to noxious stimulus (TF test); and 4 = unresponsive to noxious stimulus.

Spontaneous locomotion was assessed using an automated measurement system (Kungsbacka Mät-Reglerteknik AB, Kungsbacka, Sweden). Immediately after intrathecal injection of the agonist, each rat was placed in a sound-isolated box (70 × 70 × 35 cm) containing two series of photocells located 2 cm and 12 cm above the box floor. This system provides a quiet, dark environment while electronically measuring and recording the amount of animal movement in the box. During the continuous 15-min monitoring period, measurements were recorded for three successive 5-min periods.

Because the results of the TF test with MPV-2426 differed significantly from those obtained in earlier studies from the same laboratory (see Discussion), we determined the *post hoc* effect of MPV-2426 on antinociception in an additional six animals using a two-way cross-over design. Animals were randomized to be instrumented for one day with EMG needle electrodes, as described earlier, or not instrumented. On the second study day the instrumentation assignment was reversed for each animal. Antinociception was assessed via the TF test just before and 15 min after the intrathecal injection of MPV-2426 10 μg.

Statistical analysis

For each study day, the effects of dexmedetomidine, MPV-2426 and tizanidine on EMG amplitude, TF latency, and spontaneous locomotion were determined by repeated analysis of variance followed by Dunnett's *post hoc* test when appropriate. All TF tests were carried out in triplicate. The mean of the three TF tests (%MPE values) was used for analysis. Effect of the TF test on EMG amplitude was determined using the Student's paired *t*-test. Nonparametric variables were examined by the Kruskal–Wallis test. Data are expressed as the mean ± SD. $P < 0.05$ identified statistical significance.

Results

Tizanidine 50 μg (17 nM), MPV-2426 10 μg (3.9 nM) and 50 μg (19 nM), and dexmedetomidine 2.5 μg (10.5 nM) and 12.5 μg (53 nM) significantly decreased the EMG tone of the gastrocnemius ($P < 0.005$; Fig. 1). This decrease was significantly greater with 12.5 μg of dexmedetomidine and 50 μg of MPV-2426 than with 50 μg of tizanidine ($P < 0.0001$). The stimulus of the TF test 15 min after agonist administration temporarily reversed the effect on EMG response (suggesting arousability) of all drugs at all doses, except for 12.5 μg of dexmedetomidine (Table 1).

Baseline TF latency values did not differ within each group on the different days of study. We therefore calculated an average baseline latency for each group by combining the baseline values from all four experiments. The resulting baseline TF latencies were 3.7 ± 0.1 s, 3.7 ± 0.1 s and 3.5 ± 0.1 s for dexmedetomidine, MPV-2426 and tizanidine, respectively (P = NS). Dexmedetomidine 12.5 μg, MPV-2426 50 μg, and tizanidine 10 μg (3.5 nM) and 50 μg increased TF latencies (%MPE) significantly from baseline (Fig 2, $P < 0.01$ for all), but there was no significant difference among the agonists in the percentage-MPE values at the highest dose.

Dexmedetomidine alone significantly increased the magnitude of clinically assessed sedation (Fig 3, $P < 0.0001$). Five of six animals given 2.5 μg of dexmedetomidine were moderately sedated (score 3), and five of six given 12.5 μg were asleep (score 4). In comparison, only one and two of six given the highest tizanidine and MPV-2426 doses, respectively, were moderately sedated, and none were asleep.

Simultaneously measured head and gastrocnemius EMG activity decreased equally and significantly with

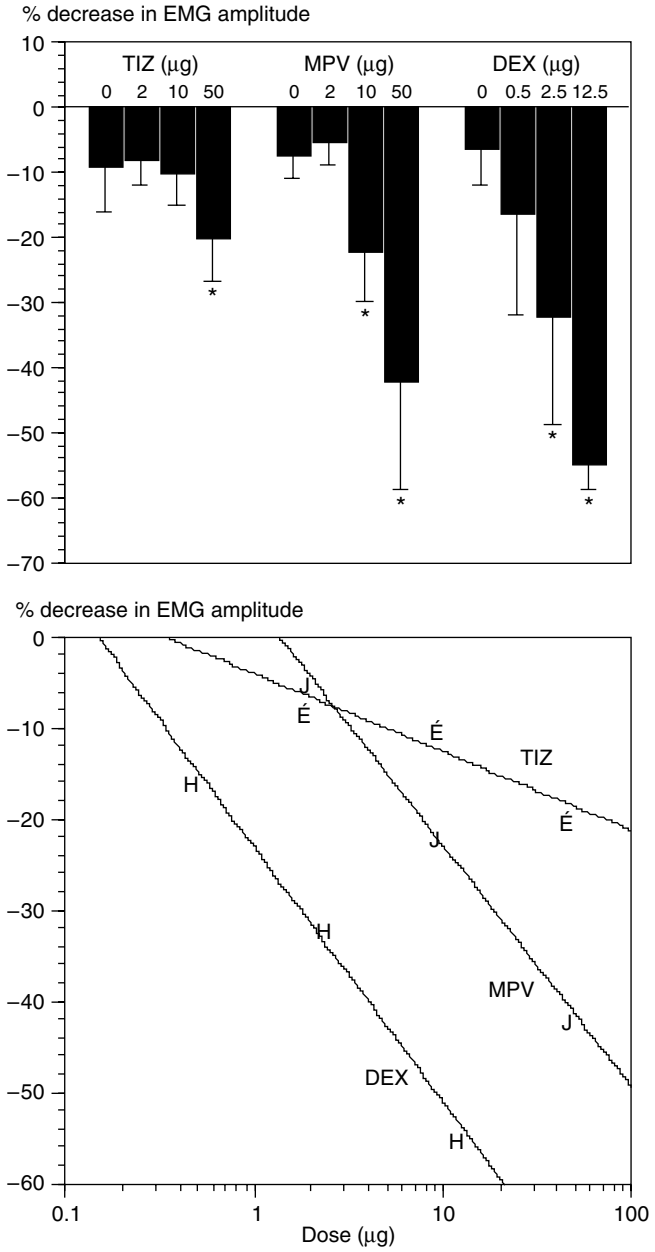

*Fig. 1. Top panel shows the percentage of the maximum possible decrease in electromyographic (EMG) amplitude values after intrathecal administration of tizanidine (TIZ), MPV-2426 (MPV) or dexmedetomidine (DEX). Data are mean ± SD. *P < 0.05 vs. placebo. Bottom panel illustrates the dose–response curves (linear regression) for DEX (▲), MPV-2426 (●) and tizanidine (○) plotting the average decrease in EMG amplitude after intrathecal drug administration.*

dexmedetomidine 12.5 µg ($P < 0.0001$, Fig. 4). Approximately 3 min after the injections, all animals became visually sedated and made an attempt to stay awake, which is reflected as a transient increase in both head and gastrocnemius EMG activity (Fig. 4, middle panel). Stimulus of the TF test caused an insignificant increase in both head and gastrocnemius EMG activity (Fig. 4, middle panel). Administration of the antagonist atipamezole reversed this effect, increasing head and gastrocnemius EMG activity simultaneously starting 2–3 min after the injection. Injection of lidocaine 500 µg in the additional two animals decreased EMG activity in the gastrocnemius but had no effect in the mimic muscles (Fig. 4). These data demonstrate that the effects of the intrathecally administered dexmedetomidine were not mediated only at the site of drug administration, whereas the effects of the intrathecally administered lidocaine did not reach supraspinal sites. These data suggest a supraspinal site of action for the EMG effects of dexmedetomidine.

Spontaneous locomotion decreased at 0–5 min in the animals given dexmedetomidine and MPV-2426 ($P < 0.0002$), and at 5–10 min and 10–15 min in all three agonist groups ($P < 0.0001$), compared with intrathecal saline (Fig. 5). At both 0–5 min and 5–10 min, tizanidine caused less depression of locomotion than dexmedetomidine and MPV-2426 ($P < 0.005$).

In the additional six animals given MPV-2426 10 µg intrathecally, baseline TF latencies were 3.7 ± 0.4 s and 3.7 ± 0.3 s, respectively, for the animals that did and did not undergo instrumentation with EMG electrodes ($P =$ NS). MPV-2426 increased TF latencies (MPE) by 46 ± 31% in the instrumented animals and 82 ± 20% in the non-instrumented animals ($P < 0.05$), suggesting that insertion of the needle electrodes had an effect on the TF response.

Discussion

This study is the first to describe the supraspinally mediated EMG effects of intrathecally administered dexmedetomidine, MPV-2426 and tizanidine in rats *in vivo*. Our findings indicate that, like dexmedetomidine, intrathecally administered MPV-2426 and tizanidine result in a decrease in supraspinally mediated motor effects. However, the magnitude of this effect differs significantly, with dexmedetomidine > MPV-2426 > tizanidine. These findings are consistent with those suggesting a more limited spread of MPV-2426 and tizanidine in the central nervous system compared with dexmedetomidine (11–16).

That the alpha-2 adrenergic agonist inducing a decrease in gastrocnemius EMG activity is supraspinally mediated is supported by several previous studies and by several observations in the present study (11, 12, 17–20). First, EMG activity of the mimic muscles (innervated by cranial nerves) and the hind limb muscles decreased simultaneously

Table 1

Electromyographic values (measured from the gastrocnemius muscle, and percent change from baseline) before and after the tail-flick test.

	Before TF	After TF
Dexmedetomidine		
Placebo	−6±6	9±5
0.5 μg	−16±16	4±3
2.5 μg	−32±17*	−2±5
12.5 μg	−55±4*	−44±22*
MPV-2426		
Placebo	−7±4	4±3
2 μg	−5±4	4±6
10 μg	−22±8*	3±3
50 μg	−42±17*	−6±11
Tizanidine		
Placebo	−9±7	4±2
2 μg	−8±4	4±4
10 μg	−10±5	0±5
50 μg	−20±7*	1±4

Values are expressed as mean ± SD.
*Significant difference from baseline (pre-drug administration).
Before TF (i.e. tail-flick test): minimum values within 15 min of drug injection, before testing.
After TF: maximum values after the TF test.

after administration of dexmedetomidine. Second, intrathecal lidocaine had an effect on gastrocnemius but not head EMG response. Third, several studies have shown that there are no known direct effects of the alpha-2 adrenergic agonists on neuromuscular activity or on motor activity, making their direct action on muscles unlikely (1, 11, 12, 17, 20). Third, systemically administered ST-91, a compound that has poor blood–brain barrier penetration, does not have an effect on spontaneous EMG activity, whereas intraventricularly and systemically administered dexmedetomidine decreases EMG activity (17–19). Finally, the reduction of gastrocnemius EMG activity by dexmedetomidine is consistent with previous

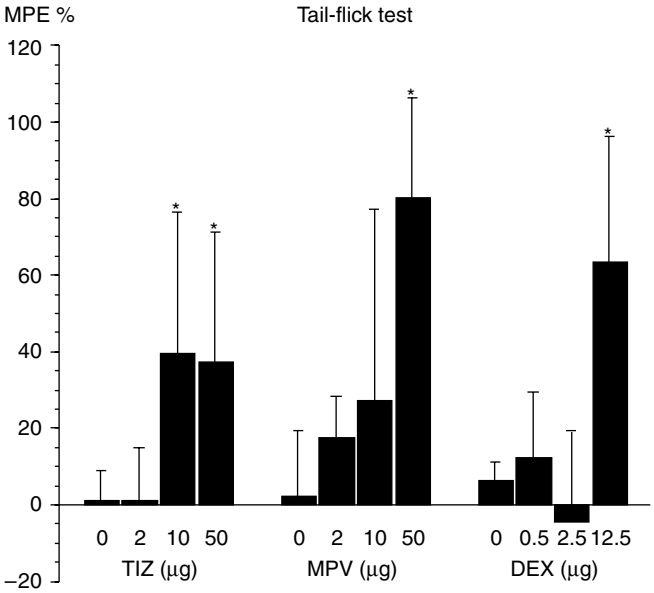

*Fig. 2. Percentage of the maximum possible effect (MPE) in tail-flick values after intrathecal administration of tizanidine (TIZ), MPV-2426 (MPV) or dexmedetomidine (DEX). Data are expressed as the mean ± SD. *P<0.05 vs. placebo.*

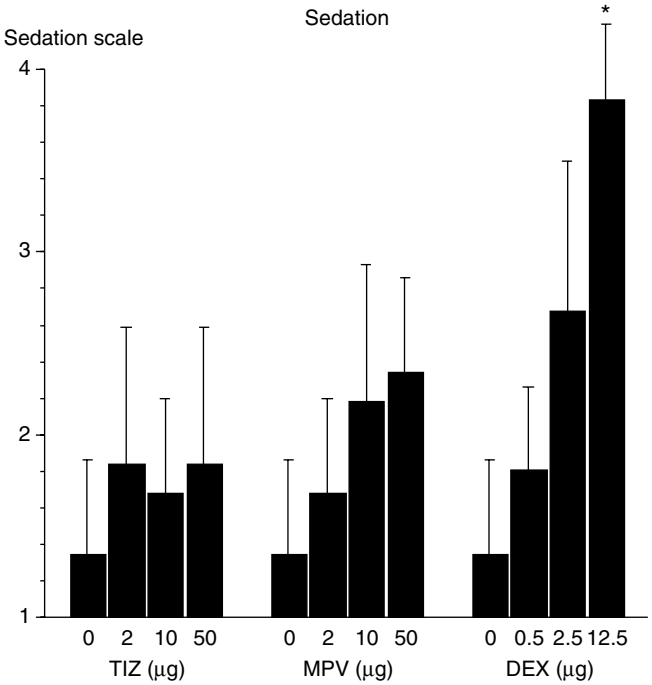

*Fig. 3. Effect of intrathecal, dexmedetomidine (DEX), MPV-2426 (MPV) and tizanidine (TIZ) on sedation. Data are expressed as the mean ± SD. *P<0.05 vs. placebo.*

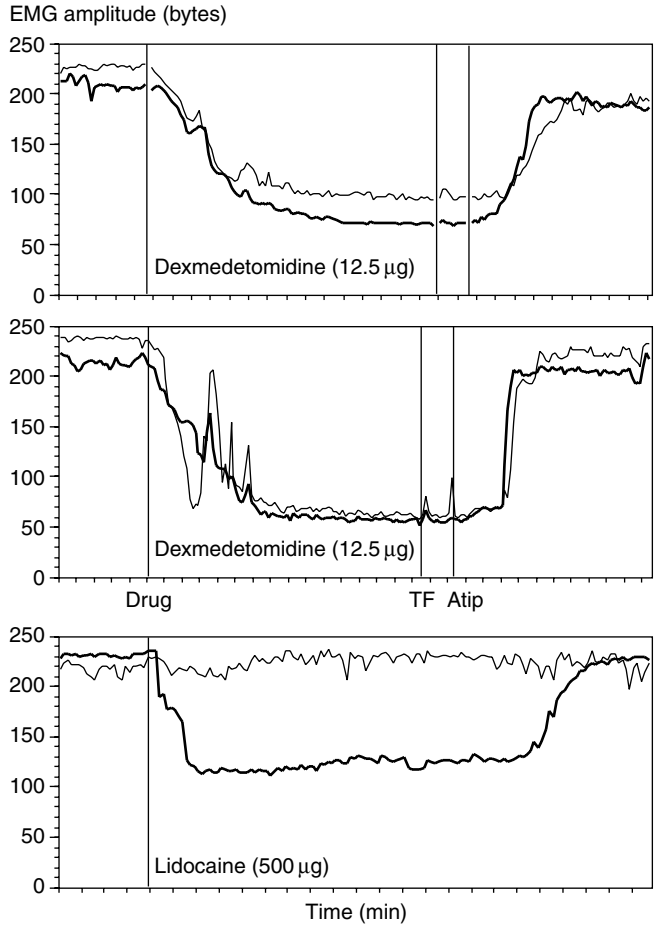

Fig. 4. Electromyographic data from the head (thin line) and the gastrocnemius muscle (thick line) of animals receiving intrathecal dexmedetomidine 12.5 μg (top and middle panels) or lidocaine 500 μg (bottom panel). Top panel shows the mean data for all six animals receiving dexmedetomidine. Middle and bottom panels show the data from an individual animal. Vertical lines mark the beginning of dexmedetomidine or lidocaine administration (drug), tail-flick test (TF) and intrathecal administration of atipamezole (Atip).

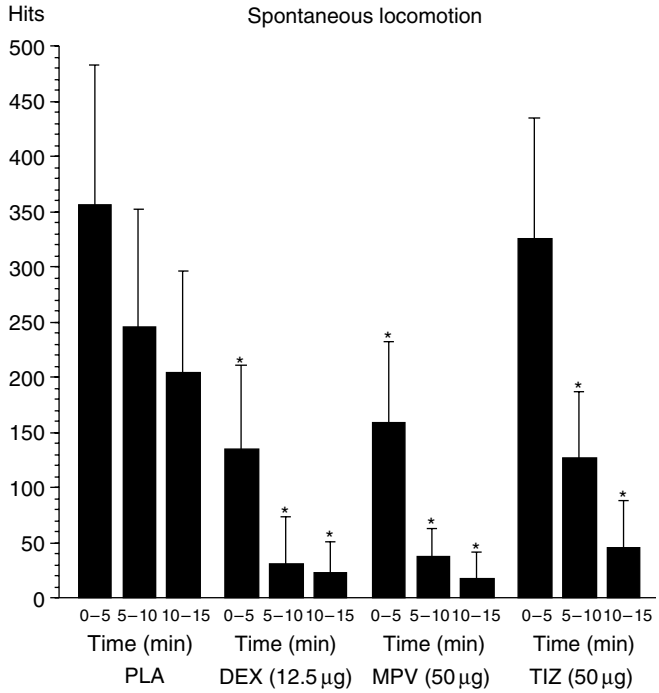

*Fig. 5. Effect of intrathecal saline (PLA), dexmedetomidine 12.5 μg (DEX), MPV-2426 50 μg (MPV) and tizanidine 50 μg (TIZ) on spontaneous locomotion. Data are expressed as the mean±SD for three consecutive 5-min time periods. *P < 0.05 vs. placebo at the corresponding time period.*

investigations demonstrating reduction in EMG activity of several different muscle groups with induction of anesthesia (22).

Several studies have demonstrated that intrathecal MPV-2426 and dexmedetomidine have an equipotent antinociceptive effect, an effect that appears to be mediated primarily at the level of the spinal cord (1–6). One previous study used spontaneous locomotion to measure sedation following intrathecal administration of dexmedetomidine and MPV-2426, and showed that at equiantinociceptive doses, MPV-2426 had less effect on spontaneous locomotion than dexmedetomidine (11). In the present study there was no difference in the decrease in spontaneous locomotion with dexmedetomidine 12.5 μg i.t. and a four-fold higher dose on weight bases (50 μg) of MPV-2426. Our findings using spontaneous locomotion, EMG activity and observer assessment are therefore consistent with those of this previous report, and indicate that 4–10-fold more MPV-2426 is required to produce similar supraspinal effects as dexmedetomidine (see Fig. 1).

Tizanidine, at an intrathecally administered antinociceptive dose, does not affect alertness in dogs, and a dose double the lowest antinociceptive dose causes only mild sedation, with animals remaining easily arousable (16). We found similar results in our rats. That is, the lower of the two antinociceptive doses (10 μg) of tizanidine had no supraspinal effects (EMG) and the higher antinociceptive dose (50 μg) had only mild supraspinal effects.

Each of the study methods for measuring the effects of the alpha-2 agonists in the present study has both strengths and limitations. The locomotion test is an objective measure of sedation, but the results can be influenced by other variables, such as anxiety, pain, lack of interest in the environment, or motor dysfunction. For example, within 30 min, even the control animals became immobile, indicating that the sensitivity of this test declines rapidly over time, thereby making it difficult to assess the influence of drugs whose effects on spontaneous locomotion develop over a prolonged period. Clinical observation,

although adequate in detecting severe sedation and sleep, is subjective and limited by poor sensitivity at lower levels of sedation. The decrease in EMG activity as a measure of supraspinal effects is objective and continuous (22).

The doses of dexmedetomidine and MPV-2426 required to achieve antinociception in the present study were approximately 10-fold higher than those determined by previous studies (11, 12). This discrepancy was particularly concerning because one of the previous studies was conducted in the same laboratory using the same techniques, with only one exception: our use of intramuscular EMG needle electrodes in the present study. We therefore studied *post hoc* the antinociceptive dose requirements of MPV-2426 via the TF test in an additional six animals with and without acutely implanted EMG needle electrodes. We found a significantly higher dose requirement in the instrumented animals, and an antinociceptive dose–response comparable to that obtained in previous studies in uninstrumented animals. Although no animal appeared to be in distress, our results suggest that the noxious stimulus of acutely implanted EMG needle electrodes in the gastrocnemius muscles caused sufficient discomfort to increase the MPV-2426 dose requirement for antinociception, which would explain the difference in dose–response between the previous and present studies.

Our effort to differentiate the centrally mediated side-effects of the three alpha-2 adrenergic agonists studied is limited by several factors. First, we did not explore the mechanism (pharmacokinetic vs. pharmacodynamic) of the different onset times and potencies of the supraspinal effects of dexmedetomidine, MPV-2426 and tizanidine. Second, we did not study several other alpha-2 adrenergic agonist-mediated effects that may limit their therapeutic potential, such as adverse hemodynamic effects. However, our results indicate that intrathecally administered alpha-2 adrenergic agonists differ in their profiles of supraspinally mediated effects. Our study of antinociception with and without EMG needle electrode instrumentation is limited by the authors inability to blind the investigators to the group assignment. However, the measurement of antinociception is electronically determined, thus reducing potential bias.

We conclude that intrathecal dexmedetomidine, MPV-2426 and tizanidine have sedative and antinociceptive effects, and that, at antinociceptive doses, their effects on EMG differ (dexmedetomidine > MPV-2426 > tizanidine). Our findings also suggest that the antinociceptive dose requirement of the alpha-2 adrenergic agonists may increase significantly in the presence of discomfort. Thus, studies on the pharmacodynamic effects of these compounds should apply to wide-ranging doses and physiological conditions to ensure useful results.

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Address:
Dr Talke
Department of Anesthesia and Perioperative Medicine
University of California
San Francisco
CA 94143–0648
USA
e-mail: talkep@anesthesia.ucsf.edu