A Double-Blind, Crossover Assessment of the Sedative and Analgesic Effects of Intranasal Dexmedetomidine

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BACKGROUND: The alpha2-receptor agonist, dexmedetomidine, provides sedation with facilitated arousal and analgesia with no respiratory depression. These properties render it potentially useful for anesthesia premedication, although parenteral administration is not practical in this setting. We designed this study to evaluate the sedative, anxiolytic, analgesic, and hemodynamic effects of dexmedetomidine administered intranasally in healthy volunteers.

METHODS: Koch's design for crossover trials (three-treatment and two-period design) was adopted. The study was double-blind and there were three treatment groups: A (placebo), B (intranasal dexmedetomidine 1 μg/kg) and C (intranasal dexmedetomidine 1.5 μg/kg). Each of the 18 subjects participated in two study periods. The study drug was administered intranasally after baseline observations of modified Observer Assessment of Alertness/Sedation Scale, visual analog scale of sedation, bispectral index, visual analog scale of anxiety, pain pressure threshold measured by an electronic algometer, systolic blood pressure (SBP) and diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation. These were repeated during the course of the study.

RESULTS: Intranasal dexmedetomidine was well tolerated. Both 1 and 1.5 μg/kg doses equally produced significant sedation and decreases in bispectral index, SBP, diastolic blood pressure, and heart rate when compared with placebo ($P < 0.05$). The onset of sedation occurred at 45 min with a peak effect at 90–150 min. The maximum reduction in SBP was 6%, 23%, and 21% for Groups A, B, and C respectively. There was no effect on pain pressure threshold, oxygen saturation or respiratory rate. Anxiolysis could not be evaluated as no subjects were anxious at baseline.

CONCLUSION: The intranasal route is effective, well tolerated, and convenient for the administration of dexmedetomidine. Future studies are required to evaluate the possible role of the noninvasive route of administration of dexmedetomidine in various clinical settings, including its role as premedication prior to induction of anesthesia.

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The alpha2-adrenoceptor agonist, dexmedetomidine, was originally developed as a sedative and analgesic drug for use in intensive care. However, it has a number of unique pharmacodynamic properties, which also make it useful in anesthesia: decreased MAC, analgesia without respiratory depression and a significant reduction in catecholamine secretion (1).

Sedative drugs are often administered preoperatively to relieve patient anxiety. Dexmedetomidine has been investigated for this purpose in both animals (2) and adult humans (3–5). The dose used in adult patients ranged from 1 to 2.5 μg/kg IM and was shown to be as effective as midazolam at inducing preoperative sedation and anxiolysis (3). Parenteral administration, however, is painful and may not be acceptable, especially to an anxious patient.

A crossover study of 12 adult subjects indicated that the bioavailability of dexmedetomidine via the buccal route is 82%, but it requires patients to attempt to retain the administered medication in the mouth (6). Intranasal administration is relatively easy and convenient, it also reduces first pass metabolism and has been used successfully for fentanyl, ketamine, and midazolam premedication (7–9). Although the pharmacokinetic properties of transmucosally administered dexmedetomidine have been demonstrated by Anttila et al. (6), the clinical effects of nonparenteral administration of dexmedetomidine have only been described in anecdotal case reports (10,11). The aim of this study was to evaluate the sedative, anxiolytic, and analgesic effects of dexmedetomidine when administered via the nasal route in healthy adults. A crossover design was chosen because it reduced the number of volunteers required. In addition, subjects acted as their own controls, which decrease

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pharmacogenetic variability. The doses of 1 and 1.5 μg/kg were chosen based on previous studies on IM dexmedetomidine in healthy volunteers (12,13) and the pharmacokinetic study by Anttila et al. (6), which demonstrated that the bioavailabilty of transmucosal dexmedetomidine was 82%.

METHODS

After approval by the local IRB, 18 healthy volunteers between the ages of 18 and 38 yr participated in the study. All subjects gave written informed consent. Exclusion criteria included ASA class II or more, history of drug, tobacco or alcohol abuse, chronic use of any medication, body mass index <18 or greater than 28 kg/m^2, and pregnancy. All subjects were asked to abstain from alcohol or any drug ingestion for 24 h prior to the investigation.

Koch's design for crossover trials (three-treatment and two-period design) was adopted (14). Each subject participated in two periods of study and there were three treatment groups:

Group A: Placebo (water) intranasally
Group B: Dexmedetomidine 1 μg/kg intranasally
Group C: Dexmedetomidine 1.5 μg/kg intranasally

Hence there were six possible treatment sequences: AB, AC, BA, BC, CA, CB.

The 18 subjects were randomly assigned to one of these treatment sequences by drawing lots; consequently there were three subjects for each. There was at least 1 wk between the first and second session for each subject. Both subjects and the observer were blinded to the drugs administered. An independent investigator, an anesthesiologist, prepared and administered the drug or placebo. Dexmedetomidine, at a concentration of 100 μg/mL, was used without further dilution. The volume of placebo (water) was equivalent to the volume of undiluted dexmedetomidine at dose 1 μg/kg. The solutions were prepared in 2.5 mL syringes. Equal volumes of the prepared solution were then dripped into both nostrils of the subjects. The drug or placebo was administered with subjects in the supine position, and they were allowed to sit up or assume a more comfortable position 5 min later. Each observation period lasted for 180 min. The investigations were performed in a fully equipped operating room with full resuscitation facilities.

After the subjects arrived for the study, they were allowed to rest for 10–15 min before the study commenced. Subjects were recumbent in a recovery bed when all the noninvasive monitors were applied. A Datex S/5 monitor (Datex-Ohmeda Inc., Madison, WI) was used and consisted of a pulse oximeter, automated sphygmomanometer, three lead electrocardiograph, and bispectral index (BIS). Oxygen saturation and heart rate (HR) were continuously measured, while systolic and diastolic blood pressure (SBP and DBP), and respiratory rate were recorded every 5 min throughout the study period. Baseline vital signs and other data were collected immediately before and repeatedly after intranasal drug or placebo administration.

Table 1. Modified Observer's Assessment of Alertness/Sedation Scale

6	Appears alert and awake, responds readily to name spoken in normal tone
5	Appears asleep but responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking
0	Does not respond to noxious stimulus

Sedation status was assessed both objectively and subjectively. Objective sedation status was measured by a blinded observer with a modified Observer's Assessment of Alertness/Sedation scale (OAA/S) (Table 1) and BIS version XP (BIS XP, Aspect Medical, Newton, MA). Sedation status was also assessed by subjects with a visual analog scale (VASsedation). To assess VASsedation, the subject moved a sliding indicator line on a 100 mm ruler, with end-points of very alert (0) and very sedated (100), to identify their level of alertness. A score of 100 was used if the subject was not rousable. OAA/S and BIS were recorded every 5 min and VASsedation was recorded every 15 min.

The anxiety level was assessed by the same blinded observer every 5 min with a 4 point anxiety score (1 = combative, 2 = anxious, 3 = calm, 4 = amiable). Anxiety level was also assessed by subjects with a visual analog scale (VASanxiety) every 15 min, where 100 was "very anxious" and 0 equivalent to "very calm."

Pain pressure threshold (PPT) was assessed by applying pressure to the forearm with an electronic algometer (Somedic, Somedic Production AB, Sweden). The transducer probe of the algometer was put on the same area of each subject's forearm, and increasing pressure was applied until the subject indicated pain. The PPT was assessed every 15 min after VASsedation was obtained. The average of three measurements was taken as the measurement at each particular timepoint. BIS was recorded just before a subject was aroused to have the VASsedation, VASanxiety, and PPT assessed.

When the 180 min observation period was over, subjects were allowed to rest until they felt that they were ready to leave. Similar precautions were taken as with day-stay surgery; hence when the subjects left, they fulfilled the discharge criteria for day surgery. The subjects were also informed that they should be accompanied by a responsible relative or adult on discharge and should not drive, handle major machinery, make major decisions or go back to work on the day of the investigation.

Demographic data were analyzed by analysis of variance (ANOVA), Fisher's exact test and the Kruskal-Wallis test. Sedation data, pain threshold data, and

Table 2. Patient and Study Characteristics

Variables	Groups AB and BA (n = 6)	Groups AC and CA (n = 6)	Groups BC and CB (n = 6)	Overall (n = 18)	*P*
Age (yr)	26.8 ± 4.8 [21–32]	26.7 ± 7.7 [19–38]	21.8 ± 1.9 [20–25]	25.1 ± 5.6 [19–38]	0.22
Sex, M:F	2:4	2:4	3:3	7:11	1.0
Body mass index (kg/m^2)	21.0 ± 3.5 [17.1–25.5]	21.3 ± 2.4 [18.4–25.5]	21.2 ± 2.6 [16.8–24.2]	21.1 ± 2.7	0.98
Time between two treatments (d)	21 [7–134]	10 [7–66]	50 [8–134]	18.5 [7–134]	0.71

Values in mean ± SD or median [range] or count.

Treatment A = Placebo (water) intranasally.

Treatment B = Dexmedetomidine 1 μg/kg intranasally.

Treatment C = Dexmedetomidine 1.5 μg/kg intranasally.

Notes: Patient characteristics in the three combination treatments were not significantly different.

hemodynamic data were analyzed by mixed model analysis for crossover trials with repeated measurements within visits (periods). (15) Bonferroni *t*-test was used for *post hoc* pairwise comparisons where appropriate. Data collected in 5 min epochs were converted to 15 min data by averaging the values during each 15 min period. The SAS System for Windows Release 9.1 (SAS Institute Inc., Cary, NC, USA.) was used. Results throughout the text, tables, and figures are presented as mean ± SD unless otherwise indicated, and statistical significance was defined as $P < 0.05$.

RESULTS

Intranasal administration of dexmedetomidine was well tolerated. No local irritation or pain occurred with the application of this drug in any of our subjects. No subject complained of a smell or taste with either intranasal drug or placebo administration. There was no severe bradycardia or conduction abnormality on electrocardiogram monitoring. The observed hemodynamic changes did not induce any subjective symptoms. There was no orthostatic hypotension when the subjects were allowed to stand at the end of the session. One of the 18 subjects reported slight dizziness when she was on public transport on a hot day about 60 min after completing the study. She insisted on leaving immediately after the observation period of 3 h was completed. She was asymptomatic when she left and was accompanied by a responsible adult. She had received 1.5 μg/kg of intranasal dexmedetomidine on that day. Her symptoms subsided completely after 2 h of rest. No other major adverse effects were observed or reported. We did not specifically inquire about dry mouth, which is a common side effect of α 2 agonists, but three subjects volunteered this information at the end of the study.

There were no significant differences in the demographic data of subjects in the three different treatment combinations (Table 2). There was no evidence of a visit effect on the sedation scores, BIS, and PPT using a mixed model analysis for crossover trials with repeated measurements within visits (periods). This implies that the order of treatments had no effect on outcome.

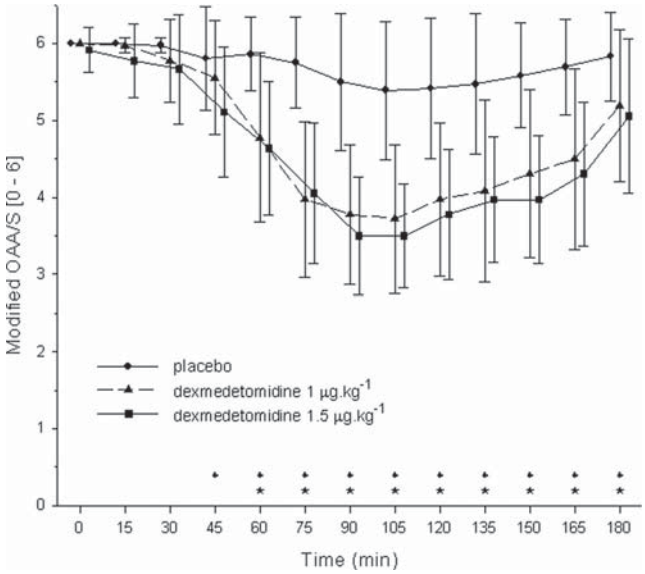

Figure 1. Mean ± SD modified Observer Assessment of Alertness/Sedation scales (modified OAA/S scales) as a function of time in the three treatment groups.

Figures 1–3 graphically display the mean ± SD modified OAA/S scores, BIS, and VASsedation in relation to time in different treatment groups. The sedation level of Groups B and C became significantly different from that of Group A 45–60 min after intranasal drug administration, and the differences remained statistically significant for the rest of the study period. The peak sedation effect occurred at 90–105 min. There were no differences in sedation status between Group B and Group C. Although the VASsedation for Group B and Group C was not statistically different, there was a tendency for it to be greater in Group C throughout the study period. The lowest mean modified OAA/S was 3.7 and 3.5 for Group B and Group C subjects respectively. The lowest mean BIS for both Groups B and C was 75. The highest mean VASsedation scores were 74 and 83.2 for Groups B and C respectively.

Figures 4 and 5 show the mean SBP, DBP, and HR in relation to time in each group. The SBP and DBP of

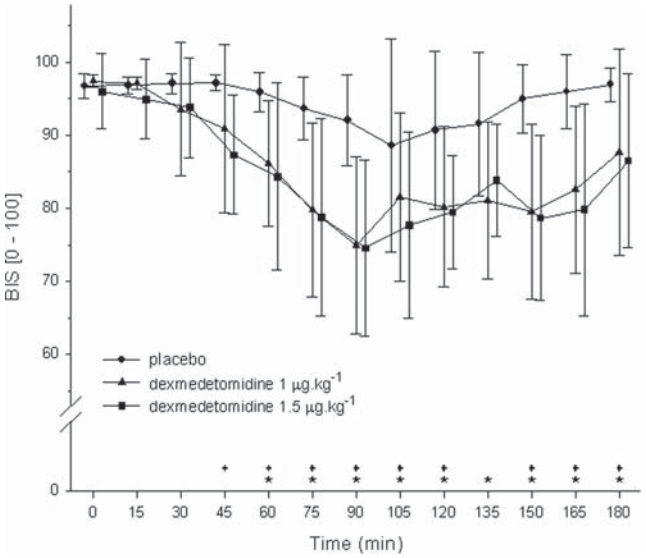

Figure 2. Mean ± SD. Bispectral index (BIS) as a function of time in the three treatment groups.

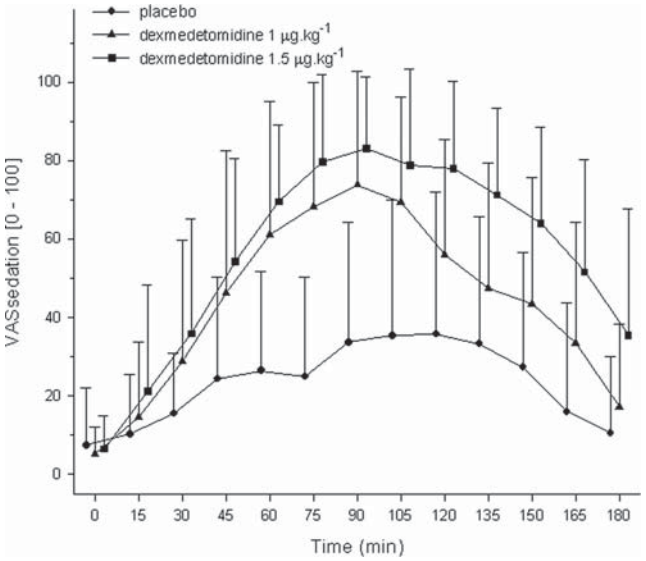

Figure 3. Mean ± SD. Visual Analog Scale (sedation) (VASsedation) as a function of time in the three treatment groups.

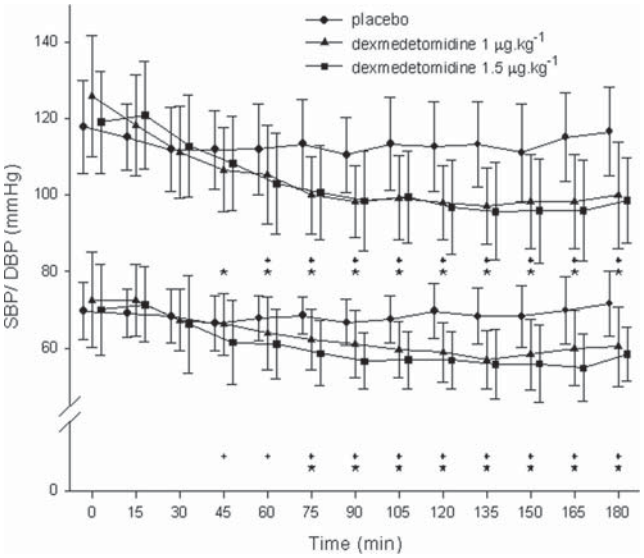

Figure 4. Mean ± SD. Systolic blood pressure (SBP) and mean ± SD. Diastolic blood pressure (DBP) as a function of time in the three treatment groups.

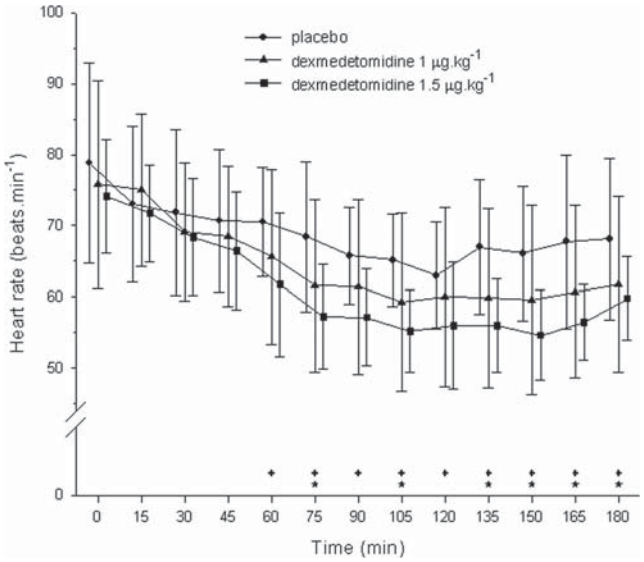

Figure 5. Mean ± SD. Heart rate (HR) as a function of time in the three treatment groups.

Group B and Group C became significantly lower than that of Group A 45–60 min after intranasal dexmedetomidine administration and remained so for the rest of the study. There was no difference in SBP or DBP between Groups B and C. The HR of Groups B and C was lower than that of Group A 60–75 min after drug administration. These differences were modest but remained statistically significant for the rest of the study between Groups A and C. The maximum decreases in SBP were 6, 23, and 21% and in HR were 16, 22, and 26% for Groups A, B, and C respectively.

None of the subjects was anxious at baseline. There were no significant differences in anxiety levels among different treatment groups during the study period. There was no difference in PPT values as assessed by the algometer between the three groups of subjects (Figures 5 and 6). The oxygen saturation and respiratory rate in the three groups were the same throughout the study period.

DISCUSSION

Sedative Effect

This is the first clinical trial evaluating the clinical effects of intranasally administered dexmedetomidine in healthy volunteers. We have shown that it produced significant sedation in all modalities of measurement: subjectively with VASsedation, objectively with BIS and by a blinded observer with modified

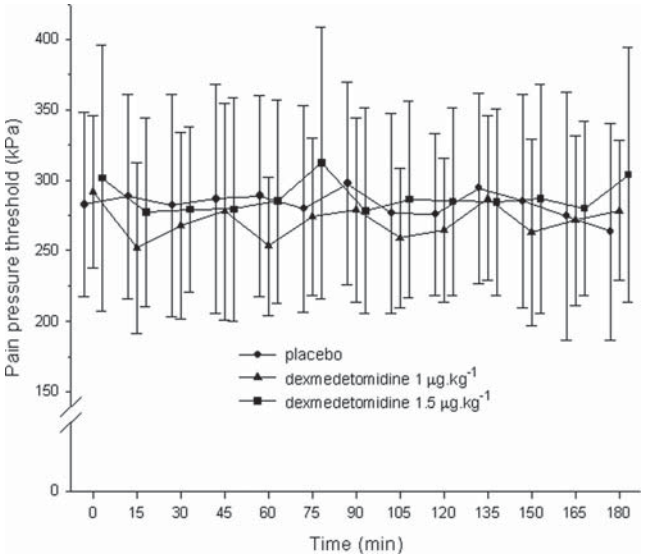

Figure 6. Mean ± SD. Pain pressure threshold (PPT) (kPa) as a function of time in the three treatment groups. Post hoc pairwise comparisons for treatment effect (T): □ indicated Treatment A and Treatment B were significantly different; + indicated Treatment A and Treatment C were significantly different; # indicated Treatment B and Treatment C were significantly different.

OAA/S scores. Previous studies in healthy volunteers have demonstrated that dexmedetomidine-induced sedation can be monitored with BIS (16) and electroencephalogram-based spectral entropy (17).

The onset and peak sedative effect correlates well with different methods of sedation assessment. Significant sedation occurred 45–60 min after both doses of intranasal dexmedetomidine with a peak sedative effect after approximately 90–105 min. This study was designed to evaluate the potential role of intranasal dexmedetomidine as premedication before induction of anesthesia; hence, 180 min of observation period was selected. Although the subjects' sedation status did not return to baseline at the end of the study period (3 h after administration), they were all easily roused and they left after meeting the criteria for discharge after day surgery.

In a study of buccally administered dexmedetomidine the clinical sedative effect correlated well with the plasma level (6) with a peak plasma concentration attained at 1.5 ± 0.2 h and the bioavailability was 82%. However, a significant proportion was swallowed by the subjects, with the average amount of drug absorbed via the buccal mucosa at about 56% (mean ± SD, 1.12 ± 0.33 μg/kg of the 2 μg/kg of dexmedetomidine administered). It is likely that the bioavailability of intranasally administered dexmedetomidine is similar, as both routes involve absorption via a mucosal membrane. However, we did not measure the plasma concentration and bioavailability in this study. Nevertheless, we have shown that approximately 75% and 92% of subjects attained a sedation level of modified OAA/S of 3 or below after 1 and 1.5 μg/kg of intranasal dexmedetomidine respectively. A study on healthy volunteers has shown that 1 μg/kg of IV dexmedetomidine produces sedation that is equivalent to a modified OAA/S of 3 or below in 67% of subjects (18). Hence, similar pharmacodynamic sedative effects were seen with the same dose of IV and intranasal dexmedetomidine, although the time to the maximal sedative effect and duration of effect was different. This probably reflects the more gradual increase in plasma concentration that would be seen after an indirect route of administration.

The pharmacokinetic profile of transmucosal administration was quite similar to that of IM administration. Scheinin et al. (12) have shown that time to maximal effect after 0.5, 1.0, and 1.5 μg/kg of IM dexmedetomidine occurred between 60 and 150 min. In another study, Dyck et al. (19) reported the bioavailability of 2 μg/kg IM dexmedetomidine to be between 70% and 80%. Anttila et al. (6) reported in their study that the bioavailability of IM dexmedetomidine was 103% and the time to peak plasma concentration was 1.7 ± 1.8 h.

Interestingly, the sedative effect of IM dexmedetomidine was shown to be less than satisfactory when given as 1 μg/kg as premedication 60 min before induction of anesthesia (4,20). In Aho et al.'s study (4) of a comparison of 0.6, 1.2, and 2.4 μg/kg of IM dexmedetomidine, only patients who received 2.4 μg/kg were significantly sedated and became less anxious prior to induction of anesthesia. Scheinin et al. (3) reported that 2.5 μg/kg of IM dexmedetomidine was effective premedication for general anesthesia. On the contrary, Virkkila et al. (5) have suggested that 1 μg/kg of IM dexmedetomidine produced short-acting sedation similar to that of midazolam in elderly patients undergoing cataract surgery under regional anesthesia. On the other hand, in Scheinin et al.'s study on healthy volunteers (12), both 1 and 1.5 μg/kg of IM dexmedetomidine produced significant sedation and impared vigilance. Mattila et al. (13) have also demonstrated that 1.2 μg/kg of IM dexmedetomidine produced subjective sedation comparable to that of 80 μg/kg of IM midazolam in healthy volunteers.

The discrepancy in the sedative effect of similar doses of IM dexmedetomidine can be attributed to different subject groups and different study designs. Healthy volunteers may be more relaxed and nonanxious at baseline. On the contrary, patients participating in premedication clinical trials could be more anxious in anticipation of surgical procedures. Hence larger doses were required to produce an adequate sedative and anxiolytic effect. However, a smaller dose could be adequate in elderly patients as suggested by Virkkila et al. (5). Therefore. although the doses of intranasal dexmedetomidine used in this study produced significant sedation in healthy volunteers in an experimental setting, whether these doses will produce clinical sedation in anxious patients facing surgery or other painful procedures will need to be evaluated. Unfortunately, the anxiolytic effect of

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