Effects of Dexmedetomidine and Propofol on Lower Esophageal Sphincter and Gastroesophageal Pressure Gradient in Healthy Volunteers

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ABSTRACT

Background: Many anesthetics reduce lower esophageal sphincter pressure (LESP). Reduced pressure and consequent reduction in the gastroesophageal pressure gradient (GEPG) thus promotes gastroesophageal reflux and may contribute to aspiration pneumonia and associated morbidity. Therefore, the authors compared LESP and GEPG during dexmedetomidine and propofol sedation.

Methods: Using a randomized, double-blind, crossover design, 11 healthy volunteers were sedated on 2 separate days. Baseline LESP and GEPG were recorded each day. Subsequently, on each day volunteers received three 40-min-long sedative infusions of increasing doses of 0.6, 1.2, and 2.4 ng/ml dexmedetomidine or 1, 2, and 4 μg/ml propofol. LESP and GEPG were recorded during inhalation and expiration at 20 and 40 min after starting each infusion phase, and these measurements were averaged. Results are presented as mean (95% confidence interval).

Results: Two subjects did not return for the dexmedetomidine study day, and the dexmedetomidine results were unusable in another; propofol results in these volunteers were nonetheless retained for analysis. There were no significant differences in LESP and GEPG as a function of drug. However, there was a small but significant 7.4 (−1.6 to −13.2) mmHg (approximately 25%) dose-dependent decrease in LESP over the range of targeted low to high blood levels of each drug.

Conclusions: Both dexmedetomidine and propofol have similar effects on LESP and GEPG. Although both of the drugs cause some decrease in LESP at high concentrations, it is unlikely that this effect would promote gastroesophageal reflux during sedation.

What We Already Know about This Topic

- ❖ Reduced lower esophageal sphincter pressure may increase the risk of aspiration.
- ❖ Bolus propofol decreases this sphincter pressure, but dexmedetomidine has not been studied.

What This Article Tells Us That Is New

- ❖ Infusion of propofol or dexmedetomidine in healthy volunteers produced similar rate-dependent sedation and reduced sphincter pressure by only a small amount.
- ❖ In healthy individuals, sedative infusions of these drugs do not reduce sphincter pressure by a clinically important amount.

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THE lower esophageal sphincter (LES) forms the border between the stomach and the esophagus and helps to prevent gastric contents regurgitating into the pharynx.[1] Sphincter function is regulated by various neurotransmitters, hormones, and peptides that are extrinsic or intrinsic to the intestinal system. Many intravenous[2] and volatile[3] anesthetics reduce LES pressure (LESP). Reduced LESP and consequent reduction in the gastroesophageal pressure gradient (GEPG) is thus the major physiologic cause of gastroesophageal reflux during anesthesia.[4,5] Reflux is a justifiably feared complication because it can result in aspiration pneumonia and associated morbidity.

Propofol is among the most commonly used sedative agents and is increasingly used by nonanesthesiologists.[6] It decreases smooth muscle contractility[7] and affects Ca^{2+}-sensitive K^+ channels and L-type Ca^{2+} channels in gastrointestinal smooth muscle, which can contribute to the LES relax-

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ation.[8] Nitric oxide and nitric oxide donors have been shown to induce relaxation of smooth muscle of the LES. Propofol induces nitric oxide production through the activation of nitric oxide synthase[9] and may thus reduce esophageal sphincter tone and barrier pressure, thereby increasing the risk of aspiration. However, the dose-dependent effects of propofol on LESP remain unclear, especially in the context of a continuous infusion as might be used during sedation.[10,11]

Lower esophageal sphincter tone is regulated by both sympathetic and parasympathetic nerves. Presynaptic α_2 adrenoceptors are present on cholinergic neurons in various gastrointestinal and other tissues.[12,13] Endogenous noradrenalin generally inhibits gastrointestinal tract muscles by reducing acetylcholine release from cholinergic motor neurons *via* presynaptic α_2 adrenoceptors.[12,13] And as with propofol, dexmedetomidine is a potent activator of nitric oxide synthase and increases endogenous nitric oxide, which in turn may decrease LESP.[14-16] Finally, dexmedetomidine administration exacerbates vagal effects,[17] which relax the LES.[18] Therefore, although the effects of dexmedetomidine on LES function remain unknown, there are compelling reasons to expect the drug to reduce tone and increase the risk of aspiration.

We therefore determined the dose-dependent effects of propofol and dexmedetomidine on LESP and GEPG. Specifically, we tested the hypothesis that dexmedetomidine reduces LESP and GEPG less than propofol does.

Materials and Methods

With approval from the Human Studies Committee of University of Louisville (Louisville, Kentucky), healthy volunteers were recruited by advertisements in the local newspapers, flyers posted at the local universities, and other measures. Eleven healthy volunteers aged 18–40 yr were enrolled in the study. Each provided written informed consent and had a detailed prestudy medical history assessment and physical examination. Exclusion criteria included obesity with body mass index more than 30 kg/m^{2}, pregnancy, drug or alcohol abuse, heartburn more than once per week, history of gastroesophageal reflux disease, or history of any esophagus or stomach surgery.

None of the volunteers took medications likely to alter gastroesophageal sphincter pressure. Prohibited drugs included anticholinergics (including atropine, glycopyrrolate), dopamine and derivatives, sodium nitroprusside, ganglionic blockers, antihistamines, corticosteroids, topical nicotine, tricyclic antidepressants, β-adrenergic stimulants, opiates, and oral contraceptives.

Protocol

We used a randomized, crossover design. Upon arrival on the first study day, volunteers were randomly allocated to propofol or dexmedetomidine sedation according to a computer-generated randomization. Treatment allocations were maintained in sequentially numbered opaque envelopes. Each volunteer participated on two separate study days, separated by at least 7 days. Study drugs were prepared by an independent investigator, and subjects were blinded to assignments. Oxygen, 2 l/min, was given through a nasal catheter. An 18-gauge catheter was inserted into a forearm vein for fluid maintenance and drug administration. Lactated Ringer's solution was infused at a rate of 1.5 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}.

Propofol and dexmedetomidine were given *via* target-controlled infusion using a Harvard infusion pump (Harvard Clinical Technology, Inc., South Natick, MA) driven by STANPUMP software‡‡ using the Schnider model.[19] Propofol was given in increasing steps to target effect-site concentrations of 1, 2, and 4 μg/ml ("low," "medium," and "high" propofol doses); dexmedetomidine was given to target plasma concentrations of 0.6, 1.2, and 2.4 ng/ml ("low," "medium," and "high" dexmedetomidine doses). Each concentration was maintained for 40 min and then, immediately after point assessment, increased to the next higher concentration.

Measurements

Monitoring included electrocardiogram, noninvasive systolic and diastolic arterial pressure, heart rate, pulse oxygen saturation, end-tidal carbon dioxide, and Bispectral Index (BIS) (BIS® XP 3.4 monitor; Aspect Medical Systems, Newton, MA). Sedation level was evaluated every 5 min with the Observer's Assessment of Alertness/Sedation Scale.[20] Defined adverse effects were noted, including nausea, vomiting, headache, desaturation, hypoventilation, bronchospasm, hypotension, hypertension, bradycardia, tachycardia, and arrhythmias.

An esophageal manometry probe was passed transnasally, without local or topical anesthesia, until all four pressure sensors (5-cm spacing) were in the stomach as confirmed by simultaneous increases in all four pressures during inspiration. The LES was identified using the station pull-through technique at 1-cm intervals as described by Mittal *et al.*[21] The LES end-expiratory pressure and the superior margin of LES, where the LES pressure decreased to esophageal baseline pressure, were determined by the mean of the measurements from each of the four pressure-channels.

The catheter was perfused with water at the rate of 0.5 ml/min per channel using a low compliance system (Arndorfer Medical Specialties, Greensdale, WI) and connected to pressure transducers (Statham Lab Inc., Hato Rey, Puerto Rico). Transducers convert the pressure measurements into computer tracing using the Medtronic Polygram software (Medtronic Inc., Minneapolis, MN), and the transducers were set to zero at the midchest position and calibrated before each measurement. The pressure tracings were recorded continuously using a multichannel recording system. This technique is well established and is used clinically to evaluate lower esophageal problems.[21]

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‡‡ STANPUMP program. Available at: http://www.opentci.org. Accessed January 10, 2009.

Distal esophageal peristaltic pressure was defined by the mean peristaltic pressure 3 and 8 cm above the LES with at least 10 wet swallows at the first baseline measurement. Infusion of the designated sedative (propofol or dexmedetomidine) was begun after recording baseline gastric, LES, and distal esophageal peristaltic pressures. Pressures were again recorded after 20 and 40 min of sedative infusion at each concentration. Esophageal and gastric pressures were evaluated by an investigator blinded to drug and dose allocations.

Statistical Analysis

For each of the primary outcomes (LESP and GEPG), a linear mixed model (adjusting for correlation between multiple measurements observed within a volunteer) was fitted with fixed effects for the baseline value of the outcome variable (LESP and GEPG), drug, and dose (dose was analyzed as baseline, low, medium, and high across the two drugs).

The association between drug and the two respective outcomes and the association between dose level and the two respective outcomes were evaluated by F tests. The Tukey–Kramer method was used to adjust confidence limits and P values to maintain an outcome-specific type 1 error rate of 0.05.

To assess whether or not the association between drug and each outcome was dependent on dose level, we tested the interaction between drug and dose level within the multivariable models (F test, using a significance criterion of 0.10). Covariables systolic and diastolic arterial pressure, heart rate, pulse oxygen saturation, and end-tidal carbon dioxide were modeled in a similar manner to the primary outcomes LESP and GEPG.

Results are presented as mean ± SD or mean (95% confidence interval). SAS software version 9.2 (SAS Institute, Cary, NC) and R software version 2.8.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analysis.

Results

Eleven volunteers (three women and eight men) participated; they were aged 24 ± 4 yr, had a body weight of 70 ± 12 kg, and were 175 ± 5 cm tall. Two volunteers participated on only 1 of the study days (both propofol), and the results from 1 dexmedetomidine study day proved unusable because of technical difficulties that were not appreciated during data acquisition.

Lower esophageal sphincter pressure was similar with each drug at baseline and each dose. The estimated difference (Tukey–Kramer-adjusted 95% confidence interval) in mean LESP between dexmedetomidine and propofol, regardless of the sedative dose administered, was only −1.4 (−5.1 to +2.3) mmHg. This difference was not statistically significant (Tukey–Kramer-adjusted $P = 0.39$, mixed model F test). The difference between drugs was not significantly related to the dose level, which is to say the interaction between drug and dose was insignificant ($P = 0.63$).
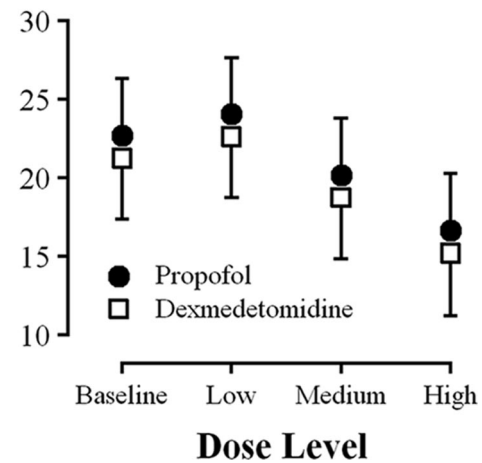

Fig. 1. Lower esophageal sphincter pressure (LESP) at baseline and as a function of dose, adjusting for the intrasubject correlation among repeated measurements using a linear mixed model among 11 healthy volunteers. *Error bars* represent 95% confidence intervals for the mean. Low, Medium, and High correspond, respectively, to doses of 0.6, 1.2, and 2.4 ng/ml for dexmedetomidine and 1, 2, and 4 μg/ml for propofol.

Lower esophageal sphincter pressure was slightly (and not significantly) greater than baseline with low-dose sedation. However, there was then a significant dose-dependent decrease in LESP, with a 23% (propofol) to 31% (dexmedetomidine) reduction over the range from low to high dose. Specifically, LESP was 7.4 (−1.6 to −13.2) mmHg lower with high-dose than low-dose sedation ($P = 0.01$; fig.1).

Gastroesophageal pressure gradient was comparable at baseline with each drug, and there was no apparent effect of increasing drug dose. The two drugs under study did not
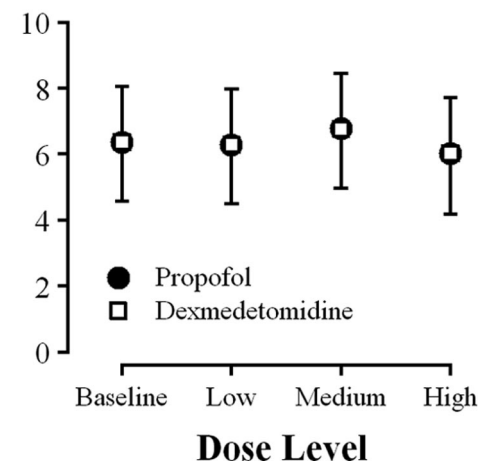

Fig. 2. Gastroesophageal pressure gradient (GEPG) at baseline and as a function of dose, adjusting for the intrasubject correlation among repeated measurements using a linear mixed model among 11 healthy volunteers. *Error bars* represent 95% confidence intervals for the mean. Low, Medium, and High correspond, respectively, to doses of 0.6, 1.2, and 2.4 ng/ml for dexmedetomidine and 1, 2, and 4 μg/ml for propofol.

Table 1. Differences in LESP and GEPG as a Function of Drug and Dose

| | Difference (adjusted 95% CI) in Means* | | P Value* | |
	LESP	GEPG	LESP	GEPG
Drug (dexmedetomidine − propofol)	−1.4 (−5.1 to +2.3)	−0.0 (−1.5 to +1.4)	0.39	0.99
Dose level				
Low − baseline	+1.4 (−4.3 to +7.1)	−0.1 (−2.3 to +2.1)	0.92	0.99
Medium − baseline	−2.5 (−8.2 to +3.2)	+0.4 (−1.8 to +2.6)	0.63	0.96
High − baseline	−6.1 (−11.9 to −0.3)†	−0.3 (−2.6 to +1.9)	0.04†	0.97
Medium − low	−3.9 (−9.6 to +1.8)	+0.5 (−1.7 to +2.7)	0.27	0.93
High − low	−7.4 (−13.2 to −1.6)†	−0.3 (−2.5 to +2.0)	0.01†	0.99
High − medium	−3.5 (−9.3 to +2.3)	−0.7 (−3.0 to +1.5)	0.36	0.80

* Confidence intervals (CIs) and *P* values were adjusted using the Tukey–Kramer method for repeated measurements to maintain an overall type 1 error rate of 0.05 for the study. † Statistically significant Tukey–Kramer-adjusted *P* value.
GEPG = gastroesophageal pressure gradient; LESP = lower esophageal pressure.

significantly differ on mean GEPG (*P* = 0.99); the difference in mean GEPG (Tukey–Kramer-adjusted 95% confidence interval) between dexmedetomidine and propofol was −0.0 (−1.5 to +1.4) mmHg. This estimated difference was not significantly related to the dose level (*P* = 0.67), and furthermore (regardless of drug administered), dose level was not independently associated with GEPG (*P* = 0.83; fig. 2 and table 1).

Mean arterial pressure, heart rate, pulse oxygen saturation, BIS, and end-tidal carbon dioxide values at baseline and at each drug concentration are presented in figure 3. Propofol and dexmedetomidine significantly differed for mean arterial pressure and heart rate (*P* = 0.001 for each; fig. 3).

Discussion

Baseline LESP and the GEPG were within the normal range,[10] suggesting that our manometry system worked properly and that the volunteers were in fact healthy. At each of the three doses tested, the effects on LESP were virtually identical for propofol and dexmedetomidine. Specifically, we found that the drugs under study did not differ in mean LESP by an amount any greater than 5.1 mmHg (with 95% confidence) and likewise, the difference in mean GEPG was not more than 1.5 mmHg, regardless of the dose administered. Clinical decisions about which to choose for sedation should therefore be based on characteristics other than their effects on LESP.

Propofol and dexmedetomidine each produced a comparable linear reduction in LESP. However, the effect was small, being only approximately 7 mmHg over the entire dose range. Although there is a reported correlation between LESP and reflux,[4,5] there is not currently a distinct LESP below which the risk of reflux increases substantially.[1,3] It nonetheless seems unlikely that a reduction of only approximately 25% will prove clinically important.

Our conclusion that neither drug much increases aspiration risk is supported by the further observation that neither propofol nor dexmedetomidine had any significant effect on GEPG—which may be the more important protection against reflux—even at the highest tested drug doses. Our results are generally consistent with two previous volunteer

studies in which bolus doses of 0.3, 0.9, and 1 mg/kg propofol had little effect on LESP and barrier pressure.[10,11] Therefore, clinicians might better focus on other side effects of propofol and dexmedetomidine, such as respiratory depression and bradycardia.

There is also little reason to believe that other available sedatives produce much less reduction in LESP. The effects of benzodiazepines on LESP are controversial; studies with midazolam show some decrease or no change.[22,23] Similarly,
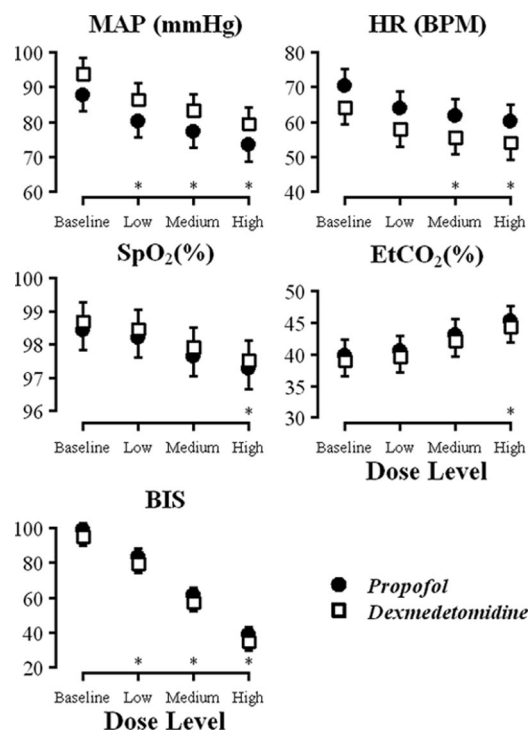
Fig. 3. Average mean arterial pressure (MAP), heart rate (HR; beats/min [BPM]), pulse oximetry (SpO₂), end-tidal carbon dioxide concentration (ETCO₂), and Bispectral Index (BIS) over four dose levels of propofol and dexmedetomidine. Means are estimated using a linear mixed model (which adjusts for any correlation present among repeated measures within a volunteer) incorporating fixed effects for drug and dose; *error bars* represent 2 SEMs. Propofol and dexmedetomidine significantly differed for MAP (*P* = 0.001) and HR (*P* = 0.001). * Significant dose differences from baseline.

Hall *et al.* [24] showed that diazepam reduced the amplitude of the LESP. In contrast, Weihrauch *et al.*[25] demonstrated no significant change in LESP after administration of 5 and 10 mg diazepam and an unexpected transient increase in LESP after 20 mg diazepam. Controversy continues with the opioids; *e.g.*, morphine[18] and meperidine[24,26] have been reported to decrease LESP, but there is also reportedly a slight increase in LESP with morphine[27] and no effect with remifentanil.[10]

Dexmedetomidine and propofol are both widely used, usually for similar indications, but each drug has unique properties. For example, dexmedetomidine is an effective sedative but leaves patients easily aroused. In contrast, propofol is short acting and easy to titrate. Low-dose propofol only minimally depresses tidal volume and minute ventilation,[28] although higher doses can depress the hypoxic ventilatory response and cause apnea.[29] Dexmedetomidine, in contrast, provides better respiratory stability and does not cause ventilatory depression even in high doses.[30] Nonetheless, we were unable to identify significant differences between the drugs in ventilation or pulse oxygen saturation values at any of the doses we tested.

Both propofol and dexmedetomidine reduced mean arterial pressure, but the reduction was significantly greater during propofol. The hypotensive effects of propofol are well known; dexmedetomidine can also cause hypotension, but there is a biphasic dose response with an initial hypotension replaced with hypertension at higher doses.[31] Our results are consistent with previous reports showing that dexmedetomidine reduces heart rate more than propofol.[30] However, none of the hemodynamic responses to either drug at any dose required intervention, suggesting that the effects are of little consequence in otherwise healthy subjects.

Unlike volatile anesthetics, which can be directly compared on the basis of minimum alveolar concentration (MAC) fractions, there is no certain way to determine comparability of sedatives. Therefore, we chose our "low," "medium," and "high" target plasma concentrations based on clinical experience with the goal of spanning the range from moderate sedation to nearly a full general anesthetic. For example, MAC_{awake} for propofol is approximately 2 $\mu g/ml$[32] which was our medium dose. Dexmedetomidine administered at a plasma concentration of 1.25 ng/ml, which was our medium dose, caused moderate sedation, and higher dose was associated with deep sedation and even unresponsiveness.[31]

The BIS is probably the best single measure of hypnotic effect and has been used with propofol[33,34] and dexmedetomidine[35] sedation. The BIS values were virtually identical with each drug, suggesting that the doses we used in fact produced comparable degrees of sedation. Furthermore, BIS values decreased linearly from approximately 100 before drug administration to approximately 40 at the highest concentration. A BIS of 40 is a level associated with general anesthesia and supports our contention that the range of plasma concentrations we tested is clinically relevant. A corollary is that few

patients will actually experience the amount of LESP depression we observed at the highest drug concentrations.

A limitation of our study is that it was conducted in healthy volunteers under controlled conditions; results may well differ in patients with various diseases or taking various drugs or various surgical stimuli—especially those affecting esophageal function. Similarly, responses may differ with longer-term use in critical care setting. We did not confirm plasma concentrations, instead depending on target concentrations. However, the pharmacokinetic models we used are well established and remarkably accurate and precise.

In summary, the effects of three different doses of dexmedetomidine and propofol on LESP and GEPG were similar. Increased sedation, independent of the drug used, decreased LESP. However, even at high concentrations, the reductions produced by propofol or dexmedetomidine were small and therefore unlikely to provoke gastroesophageal reflux during sedation in healthy volunteers with no gastrointestinal system problems.

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