Dexmedetomidine Sedation With and Without Midazolam for Third Molar Surgery

Megann K. Smiley, DMD, MS* and Simon R. Prior, BDS, PhD, MS†

*Nationwide Children's Hospital, Columbus, Ohio, and †Dental Surgeon and Anesthesiologist, Assistant Professor, College of Dentistry, The Ohio State University, Columbus, Ohio

Twenty-four patients were randomly divided into 2 groups. Intraoperatively, one group received a continuous intravenous infusion of dexmedetomidine alone, whereas the other received a continuous dexmedetomidine infusion plus a small dose of midazolam. Early measurements of patient anxiety and psychomotor performance were lower in patients who had received midazolam. This difference was not seen later in the appointment. An amnesic effect was observed in those patients who received midazolam. This effect, however, did not translate into increased patient satisfaction in the group receiving midazolam. Our findings suggest a prolonged discharge time for patients who had been given midazolam that may be clinically significant. Overall, dexmedetomidine showed an unpredictable sedative response and may be less practical than more common alternatives for oral surgery procedures.

Key Words: Dexmedetomidine; Anesthesiology; Oral surgery; Sedation; Third molars.

Alpha-2 (α -2) adrenergic receptor agonists were first used as nasal decongestants but soon were valued for the treatment of hypertension and withdrawal symptoms. The sedative and amnesic qualities of clonidine, the prototypic representative of this drug class, fueled interest in its use as an anesthetic adjuvant. It was also quickly noted that, at sedative doses, the normal respiratory drive was unaffected when administered as an intravenous infusion.¹⁻³ Dexmedetomidine (Precedex, Abbott Laboratories), the pharmacologically active dextroisomer of medetomidine, like clonidine, has an imidazoline structure and is a potent and selective agonist of the α -2 adrenoceptor. Compared with clonidine, dexmedetomidine shows 8 times greater selectivity for α -2 than α -1 receptors and is considered a full agonist. It has been used in veterinary anesthesiology for more than 20 years and has demonstrated

dose-dependent sympatholytic, sedative, and analgesic properties in human volunteers.⁴⁻⁶ Dexmedetomidine, when administered in the perioperative period, has been shown to reduce the dose requirements of other anesthetics and attenuate the sympathetic response to stressful events.⁷⁻¹⁰

Alpha-2 adrenergic receptors are G-protein-coupled receptors.¹¹⁻¹³ Presynaptic α -2 receptors are found in sympathetic nerve endings and noradrenergic neurons of the central nervous system (CNS), where their primary function is to inhibit release of norepinephrine. Postsynaptic α -2 receptors exist in various tissues, including the liver, pancreas, kidney, adipose tissue, eye, and vascular smooth muscle, where they play a complex physiologic role.¹⁴ A high density of α -2 receptors exists in the locus ceruleus, a small brain stem structure that is important in modulating vigilance. Evidence exists that suggests that the locus ceruleus is part of an endogenous sleep-promoting pathway.¹⁵ These neurons have inhibitory control over γ -aminobutyric acid (GABA)-containing neurons in the ventrolateral preoptic nucleus of the anterior hypothalamus and, in turn, affect the higher

Received February 28, 2013; accepted for publication November 24, 2013.

Address correspondence to Simon Prior, College of Dentistry, Ohio State University; 2147 Postle Hall, 305 W. 12th Avenue, Columbus, OH 43218; prior.20@osu.edu.

Anesth Prog 61:3-10 2014

© 2014 by the American Dental Society of Anesthesiology

ISSN 0003-3006/14

SSDI 0003-3006(14)

centers in the brain associated with loss of wakefulness. The clinical sedative response of α -2 adrenergic agonists is similar to natural sleep, where patients remain easily arousable and able to follow commands after minimal stimulation.^{2,16,17}

Midazolam is a benzodiazepine that exerts its pharmacologic effect by facilitating GABA, the major inhibitory neurotransmitter of the CNS. The subsequent enhanced opening of chloride channels leads to hyperpolarization of the neuron and resistance to stimulation.¹⁸ Clinically, the anesthetic properties of midazolam include anxiolysis, sedation, and amnesia. In rats, a synergistic interaction has been observed for multiple measures of CNS depression when a combination of dexmedetomidine and midazolam is administered.^{19,20}

Dexmedetomidine, with a context-sensitive half-life similar to that of fentanyl, found initial use in the short-term (<24 hours) sedation of postoperative patients requiring ventilation in the intensive care unit.²¹ The average protein binding of an intravenously administered dose is 94%, with distribution and elimination half-lives of 6 minutes and 2 hours, respectively. It is extensively biotransformed in the liver and, with metabolites, excreted primarily in the urine. A potential adverse reaction to intravenously administered dexmedetomidine is a peripherally mediated, postsynaptic α -2 receptor-activated hypertension, particularly when it is administered as an intravenous bolus rather than as an infusion.^{21,22} This reaction is most commonly seen in the early phase of administration. Conversely, attenuation of sympathetic outflow from the CNS may result in unacceptable hypotension and bradycardia. Interestingly, it appears that baroreflex sensitivity is not changed and patients will have appropriate heart rate responses to hypotension and hypovolemia.^{1,23}

At present there appear to be at least 3 major receptor subtypes for dexmedetomidine: α 2A, α 2B, and α 2C. While the role of these receptor subtypes continues to be explored, it has become evident that the α 2A and α 2C subtypes predominate in the CNS and may be responsible for the sedative, analgesic, and sympatholytic components of agonist action. The α 2B receptors are more frequently located on vascular smooth muscle and appear to mediate the hypertensive effects of high doses of dexmedetomidine.^{15,24–26}

Balanced intravenous sedation techniques are often administered during surgery to provide anxiolysis, sedation, and analgesia for the patient. These frequently include benzodiazepines, opioids, low-dose infusions of propofol, or combinations of these, titrated to achieve the desired effect. Such techniques can sometimes have the undesired effect of respiratory depression. The search continues for an ideal sedative that is safe, rapidly

acting, inexpensive, and titratable and that has minimal side effects.

An unpublished thesis of a pilot study comparing the sedative effects of a low-dose propofol infusion and opioid to those of dexmedetomidine for third molar extractions found that patients receiving dexmedetomidine were more aware of the procedure; for some, that was a source of anxiety.²⁷ We hypothesized that the addition of a small dose of a benzodiazepine (midazolam) to the dexmedetomidine infusion might improve the patient's experience.

MATERIALS AND METHODS

Following institutional review board approval, 24 patients between the ages of 18 and 32, who were classified as American Society of Anesthesiologists I or II, participated in the study. Exclusion criteria included allergies or adverse drug reactions to local anesthetics, nonsteroidal anti-inflammatory drugs, or α -2 adrenergic agonists. The sample was obtained from a pool of patients who had already consented to third molar extraction under intravenous (IV) moderate sedation. Volunteer patients had to require the extraction of at least 3 third molars, 1 of which was a mandibular bony impacted tooth requiring surgical exposure via osteotomy.

No food taken orally for at least 6 hours and, for women, a negative urine pregnancy test were additional prerequisites on the day of surgery. Baseline psychomotor testing was performed and included a Trieger test and the Digit Symbol Substitution Test (DSST). The patient was asked to rate their level of anxiety on a 100-mm-visual analog scale (VAS) on which 0 represented "calm and comfortable" and 100 "very anxious and stressed." To aid the testing of amnesia, a labeled picture of an animal was shown at this point. An Observer Assessment of Alertness/Sedation (OAA/S) rating was then recorded. Electrocardiogram (ECG), pulse oximetry, blood pressure, and bispectral analysis (BIS) monitors were applied and baseline recordings made. Supplemental oxygen was administered at 2 to 3 L per minute via nasal cannula, and peripheral IV access was established.

Patients were randomly assigned to 1 of 2 study groups to which the surgeon, anesthesiologist, and patient were blinded.

- Group 1 patients received a loading infusion of dexmedetomidine, 0.1 μ g/kg/min, for 10 minutes (1 μ g/kg total over 10 minutes); a volume of saline equal to the volume of a 0.03-mg/kg dose of midazolam (1 mg/mL); and a dexmedetomidine maintenance infusion of 0.012 μ g/kg/min (0.7 μ g/kg/hr) for the duration of the procedure.

- Group 2 patients received a loading infusion of dexmedetomidine as in group 1, 0.03 mg/kg of midazolam (1 mg/mL), and a dexmedetomidine maintenance infusion as in group 1.

After a 10-minute loading infusion and administration of midazolam if applicable, vital signs, BIS scores, and OAAS ratings were recorded; a memory card was shown; and Trieger test and DSST were performed. The patients again rated their anxiety level using the VAS.

Local anesthetic (2% lidocaine with 1 : 100,000 epinephrine) was then administered as needed by the surgeon and the volume given was recorded. The continuous dexmedetomidine infusion was discontinued as the surgeon indicated the extractions were complete. Intraoperatively, vital signs, BIS scores, and OAAS were recorded at 5-minute intervals. At the end of surgery, a memory card was shown and Trieger test, DSST, and anxiety VAS were administered. The surgeon and the investigator rated the quality of the sedation on a 100-mm VAS, with a mark at 0 mm indicating “very poor” and 100 mm indicating “excellent.”

Postoperatively, vital signs, BIS scores, and OAAS ratings were recorded, and Trieger test and DSST were performed at 15-minute intervals for 90 minutes. A final memory card was shown 15 minutes into recovery. After the patient had met standard discharge criteria, and after at least 90 minutes’ recovery, he or she was discharged according to our institutional policies. The postoperative course was evaluated by the patient the following day via a questionnaire and returned to the investigator in a stamped, addressed envelope. Recall was evaluated via several “yes/no” questions to specific surgery/treatment events and their recall of memory cards. Participants were compensated for their involvement in this study.

Between-group differences were assessed using the Mann-Whitney Wilcoxon test and gender distribution with a chi-square test. Postoperative questionnaires were analyzed using the Fisher exact test. Analysis of covariance was used, with the baseline reading as covariate, for Trieger test and DSST. Post hoc testing was done with the Tukey-Kramer procedure. BIS scores were analyzed using the exact Wilcoxon test adjusted with the step-down Bonferroni method of Holm. Nonparametric methods were required for continuous data. A P value $< .05$ was considered significant.

RESULTS

One patient in the dexmedetomidine-only group (group 1) withdrew from the study, citing inadequate sedation. At the close of the study, there were 11 patients in group

1 and 12 patients in group 2 (dexmedetomidine + midazolam). The groups were comparable in age, weight, surgery time, and gender distribution (Figure 1).

Each patient recorded their anxiety level 4 times: at the beginning of the appointment (baseline), after completion of the loading infusion, immediately after completion of the extractions, and the day after surgery via a postoperative questionnaire (Figure 2). After the loading infusion, individuals in group 2 reported lower anxiety levels than those in group 1, with the difference approaching statistical significance ($P < 0.084$). Reported anxiety levels at the end of surgery and the following day showed no significant difference between the groups.

Patients in both groups could recall the IV being started. Six patients in group 1 but only one in group 2 reported remembering the local anesthetic injections ($P < 0.027$). When questioned about recall of any part of the extractions themselves, all members of group 1 reported some awareness of the procedure, while only 8 members of group 2 reported a memory of the extractions (Figure 3), with a trend toward significance ($P < 0.093$). Of the 4 memory cards shown, 1 person in each group failed to remember the initial memory card, which had been shown before any sedative medication was given. Patients in group 2 were significantly less likely to remember the last 3 memory cards shown ($P < 0.023$).

The quality of sedation was rated similarly for each group by the patients, the surgeon performing the extractions, and the investigator/anesthesia provider (Figure 4). There were no significant differences in any sedation quality scores.

While all patients were observed for 90 minutes postoperatively, regardless of alertness, in accordance with the research protocol, the time at which the patient had met discharge criteria and would have been discharged in a nonresearch situation was recorded. The mean time to ready-for-discharge for patients in

Figure 1. Pretreatment comparison of study groups.

Figure 2. Posttreatment comparison of information gathered throughout the study.

group 1 was 28.6 minutes, versus 45.0 minutes for group 2 ($P < 0.080$). All patients were discharged after 90 minutes of observation.

Figure 5 details the adjusted Trieger test scores of the 2 groups. At Assessment Period 1 (after initial drug delivery, but before surgery), the patients in group 2 had significantly worse scores than those in group 1 ($P < 0.008$). For all other assessment periods, the differences between the groups were not significant.

A similar situation was found when analyzing the results of the baseline-adjusted DSST (Figure 6). At Assessment Period 1, the scores of the groups differed significantly, with group 1 outperforming group 2 ($P < 0.015$). At all other assessment periods, there was no significant difference.

BIS scores were graded on an ordinal scale. Scores above 70 were considered to represent a high likelihood of patient awareness and were therefore assigned a value of 1. Scores between 60 and 69 were assigned a value of 2, and scores below 59 were given a value of 3. At no assessment period during the surgery or recovery were BIS scores significantly different between the groups (Figure 4).

One patient in group 2 and 2 patients in group 1 experienced unusual episodes during the study, 2 of whom required intervention. At approximately 45 minutes into recovery, the group 2 patient, who had previously been resting, became briefly agitated. They then became unresponsive to loud calling of their name and a firm shoulder shake. A jaw thrust and sternal rub also elicited no response. The vital signs remained stable and the patient continued to breathe spontaneously, maintaining pulse oximetry saturations of 100%. Throughout the episode, the BIS monitor registered a score in the high 90s. After approximately 3 minutes, the patient recovered spontaneously and was able to perform the Trieger test and DSST without difficulty. They were observed for another 45 minutes without

incident. The 2 patients in group 1 experienced ECG alterations. At 45 minutes into the recovery period, one patient experienced a progressively decreasing heart rate. The ECG showed a lengthening P-R interval until it appeared there was a third-degree heart block. The slowest heart rate noted was in the low 30s. The patient remained sluggish, though responsive, and had a strong carotid pulse. Following two 0.5-mg doses of atropine, a normal sinus rhythm returned, with no further incident. The third patient displayed an accelerated junctional rhythm (about 60 beats per minute) about 5 minutes into the maintenance infusion of dexmedetomidine. Inverted p-waves were noted on lead II of the ECG. The patient was given 0.4 mg of glycopyrrolate intravenously and observed to be in normal sinus rhythm 10 minutes later. A blood pressure of about 115/85 was maintained throughout. This patient, like the others, had no further incidents during the appointment and was discharged after 90 minutes of observation.

DISCUSSION

The pharmacologic properties of dexmedetomidine may make it an attractive choice of sedative agent for ambulatory surgical procedures. Arain and Ebert demonstrated that patients are able to tolerate procedures such as hernia repair and hip and/or knee replacement with regional anesthesia and sedation using dexmedetomidine.⁵ In these situations, however, it is possible to isolate the surgical field from the patient's view and achieve minimal patient stimulation. The surgical field in the present study was difficult to isolate from patient view. It was also impossible to prevent the patient from perceiving sensations of pressure, stretching, and vibration, even with profound local anesthesia of the teeth and surrounding soft tissues. The fact that dexmedetomidine appears to have some analgesic effect^{2,5,24,27} may be beneficial in an oral surgery milieu;

Figure 3. Comparison of study group's recollection of well-defined treatment events.

Figure 4. Mean adjusted bispectral analysis values at defined times during patient care.

however, this aspect of the dexmedetomidine sedation was not examined in this study.

The unique property of easy arousability appears to make dexmedetomidine a popular choice of sedative agent in the intensive care unit, allowing intubated patients to tolerate mechanical ventilation yet remain easily roused to cooperate with necessary procedures.⁴ The easy arousability of patients was also noted in this study. When a patient happened to doze during the loading infusion, they were often wakened by their own snoring. During the local anesthetic injections and dental extractions, however, many patients were stimulated to the point of being awake and aware, with BIS scores

rapidly returning to the 90s. The addition of midazolam to the sedation, at least initially, appeared to attenuate this easy arousability; some patients, having been unaware of the surgeon's presence or his announcement that he was about to begin, were clearly startled by the local anesthetic injection.

There was no difference in anxiety reported by patients at the beginning of the appointment. It should be noted that the patient who withdrew from group 1 was very anxious and required a large amount of coaxing and reassurance to even allow the IV equipment to be placed. By the end of the loading infusion, after administration of midazolam to those in group 2,

Figure 5. Mean adjusted Trieger scores.

Figure 6. Mean adjusted Digit Symbol Substitution Test.

significantly less anxiety was reported in group 2. By the end of the surgery, this difference was no longer detectable. According to the questionnaires completed the day after surgery, patients in both groups reported a similar level of anxiety during the procedure. A wide range of anxiety levels was reported on the questionnaire in both groups, with those in group 1 reporting anywhere from 9 to 94 on the 100-mm VAS and those in group 2 reporting a range from 0 to 89. This high variability was seen repeatedly in the collected data.

As might be expected, there was an apparent amnesic effect from the midazolam in group 2. This amnesia seemed most reliable for events earlier in the appointment. While all participants reported recall of insertion of the IV needle in their arm, those in group 2 were less likely to remember the local anesthetic injections given at the beginning of surgery. This group was also less likely to remember elements of the surgery itself. Some patients in group 2 reported that they remembered being aware of the “extraction of the last tooth” or “the stitches.” One patient reported recall of “opening my eyes,” and another noted that they were aware of the surgery but could not decide if it was real or a dream and so they did not open their eyes. The patients receiving dexmedetomidine alone were more likely to report having remembered “the whole surgery” and sometimes more; one patient in this group also reported seeing “rabbits running around on the floor.”

Interestingly, the results perhaps imply that amnesia of events is not an essential component of patient satisfaction. Despite less recall of events by those in group 2, overall patient ratings of the sedation did not differ between the groups. However, a wide range of

ratings was reported. On the 100-mm VAS used, group 1 patients scored between 10 and 100 and group 2 ratings ranged from 18 to 100.

The value of adding midazolam to dexmedetomidine for sedation would have to be weighed against the possibility of greater recovery time, especially in an ambulatory surgery setting. Although all patients were observed for 90 minutes following the end of the sedation, the average time at which a patient in group 1 was ready for discharge was 28 minutes, compared to 45 minutes in the midazolam group. Although this result was not statistically significant, a larger sample size may have shown a difference. Fifteen minutes may also be considered clinically significant for a practitioner who must recover and discharge the patient before the next patient can be seen.

The variability in the collected data reflected the variability of patient responses observed clinically. There were patients in both groups who seemed minimally sedated and maintained BIS scores above 70 throughout the procedure. There were also patients in both groups who showed signs of being heavily sedated and had BIS scores below 50, particularly during the recovery period. One patient receiving midazolam had a BIS score of 30 early in the recovery period, which was the lowest BIS score observed in this study. Although some patients remained aware, they generally tolerated the procedure well.

The sedation provided in this study could be characterized as unpredictable and variable, making it difficult to predict which patients would benefit from the addition of midazolam to the dexmedetomidine sedation. This is not a dilemma unique to sedation with dexmedetomi-

dine. Often, in the clinical setting, patients who appear to be less anxious before surgery are merely skilled at coping and may require more medication to achieve sedation. Conversely, patients who seem very anxious preoperatively can sometimes relax once the procedure has begun and sometimes require less medication to achieve adequate sedation. The design of this study did not allow for increases or decreases in the infusion level; instead a fixed, weight-based infusion was selected based on the maximum maintenance infusion used for intensive care unit sedation. It is worth noting that patients in intensive care are generally older and less healthy than the typical patient seen for third molar extraction. The generally young, healthy patient population from which this sample was drawn may be expected to have a higher drug requirement. These patients are often found to have higher parasympathetic tone and resting heart rates below 60 beats per minute. One patient in this study had a baseline heart rate of 49 beats per minute. Given the propensity for dexmedetomidine to cause bradycardia, its use in such patients may be considered a relative contraindication. Indeed, profound bradycardia was observed in this study, and we would recommend that anticholinergic and sympathomimetic agents be available immediately when sedating patients with dexmedetomidine.

A review of the literature revealed cardiac events observed by other researchers administering dexmedetomidine. Bloor et al administered infusions to healthy volunteers and observed an episode of heart rate of 24 beats per minute and 2 episodes of junctional rhythm.²² Lawrence and De Lange administered single doses of dexmedetomidine to patients preoperatively and reported that 1 patient experienced a heart rate of 33 beats per minute.¹⁰ Ebert et al administered increasing infusions of dexmedetomidine to healthy volunteers and reported that the infusion was discontinued in 1 patient because of “relatively profound and unexplainable agitation.”¹ Investigating the pharmacokinetics and pharmacodynamics of dexmedetomidine, Dyck and Shafer administered infusions to healthy volunteers and reported that “one patient... without any obvious provocation sustained a period of cardiac electrical silence lasting 11.5 seconds with spontaneous recovery.”²¹

Patients who are likely to benefit from sedation with dexmedetomidine are those who cannot tolerate respiratory depression and those who need protection from catecholamine release and the resultant tachycardia and hypertension. Overall, in the oral surgery model, in which it is impossible to shield the surgical site from the patient, the unpredictable sedative response of dexmedetomidine using these fixed dosages suggests a somewhat less practical approach versus traditional sedative techniques. Because of the potential advantages, further

research, particularly focused on varying dosing patterns, is warranted in these patient populations.

CONCLUSION

Early measurements of patient anxiety and psychomotor performance were lower in patients who had received dexmedetomidine plus midazolam versus those who received dexmedetomidine alone; however, this difference was not detected later in the appointment. An amnesic effect was observed in those patients who received midazolam. This effect, however, did not translate into increased patient satisfaction in the group receiving midazolam. Our findings suggest that a prolonged discharge time for patients who had been given midazolam may be clinically significant. Overall, dexmedetomidine showed an unpredictable sedative response and may be less practical than more common alternatives for oral surgery procedures.

REFERENCES

1. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colino MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology*. 2000;93(2):382–394.
2. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnesic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg*. 2000;90:699–705.
3. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I: Sedation, ventilation, and metabolic rate. *Anesthesiology*. 1992;77:1125–1133.
4. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *Br J Anaesth*. 2001;87(5):684–690.
5. Arain SR, Ebert TJ. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. *Anesth Analg*. 2002;95:461–466.
6. Aantaa R, Jaakola ML, Kallio A, Kanto J. Reduction of the minimum alveolar concentration of isoflurane by dexmedetomidine. *Anesthesiology*. 1997;86(5):1055–1060.
7. Talke P, Richardson CA, Scheinin M, Fisher DM. Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. *Anesth Analg*. 1997;85:1136–1142.
8. Khan ZP, Munday IT, Jones RM, Thornton C, Mant TG, Amin D. Effects of dexmedetomidine on isoflurane in healthy volunteers. 1: Pharmacodynamic and pharmacokinetic interactions. *Br J Anaesth*. 1999;83(3):372–380.
9. Scheinin B, Lindgren L, Randell T, Scheinin H, Scheinin M. Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and perioperative fentanyl. *Br J Anaesth*. 1992;68:126–131.

10. Lawrence CJ, De Lange S. Effects of a single pre-operative dexmedetomidine dose on isoflurane requirements and peri-operative haemodynamic stability. *Anaesthesia*. 1997;52:736–744.
11. Smith H, Elliot I. Alpha-2 receptors and agonists in pain management. *Curr Opin Anaesthesiol*. 2001;14:513–518.
12. Gabriel JS, Gordin V. Alpha-2 agonists in regional anesthesia and analgesia. *Curr Opin Anaesthesiol*. 2001;14:751–753.
13. Hayashi Y, Maze M. Alpha-2 adrenoceptor agonists and anaesthesia. *Br J Anaesth*. 1993;71:108–118.
14. Khan ZP, Ferguson CN, Jones RM. Alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia*. 1999;54:146–165.
15. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha 2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology*. 2003;98:428–436.
16. Hall JE, Uhrich TD, Ebert TJ. Sedative, amnestic, and cognitive effects of clonidine infusions in humans. *Br J Anaesth*. 2001;86:5–11.
17. Aantaa R. Assessment of the sedative effects of dexmedetomidine, an α_2 adrenoceptor agonist, with analysis of saccadic eye movements. *Pharmacol Toxicol*. 1991;68:394–398.
18. Goodchild CS. GABA receptors and benzodiazepines. *Br J Anaesth*. 1993;71:127–133.
19. Salonen M, Reid K, Maze M. Synergistic interaction between alpha 2-adrenergic agonists and benzodiazepines in rats. *Anesthesiology*. 1992;76:1004–1011.
20. Bol CJ, Vogelaar JP, Tang JP, Mandema JW. Quantification of pharmacodynamic interactions between dexmedetomidine and midazolam in rats. *J Pharmacol Exp Ther*. 2000;294(1):347–355.
21. Dyck JB, Shafer SL. Dexmedetomidine pharmacokinetics and pharmacodynamics. *Anaesth Pharmacol Rev*. 1993;1:238–245.
22. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II: Hemodynamic changes. *Anesthesiology*. 1992;77:1134–1142.
23. Hogue CW, Talke P, Stein PK, Richardson C, Domitrovich PP, Sessler DI. Autonomic nervous system responses during sedative infusions of dexmedetomidine. *Anesthesiology*. 2002;97:592–598.
24. Hunter JC, Fontana DJ, Hedley LR, et al. Assessment of the role of α_2 -adrenoceptor subtypes in the antinociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice. *Br J Pharmacol*. 1997;122: 1339–1344.
25. Talke P, Lobo E, Brown R. Systemically administered-agonist-induced peripheral vasoconstriction in humans. *Anesthesiology*. 2003;99:65–70.
26. Laakola M, Salonen M, Lehtinen R, Scheinin H. The analgesic action of dexmedetomidine—a novel α_2 -adrenoceptor agonist—in healthy volunteers. *Pain*. 1991;46:281–285.
27. Fukami MC. *Dexmedetomidine Intravenous Sedation for Third Molar Extractions* [master's thesis]. Columbus, OH: Ohio State University, 2003. OCLC# 55056943. Isn/Std# .b5798492x