

Sympathetic and Hemodynamic Effects of Moderate and Deep Sedation with Propofol in Humans

Thomas J. Ebert, M.D., Ph.D.*

Background: The objective of this study was to determine the mechanisms involved in the hypotension associated with sedative doses of propofol in humans.

Methods: Ten healthy volunteers (aged 21–37 yr) participated on two occasions and in random order received placebo or propofol infusions. Standard monitoring and radial artery blood pressure were combined with measurement of forearm blood flow (plethysmography) and derivation of forearm vascular resistance, recording of peroneal nerve sympathetic activity, and blood sampling for norepinephrine concentrations. A computer-controlled infusion pump delivered placebo or two concentrations of propofol, adjusted to achieve moderate and deep sedation based on the Observer Assessment of Alertness/Sedation score (responsiveness component) of 4 and 3. Level of sedation was quantitated using bispectral analysis of the electroencephalogram. Baroreflexes were assessed with a hypotensive challenge *via* administration of sodium nitroprusside.

Results: Baseline neurocirculatory and respiratory parameters did not differ between sessions. Progressive infusions to achieve moderate and deep sedation resulted in average Bispectral Index values of 70 and 54, respectively. Propofol significantly reduced sympathetic nerve activity at both levels of sedation and decreased norepinephrine and forearm vascular resistance at deep sedation. These effects resulted in significant decreases in mean blood pressure of 9% and 18% at moderate and deep sedation, respectively. Propofol also reduced reflex increases in sympathetic nerve activity.

Conclusions: These data from healthy subjects indicate that sedation doses of propofol, which did not compromise respiratory function, had substantial inhibitory effects on sympathetic nerve activity and reflex responses to hypotension resulting in vasodilation and significant decreases in mean blood pressure.

IN the United States, 50–70% of surgical procedures are performed in outpatient, ambulatory settings. These procedures often require moderate to deep sedation to ensure the patient's comfort. Propofol commonly is used to accomplish sedation goals in the operating room, and this has engendered a growing interest from nonanesthesia providers in using propofol rather than conventional opioid-benzodiazepine combinations for sedation in the outpatient setting. A concern, however, has been the possibility of oversedation and respiratory compromise due to the rather narrow therapeutic window afforded by propofol. The growing literature describing the use of propofol for sedation outside of the operating

room by nonanesthesia personnel has described another serious side effect, namely hypotension.^{1–3} Sedative doses of propofol have larger effects on blood pressure (BP) when compared with midazolam, another commonly used sedative agent; however, the mechanism of this heightened response has not been explored.^{4,5}

In previous work from our laboratory, larger (general anesthetic) doses of propofol have led to substantial inhibition of sympathetic nerve activity (SNA) and decreases in plasma norepinephrine concentrations in humans.^{6,7} The current study used targeted, controlled infusions of propofol in healthy volunteers to achieve moderate to deep sedation. We sought to determine whether sympathetic nervous system inhibition would be present at sedation doses of propofol. In addition, baroreflex responsiveness was evaluated during sedation because previous work with general anesthetic doses of propofol revealed profound disturbances in the reflex control of SNA.⁷

Materials and Methods

After approval by the Human Research Review Committee (Veterans Affairs Medical Center, Milwaukee, Wisconsin), written informed consent was obtained from healthy volunteers (aged < 40 yr; American Society of Anesthesiologists physical status of I) to participate on two occasions to receive placebo or propofol in a randomized fashion. Volunteers were blinded to the treatment. Heart rate (HR; two-lead electrocardiogram), oxygen saturation (pulse oximetry), level of sedation (Bispectral Index, A1050 BIS[®] monitor; Aspect Medical Systems, Newton, MA), and respiratory rate and end-tidal carbon dioxide with capnography (infrared spectrometry) *via* a nasal cannula were monitored. BP was monitored with a radial arterial line.

Baroreflex testing was performed by administration of an infusion of $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ sodium nitroprusside over 2.5 min, with sampling of HR, BP, and SNA during the last 60 s. The dose of sodium nitroprusside was then increased to $1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and after 90 s, another 60-s data sample was acquired.⁸ The sampling rate was 250 Hz per channel. Data during each 60-s data collection were averaged. Linear regression analyses of the average SNA and diastolic pressure at baseline and low-dose and high-dose infusions of sodium nitroprusside provided the calculated peripheral baroreflex slope. Similarly, linear regression analyses of the average HR and mean arterial pressure at baseline and low-dose and high-dose infusions of sodium nitroprusside provided the calculated cardiac baroreflex slope.

* Professor, Department of Anesthesiology, The Medical College of Wisconsin, and the Veterans Affairs Medical Center, Milwaukee, Wisconsin.

Received from the Zablocki Veterans Affairs Medical Center, Department of Anesthesiology, Milwaukee, Wisconsin. Submitted for publication November 15, 2004. Accepted for publication March 11, 2005. Supported by a Veterans Affairs Merit Review grant, Washington, D.C.

Address reprint requests to Dr. Ebert: Veterans Affairs Medical Center, 112A, 5000 West National Avenue, Milwaukee, Wisconsin 53295. Address electronic mail to: tjebert@mcw.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Microneurography was used to directly measure muscle SNA. To do this, the lower leg was supported and cushioned. The bony prominence at the proximal head of the fibula on the lateral aspect of the leg was identified and marked. Brief, external, electrical impulses (1 Hz, 3–7 mA, constant current stimulator) were delivered *via* a small, metallic probe below this mark until a muscle twitch could be seen distal to the site, thereby identifying the location of the peroneal nerve. The skin was then cleansed, and two epoxy-coated tungsten needles with 3- to 5- μ m exposed tips (TMI Electronics, Iowa City, IA) were inserted. One needle was advanced to an area near the site of the peroneal nerve, and the second needle was advanced into the peroneal nerve. The placement of the second needle within the peroneal nerve was verified with the application of brief impulses (1 Hz, 0.03–0.05 mA) to the needle. These electrical stimuli elicit distinct muscle contractions in the distribution of the deep or superficial peroneal nerve when a nerve fascicle that innervates skeletal muscle has been entered. The stimulus was halted, and neural activity was amplified (100,000 \times), rectified, and integrated. A custom-made preamplifier used common-mode rejection to remove unwanted signals (noise) simultaneously received by both needles (*e.g.*, 60-Hz noise).

The neural signal was then fed through a variable band-pass filter (typically 200–2,000 Hz). Characteristic integrated “bursts” of muscle sympathetic efferent activity were sought by fine manipulations of the needle within the nerve fascicle. The identity of these bursts and their distinction from skin sympathetic efferent nerve activity have been described in detail elsewhere.⁷ Briefly, muscle SNA is pulse synchronous and can be increased during prolonged breath holding by phases II and III of the Valsalva maneuver and by drug-induced hypotension.

Forearm blood flow (FBF) was determined by venous occlusion plethysmography. In the supine position, the elbow (opposite to the infusion arm) was slightly flexed, and the arm was supported underneath the elbow and at the wrist to be above heart level to ensure adequate venous drainage before and between measurements. Uninflated BP cuffs were placed about the wrist and upper arm, and a double-stranded, mercury-in-Silastic, temperature-compensated strain gauge was placed around the forearm at its greatest girth (DE Hokanson, Issaquash, WA). The underlying principle of this technique is that the initial rate of expansion of the forearm during venous occlusion is proportional to the rate of arterial inflow.^{9,10} Arterial occlusion at the wrist *via* cuff inflation to suprasystolic pressure of 250 mmHg was used during FBF measurements to exclude the hand circulation from measurements. FBF was determined by automated, custom-written software that calculated the rate of the increase (slope) in forearm volume during inflation of the upper arm cuff to 50 mmHg for 8-s periods. Inflations

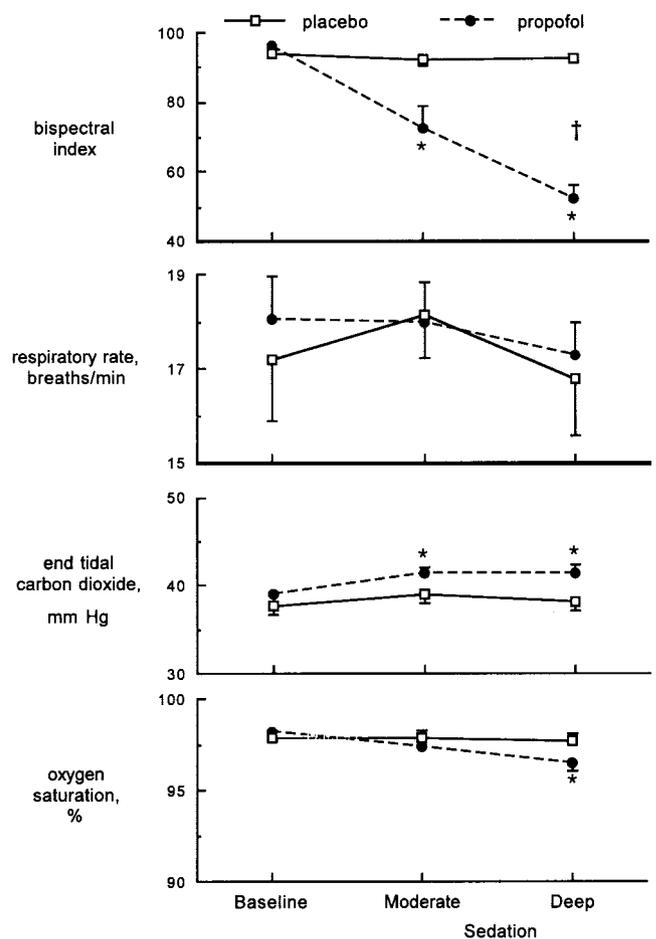


Fig. 1. Bispectral analysis (index) of the electroencephalogram and respiratory parameters (respiratory rate; oxygen saturation; end-tidal carbon dioxide). There were small but significant changes in end-tidal carbon dioxide and oxygen saturation, whereas the Bispectral Index demonstrated a significant level of sedation achieved with both levels of propofol. Data are presented as mean \pm SEM. * Significant change from baseline ($P < 0.05$). † Significantly different response from placebo ($P < 0.05$).

were repeated six times during each data acquisition period. The six slopes were visually verified by a trained member of the research team and were averaged to obtain a single value of FBF for that time period. Forearm vascular resistance was calculated by dividing mean arterial BP by FBF.

Volunteers participated on two separate occasions and received either placebo or two targeted, effect site concentrations of propofol (1 and 2 μ g/ml) delivered by a programmed (StanPump, Stanford, CA), computer-controlled infusion pump (Harvard Pump, Holliston, MA). The selected target levels were adjusted to achieve moderate and deep sedation, respectively, based on the responsiveness component of the Observer Assessment of Alertness/Sedation scale of 4 and 3.¹¹ This involved presentation of progressively more intense stimuli to the volunteer, with a score of 4 representing a lethargic response to the volunteer’s name spoken in a normal tone, termed in this article *moderate sedation*, and a

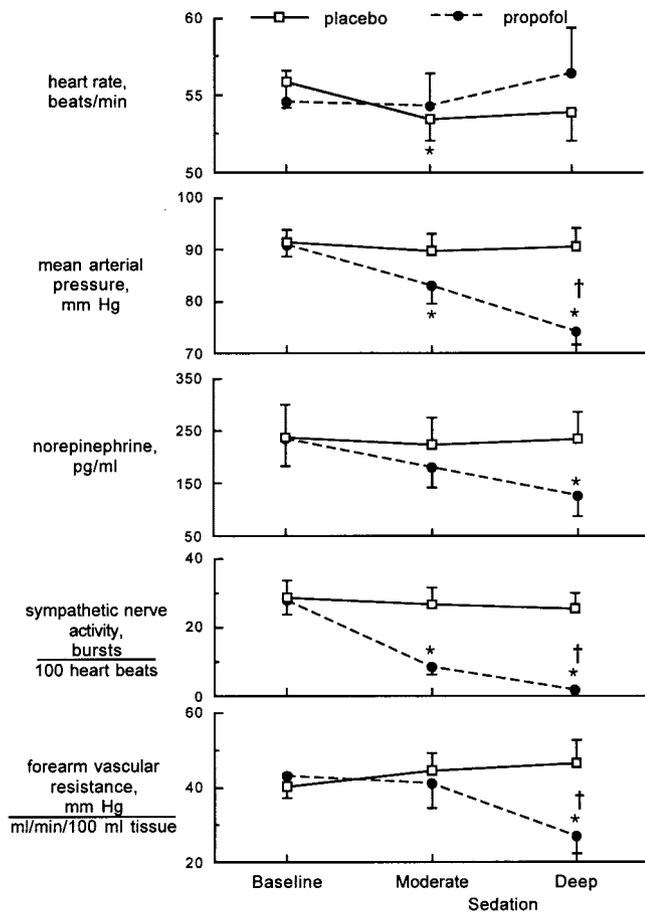


Fig. 2. Mean arterial pressure, norepinephrine, muscle sympathetic nerve activity, and forearm vascular resistance diminished significantly with propofol. Heart rate was unchanged. The changes over time (interaction) for mean arterial pressure, sympathetic nerve activity, and forearm vascular resistance (mean arterial pressure/forearm blood flow) were different for propofol compared with placebo. Data are presented as mean \pm SEM. * Significant change from baseline ($P < 0.05$). † Significantly different response from placebo ($P < 0.05$).

score of 3 representing a response only to loud or repeated name calling, termed *deep sedation*.

After all monitors were applied, a 10-min quiet rest period was observed, followed by a 3-min period of baseline measurements consisting of Bispectral Index, BP, HR, respiratory rate, FBF, end-tidal carbon dioxide, oxygen saturation, SNA, and blood sampling for baseline norepinephrine. This was followed with a 10-min period to obtain baroreflex data. A 12-min recovery was observed, after which propofol or placebo (saline) was infused *via* a computer-controlled pump to each of two sedation levels. The data collection was repeated 2 min after achieving the desired Observer Assessment of Alertness/Sedation score or after 10 min of placebo infusion. In all cases, the order of target infusions was moderate sedation first, followed by deep sedation.

Arterial samples were taken at baseline and at targeted sedation periods to determine norepinephrine concentrations. Samples were placed in EGTA tubes and centri-

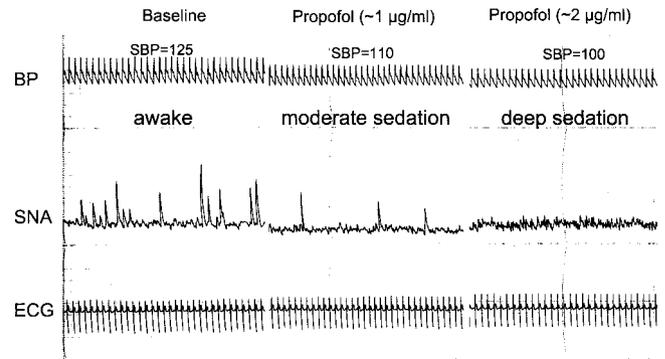


Fig. 3. Representative tracings of electrocardiogram (ECG), arterial pressure (BP), and integrated sympathetic nerve activity (SNA) at baseline and during two targeted levels of sedation with propofol. Note the incremental decreases in BP and SNA with increasing doses of propofol. SBP = systolic blood pressure.

fused at 4°C for 10 min. The serum was removed and stored at -70°C until later analysis by high-performance liquid chromatography. Specifications of the assay are as follows: The lower limit of detection is 12 pg; recovery of a sample spiked with 60 pg norepinephrine standard is 82%; intraassay variability ($n = 7$) is 4.2%; and interassay variability of a commercial pool ($n = 22$) is 9.7%.

Statistical Analysis

Data are presented as mean \pm SEM. Consecutive hemodynamic measurements were compared over time (baseline, moderate and deep sedation) and between groups (placebo or propofol) with repeated-measures analysis of variance; Scheffé *post hoc* analysis was done where appropriate. A level of $P < 0.05$ was considered significant. Baroreflex responses to hypotension from sodium nitroprusside were determined with linear regression of the relation between diastolic pressure and SNA or mean pressure and HR (R-R interval). The slope of the relation was used to derive the sensitivity of the baroreflex.

Results

We studied 10 young, healthy volunteers with American Society of Anesthesiologists physical status of I. On average, they were aged 25 yr (range, 21-37 yr), were 175 cm tall (range, 161-188 cm), and weighed 73 kg (range, 57-91 kg). Four were female, and all were white. The targeted sedation levels resulted in significant effects compared with the placebo trial, confirmed by decreasing Bispectral Index values (fig. 1). There were no differences in the placebo group for any measured variable over time (*i.e.*, from baseline) (figs. 1 and 2). HR and respiratory rate were not affected by deep sedation with propofol, and although oxygen saturation and end-tidal carbon dioxide did demonstrate statistically significant changes, these were not of clinical significance (figs. 1 and 2). SNA diminished significantly with propo-

Table 1. Cardiac (R-R Interval vs. Mean Arterial Pressure) and Peripheral (Sympathetic Nerve Activity vs. Diastolic Pressure) Baroreceptor Slopes during Placebo or Sedation

	Sedation Level		
	Baseline	Moderate	Deep
Cardiac baroslope to nitroprusside (ms/mmHg)			
Placebo	19.4 ± 3	22.2 ± 3	21.8 ± 2
Propofol	23.4 ± 7	16.0 ± 3	14.0 ± 1
Peripheral baroslope to nitroprusside ((bursts × amplitude) × mmHg ⁻¹)			
Placebo	-29.3 ± 7	-31.1 ± 5	-31.0 ± 6
Propofol	-31.8 ± 5	-22.9 ± 6*	-14.7 ± 5*†

Data are presented as mean ± SEM.

* Different from baseline value. † Different from placebo, $P < 0.05$.

fol by 65% and 92% at moderate and deep sedation, respectively (fig. 2). Propofol decreased forearm vascular resistance by 6% during moderate sedation (not significant) and by 38% (significant) during deep sedation. In addition, propofol decreased norepinephrine by 18% and 44% and mean arterial BP by 9% and 18% during moderate and deep sedation, respectively (fig. 2). Representative segments of recordings of integrated SNA, electrocardiogram, and direct BP at baseline and increasing sedation levels are shown in figure 3.

Propofol attenuated the baroreceptor reflex sensitivity relating increases in SNA to decreasing BP but did not change the reflex HR increase (table 1).

Discussion

The major finding of this research using two sedation levels of propofol was a significant decrease in mean arterial BP that could be attributed to a combination of decreases in basal SNA and in the reflex control of SNA. This resulted in progressive decreases in norepinephrine and in forearm vascular resistance. The targeted infusions achieved both moderate and deep sedation without clinically significant compromise of respiratory rate, end-tidal carbon dioxide, and oxygen saturation.

Propofol (2,6-di-isopropylphenol) was introduced in the United States in 1989 and has gained popularity as a sedative/hypnotic to provide moderate sedation. Anesthesia caregivers commonly use propofol for monitored anesthesia care procedures where respiratory depression and hypotension are closely monitored and routinely managed. Nonanesthesia caregivers are now gaining experience with propofol and reporting that it provides rapid onset of sedation, better titratability, quicker recovery time, and better patient satisfaction compared with other sedation alternatives.^{5,12-19} However, it is well documented that sedation with propofol can have significant consequences on respiration and BP.^{3-5,20,21} Recently, a study evaluating the predictive nature of a test dose of propofol (approximately 30 mg in a 70-kg adult) for hypotension on induction of anesthesia indicated that the test dose alone resulted in a

17-mmHg decrease in BP.²⁰ In a recent publication, a gastroenterologist's protocol for "safe and effective administration of propofol" was evaluated for endoscopic examinations.³ Hypoxemia (oxygen saturation < 90%) occurred in 9% of the 819 patients, whereas hypotension (BP decrease > 20 mmHg) occurred in 27% of the patients. These findings amplify concerns with the use of propofol by nonanesthesia personnel: Respiratory depression may be the primary focus for concern, but hypotension may be the more common effect.

Surprisingly little is known about the mechanisms of the BP changes noted with sedative doses of anesthetics. Previous work from this laboratory explained the significant hypotension from induction doses (2.5 mg/kg) of propofol by demonstrating both profound sympathoinhibition as well as impaired reflex activation of the sympathetic nervous system during hypotension.^{6,7} In addition, during maintenance of general anesthesia with infusions of propofol, sympathetic outflow remained low, and baroreflex activation of the sympathetic nervous system during brief impositions of a hypotensive stimulus was attenuated.⁷

In previous work, we evaluated another possible mechanism by which propofol might reduce BP. We sought a direct dilating effect of propofol on human blood vessels by infusing propofol into the brachial artery.²² The local infusions did not change FBF. In contrast, systemic infusions of propofol were noted to increase blood flow only if sympathetic innervation to the forearm was intact. Therefore, we concluded that propofol did not decrease BP *via* a direct effect on blood vessels; rather, its mechanism was *via* sympathoinhibition.

The current research was undertaken in healthy volunteers. Extrapolation of these findings to older, less healthy patients should be done with caution but might enhance concerns. Older and sicker patients generally have higher basal levels of sympathetic tone and impaired baroreflexes. This might amplify the hemodynamic effects of propofol-mediated sympathoinhibition. In addition, volume status and concurrent autonomically active prescription medication also might adversely in-

fluence responses in a less healthy patient population. As more patients in poor health are scheduled to undergo increasingly complex procedures in non-operating room settings, the use of propofol by nonanesthesia providers will become increasingly troublesome.

In summary, propofol is gaining in popularity for use outside the operating room setting because of its faster onset and recovery compared with the other sedatives/hypnotics. This research points out hemodynamic disadvantages of propofol. Targeted to moderate and deep sedation, propofol did not clinically compromise respiration but substantially reduced sympathetic nervous system activity and baroreflex responses to hypotension, which resulted in vasodilation and hypotension. Even at moderate sedation levels, we noted significant decreases in mean arterial BP and SNA. Deep sedation decreased forearm vascular resistance and norepinephrine and further decreased mean arterial BP and SNA. The results of this study indicate that propofol should be used with attention to hemodynamic monitoring during moderate to deep sedation. Furthermore, in patients at risk of adverse events resulting from a decrease in BP, the caregiver responsible for the administration of propofol must be skilled in rescue, not only for impaired ventilation but also for treatment of hypotension.

The author thanks Shahbaz Arain, M.D. (Clinical Research Fellow, Medical College of Wisconsin, Milwaukee, Wisconsin), Toni Uhrich, M.S. (Research Technologist, Medical College of Wisconsin), and Jill Barney, M.S. (Research Technologist, Veterans Affairs Medical Center, Milwaukee, Wisconsin), for their assistance with the conduct of the study, analyses of the data, and preparation of this manuscript.

References

- Campbell L, Imrie G, Doherty P, Porteous C, Millar K, Kenny GN, Fletcher G: Patient maintained sedation for colonoscopy using a target controlled infusion of propofol. *Anaesthesia* 2004; 59:127-32
- Heuss LT, Drewe J, Schnieper P, Tapparelli CB, Pflimlin E, Beglinger C: Patient-controlled versus nurse-administered sedation with propofol during colonoscopy: A prospective randomized trial. *Am J Gastroenterol* 2004; 99:511-8
- Cohen LB, Dubovsky AN, Aisenberg J, Miller KM: Propofol for endoscopic sedation: A protocol for safe and effective administration by the gastroenterologist. *Gastrointest Endosc* 2003; 58:725-32
- Seifert H, Schmitt TH, Gültekin T, Caspary WF, Wehrmann T: Sedation with propofol plus midazolam versus propofol alone for interventional endoscopic procedures: A prospective, randomized study. *Aliment Pharmacol Ther* 2000; 14:1207-14
- Koshy G, Nair S, Norkus EP, Hertan HI, Pitchumoni CS: Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am J Gastroenterol* 2000; 95:1476-9
- Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP: Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. *ANESTHESIOLOGY* 1992; 76:725-33
- Ebert TJ, Muzi M: Propofol and autonomic reflex function in humans. *Anesth Analg* 1994; 78:369-75
- Ebert TJ: Differential effects of nitrous oxide on baroreflex control of heart rate and peripheral sympathetic nerve activity in humans. *ANESTHESIOLOGY* 1990; 72:16-22
- Whitney RJ: The measurement of volume changes in human limbs. *J Physiol (Lond)* 1953; 121:1-27
- Benjamin N, Calver A, Collier J, Robinson B, Vallance P, Webb D: Measuring forearm blood flow and interpreting the responses to drugs and mediators. *Hypertension* 1995; 25:918-23
- Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *ANESTHESIOLOGY* 1997; 86:836-47
- Oei-Lim VLB, Kalkman CJ, Bartelsman JFWM, Res JCJ, van Wezel HB: Cardiovascular responses, arterial oxygen saturation and plasma catecholamine concentration during upper gastrointestinal endoscopy using conscious sedation with midazolam or propofol. *Eur J Anaesthesiol* 1998; 15:535-43
- Jung M, Hofmann C, Kiesslich R, Brackertz A: Improved sedation in diagnostic and therapeutic ERCP: Propofol is an alternative to midazolam. *Endoscopy* 2000; 32:233-8
- Green SM, Krauss B: Propofol in emergency medicine: Pushing the sedation frontier. *Ann Emerg Med* 2003; 42:792-7
- Rex DK, Overley C, Kinser K, Coates M, Lee A, Goodwine BW, Strahl E, Lemler S, Sipe B, Rahmani E, Helper D: Safety of propofol administered by registered nurses with gastroenterologist supervision in 2000 endoscopic cases. *Am J Gastroenterol* 2002; 97:1159-63
- Wehrmann T, Kokabpick S, Lembecke B, Caspary WF, Seifert H: Efficacy and safety of intravenous propofol sedation during routine ERCP: A prospective, controlled study. *Gastrointest Endosc* 1999; 49:677-83
- Parworth LP, Frost DE, Zuniga JR, Bennett T: Propofol and fentanyl compared with midazolam and fentanyl during third molar surgery. *J Oral Maxillofac Surg* 1998; 56:447-53
- Manninen PH, Chan ASH, Papworth D: Conscious sedation for interventional neuroradiology: A comparison of midazolam and propofol infusion. *Can J Anaesth* 1997; 44:26-30
- Green SM: Propofol for emergency department procedural sedation: Not yet ready for prime time. *Acad Emerg Med* 1999; 6:975-8
- Sato J, Saito S, Jonokoshi H, Nishikawa K, Goto F: Correlation and linear regression between blood pressure decreases after a test dose injection of propofol and that following anaesthesia induction. *Anaesth Intensive Care* 2003; 31:523-8
- Ulmer BJ, Hansen JJ, Overley CA, Symms MR, Chadalawada V, Liangpunsakul S, Strahl E, Mendel AM, Rex DK: Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol* 2003; 1:425-32
- Robinson BJ, Ebert TJ, O'Brien TJ, Colinco MD, Muzi M: Mechanisms whereby propofol mediates peripheral vasodilation in humans. *ANESTHESIOLOGY* 1997; 86:64-72