

by Tanita L. Roberts, PharmD

Column Editor: Lee Vermeulen, MS, RPh,

Director, Center for Drug Policy, University of Wisconsin Hospital and Clinics

Dexmedetomidine

(Precedex® - Abbott Laboratories)

Summary

Indications: Dexmedetomidine is indicated as a continuous infusion for short-term sedation (less than 24 hours) of intubated and mechanically ventilated patients in an intensive care (ICU) setting. Off-label use of dexmedetomidine may include use as an adjunct to regional or general anesthesia, as a bridge to ICU sedation and analgesia, as a supplement to regional block in patients undergoing carotid endarterectomy or during craniotomy when the patient must remain awake.

Monitoring Parameters: The most common adverse events associated with intravenous dexmedetomidine include hypotension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia, and anemia.

Dose: Dexmedetomidine is generally initiated with a loading dose of 1 mcg/kg over 10 minutes followed by a maintenance dose of 0.2 to 0.7 mcg/kg/hr titrated to achieve desired effect.

Pediatrics: There are no clinical studies establishing the safety and efficacy of dexmedetomidine in children, however, preliminary case studies discussing the use of dexmedetomidine in children have been published.

Geriatrics: In patients greater than 65 years of age, a higher incidence of bradycardia and hypertension was observed. Dexmedetomidine is also renally excreted, therefore this medication should be used with caution and a dose reduction may be required in this patient population.

Pregnancy: Pregnancy Category C. Based upon animal trials it is recommended that dexmedetomidine not be used in pregnant women unless benefits outweigh the risk to the fetus. A dose four times greater than the recommended dose for humans was administered to rats resulting in fetal toxicity, lower pup weights, embryocidal toxicity and delayed motor development. Placental transfer of dexmedetomidine was observed when radiolabeled dexmedetomidine was administered subcutaneously to pregnant rats.

Breast Feeding: It is not known if dexmedetomidine is excreted in human milk. In laboratory testing radiolabeled dexmedetomidine was excreted in the milk of rats. Caution should be used when administering this medication to nursing women.

Stability and Dilution: Dexmedetomidine vials must be diluted with 48 ml of 0.9% sodium chloride solution prior to administration. The admixture is stable at room temperature.

Administration: Dexmedetomidine should be administered using a controlled infusion device. Dexmedetomidine is not intended for administration for more than 24 hours.

Cost: Dexmedetomidine is supplied as a 100 mcg/ml 2 ml clear glass vial for dilution. The average wholesale price (AWP) for a box of 25 vials is \$1,783.00 (\$71.32/vial).

Introduction

In the critically ill patient, proper sedation is just as important as the medications given to address the other aspects of the patient's illness. Published studies have shown that improper sedation can have a negative effect on the patient's outcome.^{1,2} Sedation reduces the stress response, improves tolerance of ventilatory support and facilitates nursing care.¹ An ideal sedative would have rapid onset of action, provide adequate sedation, allow rapid recovery, be easy to administer, lack drug accumulation, have few adverse effects, interact minimally with other drugs and be inexpensive.¹

Midazolam and propofol are the most commonly used sedatives in the critically ill; however, these agents have adverse effects that could lead to prolonged mechanical ventilation and increased health costs.¹ Midazolam has rapid onset and short duration of action.² The inadvertent oversedation caused by accumulation of the parent drug and its metabolites and the unpredictable awakening times make midazolam less desirable.² Propofol has been shown to be comparable to midazolam in onset and duration of action; however, it too has adverse affects that fuel the search for a better sedating agent. Propofol is known to increase pancreatic enzymes and, although a causal relationship has not been established, pancreatitis has been reported following anesthesia with propofol.² Propofol is dissolved in a lipid vehicle and therefore must be administered through a dedicated line because of increased risk of infection and some drug incompatibilities.² Dexmedetomidine (Precedex® -Abbott Laboratories) was introduced as a sedating agent that may have the characteristics of the ideal sedative and resolve some of the current challenges experienced with other agents.³

Tanita L. Roberts, PharmD is a Pharmacy Administrative Resident at the University of Wisconsin Hospital and Clinics.

The information given and views expressed herein do not necessarily reflect the opinions of PSW, its Board or members.

Pharmacology/Pharmacokinetics

Dexmedetomidine is pharmacologically related to clonidine, an α_2 agonist.^{4,5} Dexmedetomidine has an affinity for α_2 receptors eight times greater than that of clonidine.⁶ It exerts its effects by binding to α_2 receptors presynaptically and post synaptically in the locus ceruleus and in the spinal cord. It diminishes norepinephrine release and inhibits sympathetic activity.⁷ The inhibition of sympathetic activity causes decreased heart rate and blood pressure. The sedation and anxiolytic properties are exerted when dexmedetomidine binds to α_2 receptors in the locus ceruleus (a nerve cluster that lies near the brain's fourth ventricle) and analgesia produced by binding of the drug to adrenoreceptors in the spinal cord.⁷

Dexmedetomidine has an onset of action of 30 minutes, which is slower than that of midazolam or propofol (see Table 1). Dexmedetomidine has a distribution half-life of six minutes and displays linear kinetics. It has a terminal elimination half-life of 2 hours and duration of action of 4 hours.

Dexmedetomidine undergoes complete biotransformation by glucuronidation and cytochrome P450-mediated metabolism with little unchanged drug excreted in the urine and feces. Although dexmedetomidine is metabolized by cytochrome P450, *in vitro* studies have failed to produce evidence of

Table 1: Comparison of pharmacokinetic parameters of commonly used sedatives

Medication	Onset	Duration of action	Offset
Dexmedetomidine	30 minutes	4 hours	5 minutes ⁸
Midazolam	3-5 minutes	30-80 minutes	2-6 hours ⁴
Propofol	10-50 seconds	3-10 minutes	3-8 minutes ⁴

clinically significant drug interactions. Coadministration of dexmedetomidine with anesthetics, sedative hypnotics and opioids will likely lead to enhancement of its effects due to the pharmacodynamic properties of the medications involved.

Clinical trials

Sedation in the intensive care unit

Venn et al compared propofol and dexmedetomidine for sedation in the intensive care setting.⁹ Twenty adult patients expected to require a minimum of 8 hours of artificial ventilation after complex major abdominal or pelvic surgery were randomized to receive sedation with either dexmedetomidine or propofol at doses titrated to achieve a Ramsay Scale score greater than 2 (see Table 2). Dexmedetomidine was given as a loading dose of 2.5 mcg/kg/hr over 10 min followed by a maintenance infusion of 0.2 to 2.5 mcg/kg/hr. Propofol was administered at a rate of 1 to 3 mg/kg/hr, after a loading dose of up to 1 mg/kg over 10 minutes. Additional analgesia, if required, was provided by an alfentanil infusion. Depth of sedation was monitored using both the Ramsay sedation score and the bispectral index score (BIS). The BIS is a measurement

Table 2: Definition of Ramsay Scale Score

Ramsay Scale Score	Clinical assessment of level of sedation
1	Anxious, agitated, restless
2	Awake, cooperative, tranquil, orientated
3	Responds to verbal commands
4*	Brisk response
5*	Sluggish response
6*	No response

*Scores of 4-6 refer to a sleeping patient and are graded according to response to a loud noise.¹⁰

ranging from 0 (isoelectric EEG) to 100 (fully awake). Cardiovascular, respiratory, biochemical and hematological data were obtained. The patients' perception of the intensive care stay was assessed using the Hewitt questionnaire.

Two patients in the dexmedetomidine group and three patients in the propofol group received sedation for only 6 hours because extubation was clinically indicated. Four patients in the dexmedetomidine group and five in the propofol group received sedation for at least 12 hours. The median dexmedetomidine infusion rate was 0.86 (range 0.45 to 1.06)

mcg/kg/h. Patients receiving propofol infusions required significantly more alfentanil [2.5 (2.2 to 2.9) mg/hr] than patients receiving dexmedetomidine [0.8 (0.65 to 1.2) mg/hr] ($p=0.004$). The average propofol infusion rate was not

stated. The degree of sedation was comparable between the two groups. The mean RSS for the propofol and dexmedetomidine groups were 5 (4 to 5) and 5 (4 to 6), respectively ($p=0.68$). The depth of sedation was greater for propofol than for dexmedetomidine BIS 53 (41 to 64) and BIS 46 (36 to 58), respectively ($p=0.32$).

Arterial and central venous pressures in the two groups were similar at baseline and over the study period ($p=0.60$ and 0.21 respectively). No patient required inotropes, and there were no adverse cardiovascular events in either group. Patients showed no signs of a hypertensive or hypotensive response after receiving a loading infusion dose of dexmedetomidine. Heart rates were significantly lower in the dexmedetomidine group (75 vs. 90 beats per minute; $p=0.034$). Systolic and diastolic BPs did not differ between the two groups ($p=0.60$). Significant differences were found in the arterial/inspired oxygen ratio between the two groups at baseline and throughout the study ($p=0.003$). The mean extubation times for the propofol and dexmedetomidine groups were 28 (20 to 50) and 29 (15 to 50) minutes ($p=0.63$), respectively. Patients were given a

Hewitt questionnaire to complete 48 to 72 hours after discharge from the ICU. Based on results from the Hewitt questionnaire, noise and difficulty in sleeping were the principal concerns in the propofol group and discomfort on the ventilator was a major concern in those receiving dexmedetomidine.

Overall, the differences in the depth of sedation and extubation times observed between patients receiving dexmedetomidine and propofol were not statistically significant. Patients receiving dexmedetomidine required approximately 50% less opioids than those in the propofol groups. Cardiovascular response was similar between groups but lower heart rates were seen in patients receiving dexmedetomidine.

Dexmedetomidine use in surgery

Talke et al investigated the effects of perioperative dexmedetomidine in patients undergoing vascular surgery in a double blind, dose-escalation trial.¹¹ Twenty-five male patients with or at high risk for coronary artery disease were randomized to receive dexmedetomidine or placebo. Patients in the dexmedetomidine group were further randomized to receive low dose (2.64mcg/kg [range 2.30 to 3.75mcg/kg]), medium dose (5.31mcg/kg [4.40 to 5.97mcg/kg]), or high dose (8.03mcg/kg [5.57 to 9.87mcg/kg]) dexmedetomidine. Infusions began 1 hour before anesthesia and continued for 48 hours postoperatively.

Baseline blood pressure (BP), heart rate (HR), Holter ECG, 12 lead ECG and anesthetic concentrations were taken. Additional monitoring included echocardiography intraoperatively and cardiac enzymes postoperatively. Results for one male patient randomized to the high dose group were not included in the final analysis because immediate discontinuation of dexmedetomidine was needed. There were no differences in the amounts of alfentanil, thiopental or intraoperative isoflurane requirement for any group.

Intraoperatively, 4 of 6 placebo, 5 of 6 low-dose, 6 of 6 medium-dose, and 6 of 6 high-dose patients required phenylephrine to maintain systolic BP within predetermined limits. Forty-four percent of the patients receiving dexmedetomidine required anticholinergics to treat bradycardia, while the patients receiving placebo required none.

Both HR and systolic BP decreased in response to the 1-hour dexmedetomidine preoperative infusion as compared to placebo. The decrease in HR was significant for the low dose ($p=0.037$) and high dose ($p=0.004$) groups and the decrease for systolic pressure was significant for the medium dose ($p=0.01$) and high dose ($p=0.004$) groups. (See Table 3)

Heart rate and systolic BP increased in all patients in response to intubation. Both HR and BP increased above baseline during emergence from anesthesia for both placebo and dexmedetomidine groups. Postoperatively, the average HR was less in the high-dose group compared to the placebo group ($p=0.036$). Neither the low-dose nor the medium-dose groups differed significantly from the placebo. Postoperatively, tachycardia was seen less in the dexmedetomidine group than with placebo ($p=0.006$ low-dose, $p=0.004$ medium-dose, $p=0.004$ high-dose). Patients in both the placebo and low dose dexmedetomidine groups required esmolol to control HR.

Bekker et al reported their use of dexmedetomidine in awake craniotomy in a single patient.¹² A 38 yr-old male underwent resection of a left temporal brain neoplasm. Propofol 200mg and fentanyl 100 mcg/kg IV were used to induce anesthesia. Maintenance of anesthesia was achieved by 70% nitrous oxide, dexmedetomidine infusion (initial dose 1 mcg/kg/h over 30 minutes followed by 0.4 mcg/kg/h), and sevoflurane (0.3% to 0.7%). Goal sedation was set at a bispectral index score (BIS) of 50 – 60.

The patient's HR decreased from 62 to 78 beats per minutes (bpm) to 50 to 60 bpm after the initial dose of dexmedetomidine.

Table 3: Mean Heart Rate and Systolic Blood Pressure (SBP) Values¹¹

	Placebo	Dexmedetomidine		
		Low-Dose	Medium-Dose	High-Dose
Heart Rate (bpm)				
Baseline	80 ± 8	81 ± 12	70 ± 11	74 ± 11
Intraoperative	70 ± 16	70 ± 14	57 ± 5	63 ± 7
Postoperative (Rx on)	92 ± 16	92 ± 7	76 ± 7	81 ± 14
Postoperative (Rx off)	86 ± 13	94 ± 9	84 ± 10	95 ± 15
SBP (mmHg)				
Baseline	145 ± 15	142 ± 16	146 ± 23	135 ± 23
Intraoperative	134 ± 12	124 ± 13	129 ± 20	130 ± 18
Postoperative (Rx on)	144 ± 13	124 ± 5	134 ± 26	135 ± 20
Postoperative (Rx off)	150 ± 11	129 ± 10	141 ± 21	128 ± 20

Values are mean ± SD; Rx on= during study drug infusion; Rx off= first 12 hours after study drug infusion

Blood pressure also decreased from 95 to 110/55 to 65 mmHg to 90 to 100/52 to 60 mmHg. At an infusion rate of 0.2 mcg/kg/hr of dexmedetomidine, the patient was arousable but too sedated to perform counting or sentence completion tasks (BIS 75 to 80). The infusion rate was then decreased to 0.1 mcg/kg/h to achieve a BIS of 95. The patient was able to remember that he was awake during the procedure but could not recall any details.

Surgically induced motor and sensory deficits are of great concern when performing neurosurgery.¹³ Evoked potentials are used to prevent spinal cord damage during surgery. Using changes in the amplitude and occurrence of the potentials it is possible to determine the functional status of spinal cord sensory tracts.¹³ Some anesthetic medications can depress these evoked potentials to a great degree. Propofol has been used preferentially for conscious sedation because of its rapid metabolism and rapid recovery of somatosensory evoked potential depression after discontinuation of infusion.¹⁴ Propofol has also been proven to have no effect on somatosensory evoked potential when measured in the epidural space. These properties allow propofol's effect on evoked potential and depth of anesthesia to be adjusted quickly.

Bloom et al reported the effect of dexmedetomidine on intraoperative somatosensory evoked potentials in two patients.⁸ The patients were a 74-yr-old female scheduled for an occipitocervical fusion and a 47-yr-old male undergoing a C4-7 laminectomy and posterior spinal fusion. Sedation was initially maintained with a combination regimen, which included propofol. During the procedure the propofol was replaced by dexmedetomidine. The effects of the two sedatives on evoked potentials were similar.

In case one, the baseline evoked potential was 25.7; during sedation with propofol and dexmedetomidine the evoked potentials were 25.3 and 25.1, respectively. In the second patient, the amplitudes of the evoked potentials were 23.7, 23.5 and 23.9, respectively. The authors concluded that additional studies are needed to understand the effects of dexmedetomidine on evoked potentials.

Bustillo et al reported their experience with dexmedetomidine in a retrospective case report.⁷ Dexmedetomidine was used in five patients requiring interventional neurological procedures from January to April 2001. The interventions included angiography, neuropsychological testing and embolization. Each patient was to be sedated for the angiography (Ramsay 3 to 5) and embolization but awake for the neurological testing. All patients were sedated with fentanyl (160±82.2 mcg) and midazolam (2.8±1.9 mg). Two patients received dexmedetomidine loading doses of 1 mcg/kg. All five patients received continuous infusion doses of dexmedetomidine at rates of 0.2 to 0.7 mcg/kg/hr. Infusions were discontinued ten minutes before neurological testing

began. Patients were awake and followed simple verbal commands but none were able to complete more complex neurological testing. All five procedures were canceled because baseline neurological studies were unable to be completed even sixty minutes after discontinuation of the drug. The authors concluded that although dexmedetomidine preserved respiration and allowed patients to be awakened by verbal stimulation, cognitive function was significantly impaired at doses recommended by the manufacturer. They also found that these patients were unable to complete neuropsychological testing 45 minutes after infusion discontinuation whereas patient receiving propofol in their experience were able to complete the same testing 10 minutes after discontinuation of infusion.

Dexmedetomidine in renal impairment

De Wolf et al reported the pharmacokinetics of dexmedetomidine in patients with renal impairment.¹⁵ Six volunteers with severe renal disease (RD group) and six volunteers with normal renal function were matched by weight, age, sex, and smoking status. Eligible volunteers with renal disease were enrolled in the study if they had a 24-hour creatinine clearance (Cl_{CR}) of less than 30 mL/minute and had not yet undergone dialysis or renal transplantation. Eligible volunteers with normal renal function were enrolled if they had a 24-hour Cl_{CR} greater than 80 mL/minute. Dexmedetomidine 0.6 mcg/kg was infused over 10 minutes. Blood samples were drawn at baseline and periodically during and after the dexmedetomidine infusion to measure plasma concentrations of the drug. A visual analog scale for sedation was used to determine the degree of sedation at baseline, during the dexmedetomidine infusion and up to 24 hours after the infusion stopped.

There were no clinically significant differences in pharmacokinetics of dexmedetomidine between the two groups except in the elimination half-life ($t_{1/2[\beta]}$), which was shorter in the RD group (113.4 ± 11.3 vs. 136.5 ± 13.0 minutes [$p < 0.05$]). Heart rate was similar in the RD and control groups and remained unchanged during and after dexmedetomidine administration. Blood pressure was decreased in both groups after dexmedetomidine administration. There were no significant statistical differences during the study period in the respiratory rate and SpO_2 between groups. RD volunteers were sedated for a longer period of time than healthy volunteers. The decreased plasma protein binding in RD may explain this effect. Mild hypotension requiring no intervention was observed in four control volunteers. Brief episodes of minor obstructive apnea were observed in two RD volunteers, however SpO_2 remained stable. The authors concluded that doses of dexmedetomidine may need to be reduced in patients with RD to avoid oversedation.

Dexmedetomidine in pediatric-aged patients

Published information on the use of dexmedetomidine in pediatric patients is limited to a case series published by Tobias and Berkenbosch.¹⁰ This is preliminary information from an ongoing clinical evaluation of the efficacy of dexmedetomidine for sedation during mechanical ventilation in pediatric patients.

Patient 1: Dexmedetomidine was used in a 10-week old infant who required tracheal intubation and mechanical ventilation. Dexmedetomidine infusion was started at 0.25 mcg/kg/h. No bolus dose was used as the patient had recently received a midazolam dose. The patient received three doses of 0.1mg/kg morphine during the 24-hour administration of dexmedetomidine.

The Ramsay scale and Bispectral Index were used for assessment. The infant maintained a Ramsay score of 4 and mean BIS of 54 (36 to 70). No significant change in HR or BP was noted when comparing values before and after the start of infusion. After 24 hours the infusion was stopped.

Patient 2: Dexmedetomidine was used in a 14-year-old patient requiring sedation in the ICU after undergoing posterior spinal fusion for neuromuscular scoliosis. Dexmedetomidine was started at 0.25 mcg/kg/hr following a bolus dose of 0.5 mcg/kg to provide sedation during mechanical ventilation. After the bolus dose the BIS number decreased from 89 to 46, the HR decreased from 136 to 96 bpm and BP decreased from 158/108 mmHg to 126/66 mmHg. During the 10-hour period of infusion, the patient received one morphine dose of 0.05 mg/kg plus unspecified epidural analgesia. The dexmedetomidine was increased to 0.5 mcg/kg/hr in response to a Ramsay score of 2 and a BIS of 71. No significant changes in HR or BP were noted during the dexmedetomidine infusion.

Patient 3: A 14-year-old patient scheduled for anterior spinal fusion for treatment of idiopathic scoliosis required controlled hypotension during surgery. Controlled hypotension was initiated with dexmedetomidine infusion at 0.2 mcg/kg/hr and increased to 0.5 to 0.7 mcg/kg/hr to maintain a mean arterial pressure of 55 to 65 mmHg. There was a decrease in HR from 90 to 100 bpm to 70 to 80 bpm with the start of infusion. A decrease in mean arterial pressure from 75 to 80 mmHg to 55 to 60 mmHg was also seen. The BIS range decreased from 55-60 to 30-40. The infusion was continued for a total of 4 hours and 45 minutes intraoperatively.

Patient 4: An 11-year-old patient received dexmedetomidine for sedation and anesthesia while undergoing endoscopic gastroduodenoscopy for evaluation of persistent abdominal pain. Dexmedetomidine was administered as a bolus of 0.6 mcg/kg over 2 minutes followed by infusion of 0.5mcg/kg/hr. Vital signs taken immediately after the bolus were essentially unchanged.

Five minutes after bolus and initiation of the infusion, the

patient remained awake (BIS 89) and was given a second bolus of 0.6 mcg/kg. The BIS decreased to 42 and the patient became unresponsive to verbal commands. Vital signs remained stable. With the introduction of the endoscope into the oropharynx the patient became responsive and distressed. The patient calmed over the next 2 minutes but it was not possible to reinstate sedation with dexmedetomidine, so the drug was discontinued. Midazolam and ketamine were used for sedation and the endoscopy was complete without further incident.

Adverse effects

The most common adverse events associated with intravenous dexmedetomidine versus placebo include hypotension (30% vs. 15%), hypertension (16% vs. 18%), nausea (11% vs. 10%), bradycardia (8% vs. 4%), fever, vomiting, hypoxia (6% vs. 4%), tachycardia and anemia (3% vs. 2%).¹

Hypertension, hypotension and bradycardia can develop with rapid infusion of dexmedetomidine.⁶ In an unpublished trial submitted to the FDA for drug approval, there was no clinically or statistically significant difference in the development of hypertension between the placebo (18%) and the dexmedetomidine (16%) groups. There was, however, a significant difference in the development of hypotension between the placebo (15%) and the dexmedetomidine (30%) groups.

Cost, dose, how supplied

Dexmedetomidine is supplied as a 100 mcg/ml 2 ml clear glass vial for dilution. The labeled dose for dexmedetomidine is a loading dose of 1 mcg/kg followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr for a maximum of 24 hours. The AWP for a box of 25 vials is \$1,783.00 (\$71.32/vial).

Assuming a dexmedetomidine maintenance infusion rate of 0.7 mcg/kg/hr and an average patient weight of 70 kg, cost for a 24-hour infusion of dexmedetomidine is \$427.92.

Conclusion

Dexmedetomidine has been shown to be safe and effective as a sedating agent. It is comparable with propofol without the concerns raised with propofol use.⁹ However, dexmedetomidine is not recommended for use for more than 24 hours. Although dexmedetomidine preserves respiration, at higher doses it will decrease HR, cardiac output, stroke volume, and mean arterial pressures.¹⁶ When used for conscious sedation during neurosurgical procedures patients were able to wake up using verbal stimulation but could not complete neurological testing.^{7,8,12} In a head to head trial with propofol, dexmedetomidine failed to demonstrate clinical or statistical superiority in time to extubation, depth of sedation or blood pressure response.⁹ Further experience with this drug is needed in the ICU setting. Although dexmedetomidine has been proven to be just as effective as propofol, literature does not support its use over propofol.³ The cardiovascular effects, limited infusion time,

and impaired cognitive effects limit the usefulness of dexmedetomidine as a sedating agent.¹⁶

Current guidelines for the use of sedatives in the critically ill patient recommend propofol as the preferred sedative when rapid awakening (e.g. for neurologic assessment or extubation) is important.³ Many institutions are standardizing their approach to ICU sedation in an effort to decrease expenditures related to the use of sedative medications while decreasing the duration of mechanical ventilation and the length of stay in the intensive care unit. The cost of the drug (significantly higher than generically available propofol) should also be considered. Considering the clinical and economic data available, dexmedetomidine should not be added to hospital formularies without restrictions to ensure appropriate use. ■

References

- Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. *JAMA* 2000;283:1451-1459.
- Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002;30:119-36.
- Precedex® (Dexmedetomidine hydrochloride injection) prescribing information. North Chicago, IL: Abbott Laboratories, Feb. 2001.
- MICROMEDEX® Healthcare Series: MICROMEDEX, Greenwood Village, Colorado (Edition expires 3/2003).
- Hoffman BB, Lefkowitz RJ, Taylor P. Neurotransmission: the autonomic and somatic motor nervous systems. In: Hardman JG, Limbird LE, Goodman Gilman A, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw Hill Professional; 2001:chap 6.
- Coursin DB, Coursin DB, Maccioli GA. Dexmedetomidine. *Curr Opin Crit Care* 2001;7:221-26.
- Bustillo MA, Lazar RM, Finck DA, et al. Dexmedetomidine may impair cognitive testing during endovascular embolization of cerebral arteriovenous malformations: a retrospective case report series. *J Neurosurg Anesthesiol* 2002;14:209-12.
- Bloom M, Beric A, Bekker A. Dexmedetomidine infusion and somatosensory evoked potentials. *J Neurosurg Anesthesiol*. 2001;13:320-22.
- Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *Br J Anaesth* 2001;87:684-90.
- Tobias JD, Berkenbosch JW. Initial experience with dexmedetomidine in paediatric-aged patients. *Paediatr Anaesth* 2002;12:171-5.
- Talke P, Li J, Jain U, et al. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. *Anesthesiology* 1995;85:620-33.
- Bekker A, Kaufman B, Samir H, et al. The use of dexmedetomidine infusion for awake craniotomy. *Anesth Analg* 2001;92:1251-53.
- Owen JH. The application of intraoperative monitoring during surgery for spinal deformity. *Spine* 1999;24:2649.
- Sloan TB. Anesthetic effects on electrophysiologic recordings. *J Clin Neurophysiol* 1998;15L217-226.
- De Wolf AM, Fragen RJ, Avram MJ, Fitzgerald PC, Rahimi-Danesh F. The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. *Anesth Analg* 2001;93:1205-9.
- Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colino MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology* 2000;93:382-94.

Lake Country