Effects of Morphine and Midazolam on Pharyngeal Function, Airway Protection, and Coordination of Breathing and Swallowing in Healthy Adults

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ABSTRACT

Background: Drugs used for sedation in anesthesia and intensive care may cause pharyngeal dysfunction and increased risk for aspiration. In this study, the authors investigate the impact of sedative doses of morphine and midazolam on pharyngeal function during swallowing and coordination of breathing and swallowing.

Methods: Pharyngeal function, coordination of breathing and swallowing, and level of sedation were assessed by manometry, videoradiography, measurements of respiratory airflow, and a visual analog scale in 32 healthy volunteers (age 19 to 35 yr). After baseline recordings, morphine (0.1 mg/kg) or midazolam (0.05 mg/kg) was administered intravenously for 20 min, followed by recordings at 10 and 30 min after the end of infusion.

Results: Pharyngeal dysfunction, seen as misdirected or incomplete swallowing or penetration of bolus to the airway, increased after morphine infusion to 42 and 44% of swallows compared with 17% in baseline recordings. Midazolam markedly increased incidence of pharyngeal dysfunction from 16 to 48% and 59%. Morphine prolonged apnea before swallowing, and midazolam increased the number of swallows followed by inspiration.

Conclusion: Morphine and midazolam in dosages that produce sedation are associated with increased incidence of pharyngeal dysfunction and discoordinated breathing and swallowing, a combination impairing airway protection and potentially increasing the risk for pulmonary aspirations. **(Anesthesiology 2015; 122:1253-67)**

THE interplay between the pharynx and breathing is essential for protecting the airway against aspiration and to ensure safe passage of saliva, solids, and liquids from the oral cavity through the pharynx and further into the esophagus. Because the oropharynx and hypopharynx is a shared passage for swallowed oral content and inhaled/exhaled air, breathing and swallowing are carefully coordinated, and swallowing is normally initiated during expiration, interrupting the expiratory airflow with a period of apnea extending briefly before and after swallowing.[1–3] Consequently, impaired pharyngeal function and disrupted integration of breathing and swallowing increase the risk for aspiration.[4–8]

Previous studies have shown that subanesthetic levels of drugs commonly used in anesthesia (propofol, isoflurane, sevoflurane,[9] and neuromuscular-blocking agents [NMBA])[10,11] cause pharyngeal dysfunction in healthy volunteers. Moreover, nitrous oxide depresses the swallowing reflex, increasing latency to initiate swallowing and decreasing spontaneous swallow frequency.[12] In elderly volunteers (>65 yr of age) exposed to subparalyzing dosage of a NMBA, there is a distinct increase in the incidence of pharyngeal dysfunction yet with unchanged integration of breathing and swallowing.[13]

What We Already Know about This Topic

- Coordination between breathing and swallowing is essential for protecting lower airways from aspiration
- Sedation impairs the swallowing function, but the precise mechanisms are not explored

What This Article Tells Us That Is New

- By simultaneous recordings of breathing, videoradiography, and pharyngeal manometry in healthy adult volunteers, this study is the first to elucidate pharyngeal dysfunctions in conjunction with altered coordination between breathing and swallowing as possible mechanisms for pulmonary aspiration during sedation with midazolam or morphine

Morphine and midazolam, two centrally acting intravenous drugs, are less extensively studied. In clinical practice, these drugs are often considered safe to be used in sedative dosages in settings with sometimes lower degree of vital sign monitoring. It has, however, been shown that midazolam depresses the swallowing reflex, increasing the latency time to initiate a swallow even after recovery of

This article is featured in "This Month in Anesthesiology," page 1A. Presented in part at Euroanaesthesia 2012, the annual meeting for the European Society of Anaesthesiology, Paris, France, June 11, 2012.

Submitted for publication December 28, 2013. Accepted for publication January 26, 2015. From the Department of Anesthesia, Surgical Services, and Intensive Care (A.I.H.C., E.S., L.I.E.), Department of Diagnostic Radiology (K.B.), Department of Neuroradiology (H.W.H.), Department of Oto-Rhino-Laryngology (R.K.), Karolinska University Hospital, Stockholm, Sweden; Diagnostic Radiology, Malmö University Hospital, Malmö, Sweden (O.E.); and Department of Physiology and Pharmacology, Section for Anesthesiology and Intensive Care Medicine, Karolinska Institutet, Stockholm, Sweden (A.I.H.C., E.S., K.B., H.W.H., R.K., L.I.E.).

 Anesthesiology 2015; 122:1253-67

consciousness.[14] The aim of this study was to characterize the effects of morphine or midazolam on key mechanisms important for airway protection, that is, pharyngeal function and the integration of breathing and swallowing. We hypothesized that morphine or midazolam in young healthy individuals would (1) increase the incidence of pharyngeal dysfunction compared with baseline measurements, with subsequent misdirected or incomplete swallowing or penetration and aspiration of bolus to the airway and (2) that this would be associated with an altered coordination between breathing and swallowing compared with baseline measurements.

A high-resolution technique with simultaneous recordings of breathing patterns and pharyngeal swallowing has recently been developed, and the key mechanism for airway protection including coordination of breathing and swallowing has been characterized in healthy adults and elderly.[1,2,13,15] By using this technique, in this study, we investigate young healthy volunteers to gain further knowledge about the impact of clinically relevant doses of morphine and midazolam on pharyngeal function and integration between breathing and the pharynx.

Materials and Methods

Ethical Approval and Study Population

The study conforms to the standards of the Declaration of Helsinki and was approved by the Regional Ethics Committee on Human Research at the Karolinska Institutet, Stockholm, Sweden. Thirty-eight healthy adult volunteers were included (female: male, 20:18) after obtaining the written informed consent. Sample sizes were chosen based on previous results.[9] Volunteers were medication-free nonsmokers without any history of dysphagia, gastroesophageal reflux disease, or surgery to the pharynx, esophagus, or larynx. The study was stratified with regard to gender to represent a population clinically relevant to patients of both sexes. Data obtained during baseline recordings have been included in a previous radiological study[1] and a physiological study.[2] Demographic data are presented in table 1.

Respiration

A soft rubber face mask with three perforations for catheters was fixed over the nose and mouth and connected to a breathing circuit (dead space 90 ml) with a fresh gas flow rate of 12 l/min. Oral and nasal airflow was recorded as previously described[15] with an airflow discriminator (bidirectional gas flow meter, ASF1430; Sensirion AG, Switzerland), a mass flow integrator using dual temperature-compensated thermistors with an internal flow integration time of 5 ms (CMOSens®; Sensirion AG) determining beginning and end of inspiratory and expiratory airflow and apnea. Four respiratory-phase patterns have previously been described,[1–3,15] that is, inspiration-expiration-swallow apnea-expiration (E-E), inspiration-swallow apnea-expiration (I-E), inspiration-expiration-swallow apnea-inspiration (E-I), and inspiration-swallow apnea-inspiration (I-I). Respiration (bidirectional oral and nasal gas flow) and swallowing (pharyngeal manometry) were sampled (Polygraph™; SynMed, Sweden) and recorded (Polygram®; SynMed) simultaneously. In addition, a traditional nasal pressure transducer was used for visual comparisons of respiratory phases.

Swallowing and Pharyngeal Function—Videoradiography and Pharyngeal Manometry

A manometry catheter with four pressure transducers 2 cm apart was introduced through one nostril and advanced so that the most distal transducer was placed in the upper esophageal sphincter (UES).[1,2,10,11,15] Catheter placement was repeatedly validated by using fluoroscopy. Tracings of pharyngeal manometry were superimposed on the fluoroscopic image and recorded simultaneously onto a videotape equivalent to 50 half-frames (videoradiography), during swallowing of contrast medium, as previously described.[1] Three contrast medium swallows were used to assess the signs of pharyngeal dysfunction defined as: (A) premature bolus leakage from the mouth to the pharynx, (B) penetration of contrast medium into the laryngeal vestibule or the trachea, and (C) retention of contrast medium in the pharynx after completion of swallowing. In addition, each swallow was analyzed in depth and scored for severity of pharyngeal dysfunction by using three different methods: (1) degree of pharyngeal dysfunction, adding the number of signs (0 to 3) of pharyngeal dysfunction category A to C found in each of the three swallows. The individual sum (0 to 9) was thereafter divided by the maximal outcome (*i.e.*, 9), yielding the term degree of pharyngeal dysfunction (%); (2) risk of aspiration using the penetration–aspiration scale (PAS)[16]; and (3) efficiency of bolus clearance using the

Table 1. Demographics of the 32 Study Subjects and 6 Additional Control Subjects, in Total 38 Volunteers

	Morphine, n = 16	Midazolam, n = 16	Control, n = 6
Age, yr	25 ± 5 (20–35)	24 ± 4 (21–35)	22 ± 3 (19–27)
Weight, kg	70 ± 9 (55–89)	69 ± 13 (47–90)	66 ± 15 (52–95)
Height, cm	176 ± 6 (167–185)	175 ± 12 (157–192)	171 ± 11 (158–187)
BMI	22.6 ± 2.3 (19.4–26.3)	22.7 ± 2.7 (17.7–27.2)	22.3 ± 3.1 (18.9–27.2)
M/F, n	8/8	8/8	2/4

Data presented as mean ± SD and (range). n is the number of volunteers.
BMI = body mass index.

valleculae residue scale (VRS)[16] and the pyriform sinus residue scale (PRS),[16] all three being validated scales. Manometry recordings were made at the tongue base (TB), at two levels of the pharyngeal constrictor muscles (at an upper level [Ph Up] and a lower level [Ph Low]), and in the UES. The beginning and end of pharyngeal swallowing were defined as onset of pressure rise at TB (TB-start) and UES (UES-start), respectively.[1,2,15] All events regarding the timing of swallow apnea and pharyngeal manometry were referenced in time to the beginning of pharyngeal swallowing (TB-start = 0 ms). As previously described and illustrated,[13] maximum contraction pressure (amplitude, mmHg) was analyzed at three levels (TB, Ph Low, and UES). Contraction rate (slope, mmHg/s) and duration of contraction (ms) were analyzed at two levels (TB and Ph Low). Coordination between pharyngeal muscles (coordination) was measured as the time between the start of pressure increase in the lower part of the pharyngeal constrictor (Ph Low) and the start of UES relaxation (UES relaxation-start). In addition, the mean UES pressure was measured (mmHg) as previously described.[2] By using videoradiography, the time point when the head of the bolus passed the anterior faucial arches was determined and compared with (1) the start of the hyoid bone forward movement (initiation of the pharyngeal phase of swallowing [ms]) and (2) when the tail of the bolus reached below the UES (bolus transit time [ms]).[11] Moreover, the interval between when the bolus was first seen in the mouth and onset of pharyngeal swallowing was measured (bolus in mouth [s]). Videoradiographic images were interpreted by an experienced radiologist who was unblinded to study condition at the time of analysis. To minimize the radiation dose to subjects, spontaneous swallows of saliva were recorded by pharyngeal manometry without videoradiography. All swallowing maneuvers of contrast medium and three spontaneous saliva swallows (for selection criteria, see Materials and Methods, Statistical Analysis) with the respiratory-phase pattern E-E were analyzed regarding the timing of pharyngeal swallowing events and swallow apnea (all measured in relation to TB-start [ms]), durations of inspirations and expirations before and after swallow apnea (ms), swallow apnea duration (ms), UES maximum contraction pressure (mmHg), and coordination (ms). Preswallow apnea was defined as the time from onset of swallow apnea to onset of pharyngeal swallowing (TB-start) (ms) and postswallow apnea as the time from the end of pharyngeal swallowing (UES-start) to the end of swallow apnea (ms). UES pressures during inspiration and expiration (mmHg) and coordination between UES pressure changes and breathing, that is, timing of UES pressure changes in relation to onsets of inspiration and expiration (ms), were measured as previously described.[2]

Study Protocol

Volunteers were allowed solid food until 6 h and liquids until 2 h before entering the study. An intravenous cannula was placed in respectively left and right arm, one being used for drug administration and one for venous blood sampling. Volunteers were examined in the left lateral position with an 8° head-up tilt. Volunteers were randomized (lottery) to receive either morphine 0.1 mg/kg or midazolam 0.05 mg/kg dissolved in 20 ml of normal saline and administered as an intravenous infusion during 20 min using a motor syringe (Terumo, Japan) or to be included in the control group receiving no drug. Recordings were made at three occasions, that is, baseline recordings before drug administration, 10 min after drug infusion was stopped (Morphine, Mo_{10min}, Midazolam, Mi_{10min}), and finally, 30 min after end of drug delivery (Mo_{30min}, Mi_{30min}) (fig. 1). At each of these three occasions, breathing and spontaneous swallows of saliva were recorded during a 10-min period while volunteers were resting. This was followed by recordings of three bolus swallows of 10 ml water-soluble contrast medium (Omnipaque 240 mg/ml; Nycomed Imaging, Norway) administered through a syringe. Respiratory rate (breaths/min) and spontaneous swallowing frequency (swallows per minute) were calculated from recordings at rest (using the bidirectional gas flow meter and pharyngela manomtery). Vital parameters (heart rate, noninvasive blood pressure, end-tidal carbon dioxide, and peripheral oxygen saturation) were monitored continuously (Datex-Ohmeda Cardiocap®/5; GE Health Care, United Kingdom). The volunteers estimated their level of sedation on a visual analog scale (VAS-sedation, 0 equaling maximal sedation, that is, just falling asleep, and 10 equaling no sedation). Coughing associated with swallowing of contrast medium was noted.

Morphine and Midazolam: Dosages and Plasma Concentrations

The total amount of drug administered was morphine 7.1 ± 1.0 mg (5.4 to 9.4) or midazolam 3.4 ± 0.6 mg (2.4 to 4.5). Plasma concentrations of morphine, morphine-3-glucuronide

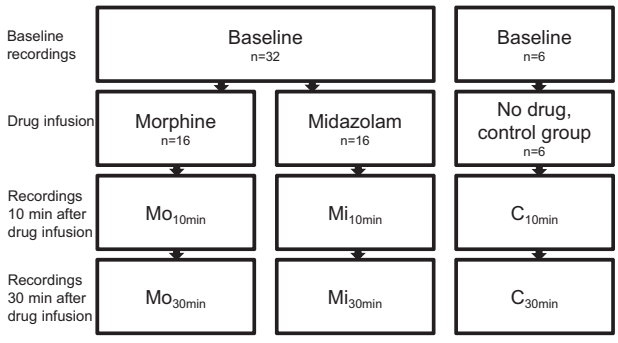

Fig. 1. Schematic presentation of study protocol. Recordings at baseline and after infusion of either morphine (0.1 mg/kg) or midazolam (0.05 mg/kg) or no drug, that is, control group. After infusion was stopped, recordings were repeated at two occasions, after 10 and 30 min, respectively (n is the number of volunteers). Baseline = baseline recordings; C = control group; Mi = midazolam; Mo = morphine; Mo_{10min}/Mi_{10min}/C_{10min}, Mo_{30min}/Mi_{30min}/C_{30min} = recordings 10 and 30 min after infusion of morphine/midazolam/no drug for control group was stopped.

and morphine-6-glucuronide, or midazolam and 1-OH-midazolam were determined at three occasions, that is, (1) immediately after the end of drug delivery (Mo_{0min}, Mi_{0min}), (2) during recordings 10 min later (Mo_{10min}, Mi_{10min}), and (3) during recordings after 30 min (Mo_{30min}, Mi_{30min}) (table 2).

Control Group

In the control group (n = 6), stability of recordings was assessed to rule out an effect of elapsed time on: pharyngeal dysfunction, respiratory-phase patterns, duration of preswallow and postswallow apnea and pharyngeal swallowing, respiratory rate, swallow frequency, UES resting tension, coordination between UES pressure changes and breathing, manometric measurements of pharyngeal contraction forces, VAS-sedation, and vital parameters. After baseline recordings, measurements were repeated two times (control, C_{10min} and C_{30min}) corresponding in time to Mo_{10min}/Mi_{10min} and Mo_{30min}/Mi_{30min} (fig. 1). For all of the above parameters, except VAS-sedation, no significant changes could be detected, confirming the stability of the model over time. Interestingly, VAS-sedation scoring (10 to 0) decreased, that is, volunteers scored themselves more sedated at C_{10min} compared with baseline (baseline, 9.3 [7.5 to 9.7]; C_{10min}, 6.2 [4.1 to 9.5]; $P = 0.043$ and C_{30min}, 8.3 [5.3 to 9.6]; $P = 0.07$).

Statistical Analysis

Degree of pharyngeal dysfunction and respiratory-phase patterns were the primary outcomes of this study. As previously described,[13] a mean value based on two or three measurements from three separate swallows or breaths was calculated for each volunteer and at each of the three study conditions (baseline, $Mo_{10min}/Mi_{10min}/C_{10min}$, and $Mo_{30min}/Mi_{30min}/C_{30min}$). For in-depth analysis of coordination of breathing and swallowing, swallows with the respiratory-phase pattern E-E were chosen because the number of recorded non-E-E swallows was too small to allow statistical analysis. When studying spontaneous swallows or breaths at rest, measurements were made in the E-E swallow occurring closest to the start, mid, and end of the recording period to avoid selection bias. For all statistical analyses, Statistica™ 10 (Statsoft® Inc., USA) and ANOVA repeated measures, followed by planned comparisons comparing measurements at $Mo_{10min}/Mi_{10min}/C_{10min}$ or $Mo_{30min}/Mi_{30min}/C_{30min}$ to baseline, were used unless otherwise stated. Results are presented as mean ± SD or the 95% CI. For degree of pharyngeal dysfunction (0 to 100%), PAS, VRS, PRS, and VAS-sedation (10 to 0) planned comparisons were made by using Wilcoxon matched-pairs test. Percentage of swallows with pharyngeal dysfunction was analyzed using ANOVA repeated measures after rank transformation. Here, the results are presented as median values and range. Respiratory-phase patterns were analyzed as previously described.[13] The correlation between degree of pharyngeal dysfunction and VAS-sedation was analyzed by the Spearman rank correlation coefficient. Exact unadjusted P values are reported. Family-wise Bonferroni corrections for multiple comparisons were made. P values less than 0.05 were considered significant (after correction $P < 0.025$).

Results

Morphine

Swallowing and Pharyngeal Dysfunction. A total of 576 swallowing maneuvers were analyzed, that is, 144 swallows of contrast medium and 432 spontaneous swallows of saliva.

Pharyngeal dysfunction was analyzed by using videoradiography in swallows of contrast medium. At baseline, 17% of swallows showed at least one of the criteria for pharyngeal dysfunction. This increased significantly following morphine

Table 2. Plasma Concentrations of Drugs and Metabolites and VAS-sedation

Morphine	**n**	**Mo_{0min}**	**Mo_{10min}**	**Mo_{30min}**
Morphine (ng/ml)	16	50 ± 18	18 ± 4	12 ± 3
Morphine-3-glucuronide (ng/ml)	16	9 ± 11	17 ± 17	23 ± 18
Morphine-6-glucuronide (ng/ml)	16	59 ± 29	93 ± 34	102 ± 30
	n	Baseline	Mo_{10min}	Mo_{30min}
VAS-sedation (10-0)	16	9.8 (7.0–10.0)	5.3* (0.2–8.8)	6.0* (0.9–9.9)
Midazolam	**n**	**Mi_{0min}**	**Mi_{10min}**	**Mi_{30min}**
Midazolam (ng/ml)	15	68 ± 37	44 ± 22	31 ± 11
1-OH-midazolam (ng/ml)	15	4 ± 2	5 ± 2	5 ± 1
	n	Baseline	Mi_{10min}	Mi_{30min}
VAS-sedation (10-0)	16	9.9 (7.0–10.0)	6.0* (0.4–9.8)	9.3* (4.2–10.0)

Plasma was sampled three times, directly after the end of drug infusion and during recordings at 10 and 30 min after infusion of morphine or midazolam was stopped. VAS-sedation, volunteers estimated the level of sedation three times on a VAS, where 0 equaled maximal sedation, that is, just falling asleep, and 10 equaled no sedation, at baseline before drug infusion, indicated "Baseline" and two times after drug exposure. Plasma concentration data presented as mean ± SD. VAS data presented as median and range.

* $P < 0.05$ *vs.* baseline.

Mi = midazolam; Mo = morphine; Mo_{0min}/Mi_{0min} = recordings directly after the end of drug infusion; Mo_{10min}/Mi_{10min}, Mo_{30min}/Mi_{30min} = recordings at 10 and 30 min after infusion of morphine/midazolam was stopped; n = number of volunteers; OH = hydroxyl; VAS = visual analog scale.

infusion to 42 and 44% at Mo_{10min} and Mo_{30min}, respectively (table 3). Moreover, the number of swallows showing more than one sign of dysfunction increased at Mo_{10min} and Mo_{30min}, and in-depth analysis of degree of pharyngeal dysfunction (fig. 2) showed an increase from a median value of 0% (0 to 33%) at baseline to 6% (0 to 44%, $P = 0.012$) and 11% (0 to 67%, $P = 0.018$) at Mo_{10min} and Mo_{30min}, respectively (fig. 2A). Analysis of airway protection revealed that penetration of contrast medium occurred to the vocal cords or to a level immediately above the vocal cords (laryngeal penetration) (table 3), whereas contrast medium was never detected below the vocal cords (aspiration). There were too few occasions of laryngeal bolus penetration or retention of bolus after swallows to allow statistical evaluation of the risk of aspiration using PAS and efficiency of bolus clearance using VRS or PRS (table 3).

Sedation Scoring and Morphine Effects. Visual analog scale-sedation scoring decreased from 9.8 (7.0 to 10.0) at baseline recordings to 5.3 (0.2 to 8.8) and 6.0 (0.9 to 9.9) at Mo_{10min} ($P < 0.001$) and Mo_{30min} ($P < 0.001$), respectively. The VAS-sedation score correlated to the measured plasma concentrations of the drug ($r = 0.70$, $P < 0.001$). However, we were unable to detect a correlation between degree of pharyngeal dysfunction and VAS-sedation ($r = -0.02$, $P = 0.88$). All volunteers completed the study at all three study occasions. None reported distress or discomfort. Two volunteers reported dizziness and nausea after the study was completed. This was relieved by administering naloxone subcutaneously.

Coordination of Breathing and Swallowing. At baseline, a majority of swallows (97.4%) occurred during expiration with expiratory airflow present both before and after swallow apnea (E-E) (fig. 3). After morphine infusion, the frequency of the E-I pattern, where swallowing is followed by and inspiration, showed an increase (fig. 3C) from 2.6% of all swallows at baseline to 8.7% at Mo_{10min} ($P = 0.042$) (fig. 2B). However, in the investigated material, this did not reach statistical significance, and at Mo_{30min}, there was no difference in respiratory-phase patterns compared with baseline (E-I 3.4%, $P = 0.75$) (fig. 2B). The respiratory-phase pattern E-I was present in 3.0, 13.4, and 3.4% of spontaneous swallows of saliva and in 0, 2.1, and 2.1% in swallows of contrast medium at baseline, Mo_{10min}, and Mo_{30min}, respectively. No swallows occurred during or directly after the inspiratory phase (I-I or I-E). The number of E-I swallows of contrast medium with signs of pharyngeal dysfunction was too low to assess an association between degree of pharyngeal dysfunction and respiratory-phase pattern. Resting respiratory rate was not affected by morphine; however, spontaneous swallow frequency decreased markedly at Mo_{10min} and Mo_{30min} compared with baseline (table 4).

When further analyzing E-E swallows, the duration of preswallow apnea in spontaneous swallows of saliva were longer at Mo_{10min} compared with baseline, but the increase in duration was not significant at Mo_{30min} (baseline, 324 ± 326 ms; Mo_{10min}, 872 ± 693 ms; $P = 0.010$; Mo_{30min}, 666 ± 661 ms; $P = 0.026$) (fig. 3B and 4A). In swallows of contrast medium, duration of preswallow apnea was longer at Mo_{10min} than at baseline (baseline, 984 ± 900 ms; Mo_{10min}, 1,748 ± 1,085 ms; $P = 0.009$) (fig. 4A). However, at Mo_{30min}, duration of preswallow apnea was unchanged compared with baseline (1,284 ± 1,152 ms, $P = 0.44$) (fig. 4A). Morphine had no effect on duration of inspiration before swallowing, expiration before swallowing, pharyngeal swallowing (fig. 4A), postswallow apnea, or expiration after swallowing. In parallel with the morphine-induced increase in duration of preswallow apnea, swallow apnea duration was longer at Mo_{10min} compared with baseline in spontaneous swallows of saliva (baseline, 1,055 ± 337 ms; Mo_{10min}, 1,642 ± 824 ms; $P = 0.020$) and swallows of contrast medium (baseline, 1,745 ± 967 ms; Mo_{10min}, 2,622 ± 1,242 ms; $P = 0.010$). However, at Mo_{30min}, swallow apnea duration was unchanged compared with baseline both in spontaneous swallows of saliva (1,379 ± 757 ms, $P = 0.07$) and swallows of contrast medium (2,139 ± 1,305 ms, $P = 0.41$).

Mechanical Properties and Timing of Pharyngeal Swallowing and Swallow Apnea. In swallowing maneuvers of both contrast medium and saliva with the respiratory-phase

Table 3. Pharyngeal Dysfunction, Penetration–Aspiration, and Bolus Clearance

Morphine		Baseline	Mo_{10min}	*P* Value	Mo_{30min}	*P* Value
Percentage of swallows with pharyngeal dysfunction	%	17	42*	0.024	44*	0.018
Swallows with premature leakage of bolus	n	6	16		15	
Swallows with penetration of bolus to laryngeal inlet	n	3	5		8	
Swallows with retention of bolus after swallow	n	1	1		5	
Total swallowing maneuvers of contrast medium	n	48	48		48	
Midazolam		**Baseline**	**Mi_{10min}**	***P* Value**	**Mi_{30min}**	***P* Value**
Percentage of swallows with pharyngeal dysfunction	%	16	48*	0.012	59*	0.003
Swallows with premature leakage of bolus	n	6	12		13	
Swallows with penetration of bolus to laryngeal inlet	n	0	2		3	
Swallows with retention of bolus after swallow	n	2	14		15	
Total swallowing maneuvers of contrast medium	n	45	42		44	

Measurements at baseline and at 10 and 30 min after infusion of morphine or midazolam.

* $P < 0.05$ (exact *P* value *vs.* baseline).

Baseline = baseline recordings; Mi = midazolam; Mo = morphine; Mo_{10min}/Mi_{10min}, Mo_{30min}/Mi_{30min} = recordings at 10 and 30 min after infusion of morphine/midazolam was stopped; n = number of swallows.

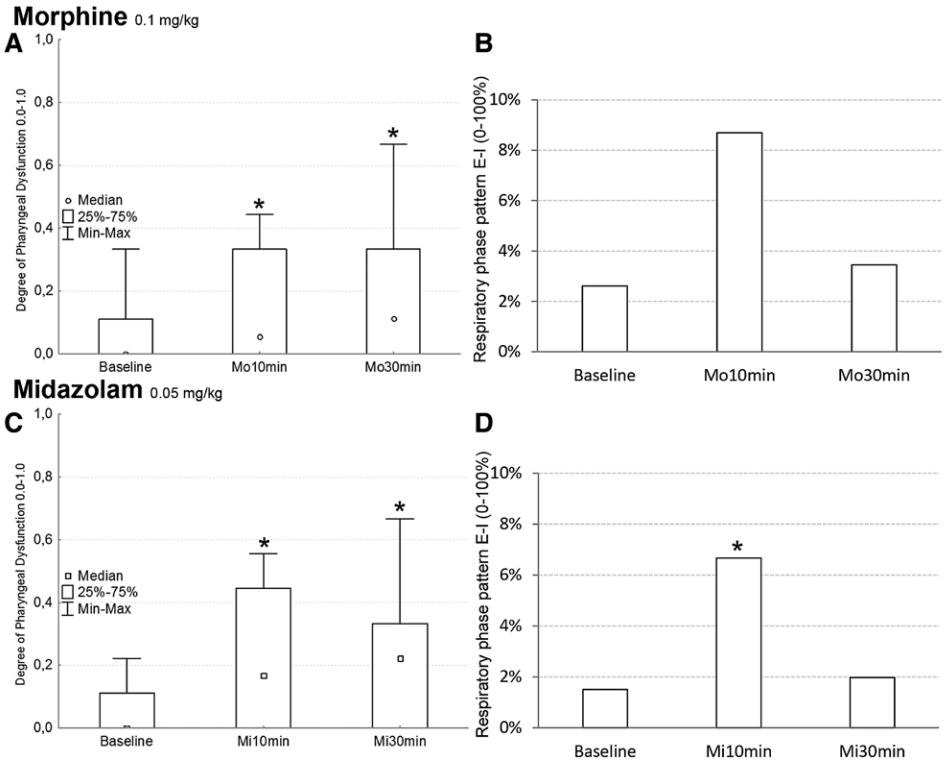

Fig. 2. (*A* and *B*) Morphine, (*C* and *D*) midazolam. (*A* and *C*) Degree of pharyngeal dysfunction at baseline recordings and after infusion of either morphine (0.1 mg/kg) (*A*) or midazolam (0.05 mg/kg) (*C*). After infusion was stopped, recordings were repeated at two occasions, that is, at 10 and 30 min, respectively. Severity of pharyngeal dysfunction increased significantly after subanesthetic doses of morphine or midazolam. *$P < 0.05$ *versus* baseline. (*C* and *D*) Frequency (%) of respiratory-phase pattern E-I, that is, the pattern inspiration-expiration-swallow apnea-inspiration recordings at baseline recordings and after infusion of either morphine (0.1 mg/kg) (*C*) or midazolam (0.05 mg/kg) (*D*). Coordination of breathing and swallowing was disrupted after midazolam (*D*), that is, there was an increased risk that swallowing would be followed by inspiration. *$P < 0.05$ *versus* baseline. Baseline = baseline recordings; C = control group; E-I = the respiratory-phase pattern with inspiration-expiration-swallow apnea-inspiration; Mi = midazolam; Mo = morphine; Mo_{10min}/Mi_{10min}, Mo_{30min}/Mi_{30min} = recordings 10 and 30 min after infusion of morphine/midazolam was stopped.

pattern E-E, we could not detect an effect of morphine on the time course of the pharyngeal muscle contraction wave (fig. 4A). Neither was there any effect of morphine on the end of swallow apnea in relation to pharyngeal swallowing (fig. 4A).

When further analyzing pharyngeal manometric pressures in swallowing maneuvers of contrast medium, morphine had only minor effects (table 5). Moreover, there was no effect of morphine on the coordination between UES relaxation and pharyngeal constrictor muscle activity (table 5).

At Mo_{10min}, initiation of the pharyngeal phase of swallowing was unchanged compared with baseline (table 5). In contrast, at Mo_{30min}, initiation was delayed (table 5). Moreover, bolus transit time was prolonged at Mo_{10min} and Mo_{30min} compared with baseline (table 5).

Cough. Two volunteers coughed when swallowing one of the three boluses of contrast medium at baseline and at Mo_{10min}. One of these coughed again at Mo_{10min}. Also at Mo_{10min} in another volunteer, one of the swallows was followed by coughing. Here, penetration to the larynx occurred; however, the other events of coughing were not associated with the signs of pharyngeal dysfunction. The total number of coughs was too small to allow statistical analysis.

UES. There was no effect of morphine on UES resting tension between swallows, residual relaxation pressure during swallowing, or maximum contraction pressures after swallowing either at Mo_{10min} or Mo_{30min} (table 5). A slower UES relaxation rate was visually noted (fig. 3, B and C); however, this was not further analyzed. Inspiratory UES pressures were significantly higher than expiratory UES pressures at baseline, and this difference remained unchanged at Mo_{10min} and Mo_{30min}.

Morphine affected the coordination between UES pressure changes and breathing, where an increase in UES pressure normally occurs before the start of inspiration, and a decrease in UES pressure is seen after expiration. At Mo_{10min} and Mo_{30min}, UES pressure increased earlier relative onset of inspiration compared with baseline (baseline, 62 ± 67 ms; Mo_{10min}, 115 ± 114 ms; $P = 0.016$; Mo_{30min}, 93 ± 70 ms; $P = 0.009$). Moreover, at Mo_{10min}, UES pressure decreased later relative onset of expiration compared with baseline (baseline, 124 ± 49 ms; Mo_{10min}, 180 ± 68 ms; $P = 0.008$). At

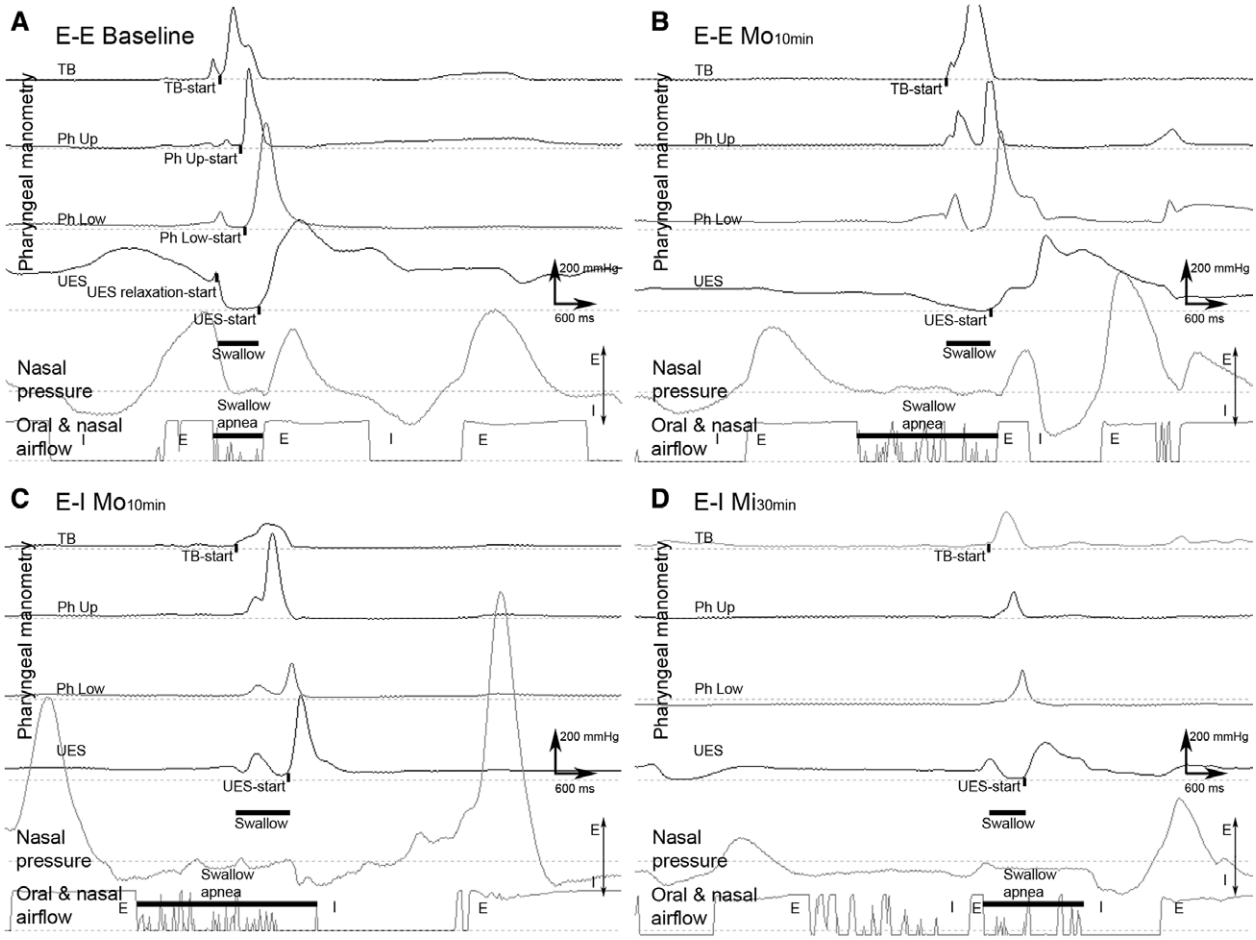

Fig. 3. Original recordings of simultaneous pharyngeal manometry, nasal pressure, and nasal/oral airflow during spontaneous saliva swallows with the respiratory-phase patterns E-E, that is, inspiration-expiration-swallow apnea-expiration at baseline recordings (*A*), E-E at recordings 10 min after infusion of morphine (*B*), E-I, that is, the respiratory-phase pattern inspiration-expiration-swallow apnea-inspiration at recordings 10 min after infusion of morphine (*C*), and E-I at recordings 30 min after infusion of midazolam (*D*). Manometry recordings made at tongue base (TB), upper and lower pharyngeal transducer, and upper esophageal sphincter (UES) levels. "Swallow" indicates duration of pharyngeal swallowing. Apnea during pharyngeal swallowing, indicated "Swallow apnea," was detected as an oscillating signal (zero airflow) from the gas flow discriminator indicated "Oral and nasal airflow." In pharyngeal manometry, the *dotted baseline* represents pressure = 0 mmHg. E-E = the respiratory-phase pattern with inspiration-expiration-swallow apnea-expiration; E-I = the respiratory-phase pattern with inspiration-expiration-swallow apnea-inspiration; Mi = midazolam; Mo = morphine; Mo_{10min}/Mi_{10min}, Mo_{30min}/Mi_{30min} = recordings 10 and 30 min after infusion of morphine/midazolam was stopped; Ph Up and Ph Low = upper and lower pharyngeal transducer level; Ph Up-start and Ph Low-start = onset of pressure rise at the upper and lower pharyngeal transducer level; TB-start = onset of pressure rise at the tongue base; UES-start = onset of pressure rise at the UES; UES relaxation-start = onset of relaxation of the UES.

Table 4. Vital Parameters

Morphine (n = 16)	Baseline	Mo_{10min}	*P* Value	Mo_{30min}	*P* Value
RR (breaths/min)	14.6 ± 2.4	14.2 ± 2.3	0.52	15.2 ± 2.7	0.12
SF (swallows per minute)	1.9 ± 1.2	0.4 ± 0.3*	<0.001	0.4 ± 0.3*	<0.001
End-tidal carbon dioxide (kPa)	5.1 ± 0.5	5.4 ± 0.5*	<0.001	5.3 ± 0.5*	<0.001
Midazolam (n = 16)	**Baseline**	Mi_{10min}	*P* Value	Mi_{30min}	*P* Value
RR (breaths/min)	14.8 ± 2.6	16.0 ± 2.4	0.034	16.8 ± 2.6*	<0.001
SF (swallows per minute)	1.4 ± 1.0	0.6 ± 0.5*	0.023	0.8 ± 0.4	0.042
End-tidal carbon dioxide (kPa)	5.1 ± 0.5	4.8 ± 0.5*	0.004	4.9 ± 0.4*	0.010

Measurements at baseline (Baseline) and at 10 and 30 min after infusion of morphine or midazolam. Data presented as mean ± SD.

* $P < 0.05$ (exact *P* values *vs.* baseline).

Baseline = baseline recordings; Mi = midazolam; Mo = morphine; Mo_{10min}/Mi_{10min}, Mo_{30min}/Mi_{30min} = recordings at 10 and 30 min after infusion of morphine/midazolam was stopped; RR = respiratory rate; SF = spontaneous swallow frequency.

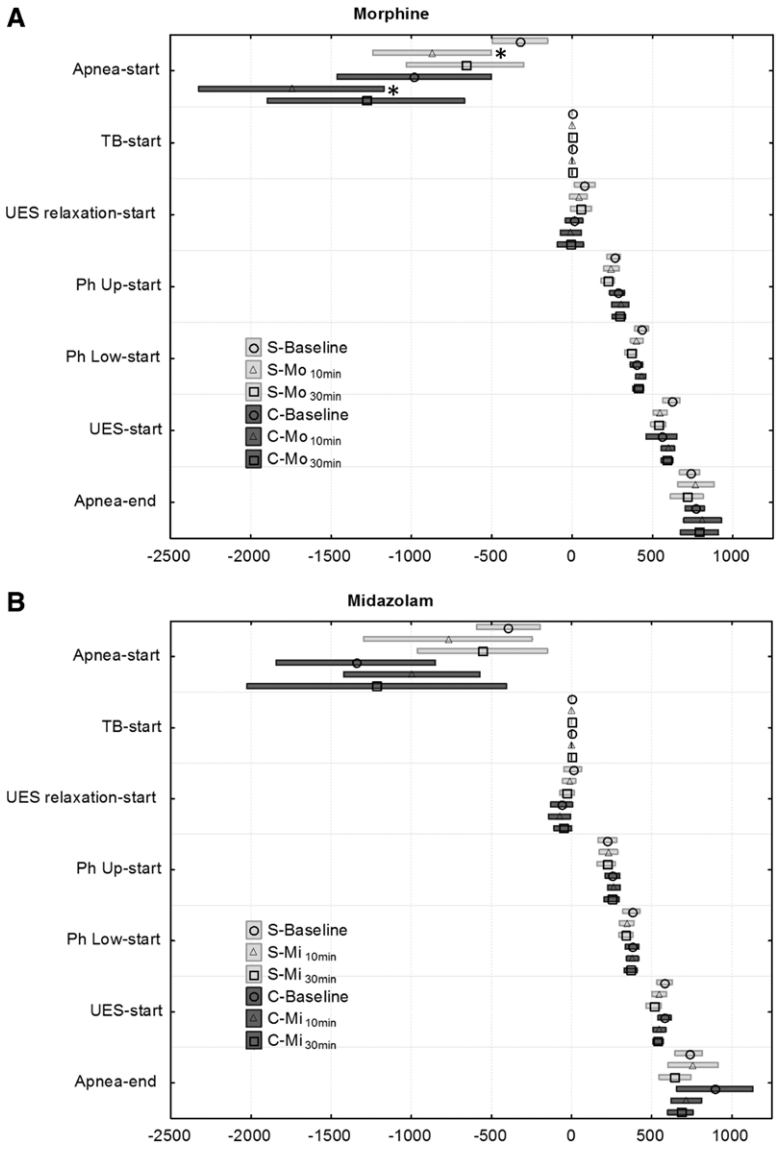

Fig. 4. Pharyngeal swallowing and swallow apnea in spontaneous swallows of saliva and swallowing maneuvers of contrast medium, with the respiratory-phase pattern E-E, at baseline recordings, indicated "baseline" and after infusion of either morphine (0.1 mg/kg) (*A*) or midazolam (0.05 mg/kg) (*B*). After infusion was stopped, recordings were repeated at two occasions, after 10 and 30 min, respectively. The start of pharyngeal swallowing was defined as the onset of pressure rise at the tongue base (TB), and all pharyngeal manometry events as well as start and end of swallow apnea were referenced in time (ms) to this event. Start of swallow apnea is indicated "Apnea-start" and end of swallow apnea as "Apnea-end." Apnea before swallowing was prolonged after morphine (*A*). Mean (ms) ± 95% CI. *$P < 0.05$ *versus* baseline. C = swallowing maneuvers of contrast medium; E-E = the respiratory-phase pattern with inspiration-expiration-swallow apnea-expiration; Mi = midazolam; Mo = morphine; Mo_{10min}/Mi_{10min}, Mo_{30min}/Mi_{30min} = recordings 10 and 30 min after infusion of morphine/midazolam was stopped; Ph Up-start and Ph Low-start = onset of pressure rise at the upper and lower pharyngeal transducer level; S = spontaneous swallows of saliva; TB-start = onset of pressure rise at the tongue base, that is, onset of pharyngeal swallowing (= time 0); UES = the upper esophageal sphincter; UES-start = onset of pressure rise at the UES; UES relaxation-start = onset of relaxation of the UES.

Mo_{30min}, the delay in pressure fall was no longer statistically significant (176 ± 72 ms, $P = 0.049$ compared with baseline).

Midazolam

Swallowing and Pharyngeal Dysfunction. In the midazolam group, 144 swallows of contrast medium and 424 spontaneous swallows of saliva were analyzed. In recordings of contrast medium swallows at baseline, 16% showed pharyngeal dysfunction, increasing markedly to 48 and 59% at Mi_{10min} and Mi_{30min}, respectively (table 3). Moreover, the degree of pharyngeal dysfunction increased from a median of 0% (0 to 22%) at baseline to 17% (0 to 56%, $P = 0.033$) at Mi_{10min}, which did not reach statistical significance, but at Mi_{30min}, there was a statistically significant increase to 22% (0 to 67%, $P = 0.008$) (fig. 2C). Penetration of contrast medium occurred only to the vocal cords

Table 5. Mechanical Properties and Timing of Pharyngeal Swallowing after Morphine

Morphine (n = 16)	Bolus	Baseline	Mo_{10min}	*P* Value	Mo_{30min}	*P* Value
Pharyngeal manometry						
TB max. contr. (mmHg)	C	323 ± 133	266 ± 131	0.09	268 ± 123	0.08
TB contr. rate (mmHg/s)	C	1,548 ± 933	1,094 ± 535	0.025	1,188 ± 759	0.049
TB contr. dur. (ms)	C	778 ± 157	700 ± 137*	0.013	693 ± 121*	0.012
Ph Low max. contr. (mmHg)	C	255 ± 116	267 ± 109	0.51	251 ± 93	0.87
Ph Low contr. rate (mmHg/s)	C	1,121 ± 380	1,118 ± 334	0.97	1,066 ± 332	0.58
Ph Low contr. dur. (ms)	C	554 ± 114	510 ± 110	0.042	514 ± 89	0.10
Coordination (ms)	C	–388 ± 120	–436 ± 127	0.15	–423 ± 122	0.21
Coordination (ms)	S	–354 ± 99	–353 ± 128	0.71	–310 ± 132	0.06
UES max. contr. (mmHg)	C	383 ± 93	369 ± 88	0.51	349 ± 114	0.20
UES max. contr. (mmHg)	S	308 ± 93	298 ± 84	0.40	328 ± 101	0.61
UES relaxation (mmHg)	C	14 ± 10	10 ± 9	0.47	10 ± 6	0.028
UES resting tension (mmHg)	C	83 ± 40	84 ± 30	0.87	74 ± 27	0.30
Videoradiography						
Initiation (ms)	C	138 ± 122	194 ± 148	0.25	226 ± 136*	0.020
Bolus transit time (ms)	C	855 ± 176	1,023 ± 193*	0.006	1,083 ± 243*	<0.001
Bolus in mouth (s)	C	1.3 ± 0.8	1.3 ± 0.6	0.91	1.3 ± 0.5	0.94

Measurements of mechanical properties and timing of pharyngeal swallowing at baseline and at 10 and 30 min after infusion of morphine. Data presented as mean ± SD.

* $P < 0.05$ (exact *P* value *vs.* baseline).

Baseline = baseline recordings; Bolus = bolus type; Bolus in mouth = without initiating pharyngeal swallowing, the interval between the times at which the bolus of contrast medium is first seen in the mouth and onset of pharyngeal swallowing, that is, the start of pressure rise at the level of the base of the tongue "TB-start"; Bolus transit time (pharyngeal) = the interval between the times at which the bolus head passed the anterior faucial arches and the tail of the bolus passed the UES; C = swallowing maneuvers of contrast medium; contr. dur. = contraction duration; contr. Rate = contraction rate; Coordination = measured as the time between the start of pressure rise at the lower part of the pharyngeal constrictor "Ph Low-start" and the start of UES relaxation "UES relaxation-start"; Initiation = of the pharyngeal phase of swallowing, the interval between the times at which the head of the bolus passed the anterior faucial arches and the hyoid bone started to move forward; max. contr. = maximum contraction pressure; Mo = morphine; Mo_{10min} and Mo_{30min} = recordings at 10 and 30 min after infusion of morphine was stopped; Ph Low = lower pharyngeal manometry transducer; S = spontaneous swallows of saliva; TB = tongue base; UES = upper esophageal sphincter; UES relaxation = residual mean UES pressure at relaxation during pharyngeal swallowing; UES resting tension = mean UES pressure during 10 s at resting conditions not swallowing.

or to a level immediately above the vocal cords (laryngeal penetration) (table 3); however, we were unable to detect contrast medium below the vocal cords (aspiration) in any of the swallowing maneuvers. Laryngeal bolus penetrations were too few to allow statistical analysis of the risk of aspiration (table 3). However, retentions of bolus after swallow increased after midazolam exposure. In-depth analysis of efficiency of bolus clearance assessed by using VRS and PRS revealed higher scores at Mi_{10min} and Mi_{30min} compared with scores at baseline; however, this did not reach statistical significance (VRS: baseline, 1.0 [1.0 to 1.3]; Mi_{10min}, 1.0 [1.0 to 2.0]; $P = 0.046$; Mi_{30min}, 1.0 [1.0 to 2.0]; $P = 0.030$; PRS: baseline, 1.0 [1.0 to 1.0]; Mi_{10min}, 1.0 [1.0 to 2.0]; $P = 0.043$; Mi_{30min}, 1.0 [1.0 to 2.0]; $P = 0.028$).

Sedation Scoring and Effects of Midazolam. We were unable to detect a correlation between degree of pharyngeal dysfunction and VAS-sedation ($r = 0.19$, $P = 0.22$). VAS-sedation scoring decreased from 9.9 (7.0 to 10.0) at baseline to 6.0 (0.4 to 9.8) and 9.3 (4.2 to 10.0) at Mi_{10min} ($P < 0.001$) and Mi_{30min} ($P = 0.005$), respectively, and correlated to measured plasma concentration of the drug ($r = 0.49$, $P < 0.001$). One male volunteer had indirect signs of airway obstruction for periods up to 10 s at Mi_{10min}, as demonstrated by no detectable airflow while regular variations in UES pressure corresponding to continued respiratory movements. Normal breathing was resumed after arousing the subject with verbal command. Midazolam infusion was therefore stopped after 14 min, and the total dose of midazolam given to this volunteer was reduced to 0.036 mg/kg. All other volunteers were breathing spontaneously without apnea. Moreover, all volunteers completed all parts of the study, and none reported distress or discomfort.

Coordination of Breathing and Swallowing. At baseline, 98.5% of swallows occurred during expiration (E-E). The frequency of swallows followed by inspiration (E-I) increased after midazolam infusion (fig. 3D) from 1.5% of all swallows at baseline to 6.7% ($P = 0.004$) at Mi_{10min} (fig. 2D). However, at Mi_{30min}, there was no difference in respiratory-phase patterns compared with baseline (E-I, 2.0%; $P = 0.60$) (fig. 2D). The respiratory-phase pattern E-I was present in 1.8, 8.8, and 2.9% of spontaneous swallows of saliva and in 0, 2.1, and 0% in swallows of contrast medium at baseline, Mi_{10min}, and Mi_{30min}, respectively. No swallows occurred during or directly after the inspiratory phase (I-I or I-E). E-I swallows of contrast medium were too few to allow statistical analysis of an association between pharyngeal dysfunction and respiratory-phase patterns.

The frequency of spontaneous swallowing of saliva decreased markedly after midazolam infusion at Mi_{10min} and at Mi_{30min} compared with baseline (table 4); however, at Mi_{30min}, this decrease did not reach statistical significance. Moreover, compared with baseline, respiratory rate was

increased at Mi_{30min}, whereas at Mi_{10min}, this was not significant (table 4).

When further analyzing E-E swallows, midazolam had no effect on duration of inspiration before swallowing, expiration before swallowing, preswallow apnea (fig. 4B), pharyngeal swallowing (fig. 4B), postswallow apnea, or expiration after swallowing. Moreover, midazolam did not affect swallow apnea duration.

Mechanical Properties and Timing of Pharyngeal Swallowing and Swallow Apnea. We were unable to detect an effect of midazolam on the time course of the pharyngeal muscle contraction wave in E-E swallows (fig. 4B). Neither was there an effect of midazolam on the start or end of swallow apnea in relation to pharyngeal swallowing (fig. 4B).

However, midazolam affected pharyngeal manometric pressures in swallowing maneuvers of contrast medium with decreased contraction duration at the TB level and maximum contraction pressure, contraction rate, and contraction duration at Ph Low (table 6). We could not detect an effect of midazolam on maximum contraction pressure and contraction rate at TB (table 6). Moreover, there was no effect of midazolam on the coordination between UES relaxation and pharyngeal constrictor muscle activity (table 6).

Initiation of the pharyngeal phase of swallowing was not significantly changed by midazolam, neither were bolus transit time nor bolus in mouth time (table 6).

Cough. Two volunteers coughed during baseline recordings when swallowing one of the three boluses of contrast medium. One of these coughed again at Mi_{10min} and another at Mi_{30min}. In the volunteer coughing at baseline and again at Mi_{10min}, there were no signs of pharyngeal dysfunction including laryngeal penetration in the swallows followed by coughing. However, at baseline and at Mi_{30min}, the swallows followed by coughing showed premature leakage of bolus and retention of bolus after swallowing, respectively. The total number of coughs was too small to allow statistical analysis.

UES. There was no effect of midazolam on UES resting tension between swallows or residual relaxation pressure during swallowing either at Mi_{10min} or Mi_{30min} (table 6). However, at Mi_{10min}, maximum contraction pressure in the UES was reduced compared with baseline (table 6). Inspiratory UES pressures were significantly higher than expiratory UES pressures at baseline, and this difference remained unchanged at Mi_{10min} and Mi_{30min}.

The coordination between UES pressure changes and breathing was affected by midazolam. There was no change in the time between UES pressure increase and onset of inspiration at Mi_{10min} compared with baseline (baseline, 32 ± 56 ms; Mi_{10min}, 70 ± 66 ms; $P = 0.19$). However, at Mi_{30min}, UES pressure increased earlier relative onset of inspiration (88 ± 41 ms, $P < 0.001$). Moreover, at Mi_{10min},

Table 6. Mechanical Properties and Timing of Pharyngeal Swallowing after Midazolam

Midazolam (n = 16)	Bolus	Baseline	Mi_{10min}	*P* Value	Mi_{30min}	*P* Value
Pharyngeal manometry						
TB max. contr. (mmHg)	C	241 ± 67	204 ± 63	0.28	225 ± 69	0.59
TB contr. rate (mmHg/s)	C	1,376 ± 575	1,050 ± 444	0.10	1,106 ± 481	0.14
TB contr. dur. (ms)	C	694 ± 125	618 ± 96*	0.016	628 ± 105	0.049
Ph Low max. contr. (mmHg)	C	316 ± 124	219 ± 85*	<0.001	237 ± 100*	0.002
Ph Low contr. rate (mmHg/s)	C	1,575 ± 554	981 ± 426*	<0.001	1,073 ± 422*	<0.001
Ph Low contr. dur. (ms)	C	555 ± 85	479 ± 72*	<0.001	475 ± 69*	0.002
Coordination (ms)	C	−440 ± 128	−447 ± 126	0.90	−424 ± 78	0.61
Coordination (ms)	S	−367 ± 95	−359 ± 125	0.87	−369 ± 92	0.74
UES max. contr. (mmHg)	C	342 ± 75	282 ± 90*	0.009	316 ± 100	0.50
UES max. contr. (mmHg)	S	328 ± 113	217 ± 86*	<0.001	261 ± 104	0.046
UES relaxation (mmHg)	C	16 ± 10	21 ± 27	0.36	16 ± 13	0.71
UES resting tension (mmHg)	C	81 ± 44	70 ± 36	0.10	73 ± 42	0.34
Videoradiography						
Initiation (ms)	C	293 ± 177	252 ± 363	0.52	188 ± 105	0.028
Bolus transit time (ms)	C	987 ± 190	1,008 ± 352	0.56	1,001 ± 178	0.55
Bolus in mouth (s)	C	1.6 ± 0.8	1.7 ± 0.7	0.32	1.9 ± 1.0	0.035

Measurements of mechanical properties and timing of pharyngeal swallowing at baseline and at 10 and 30 min after infusion of midazolam. Data presented as mean ± SD.

* $P < 0.05$ (exact *P* value *vs.* baseline).

Baseline = baseline recordings; Bolus = bolus type; Bolus in mouth = without initiating pharyngeal swallowing, the interval between the times at which the bolus of contrast medium is first seen in the mouth and onset of pharyngeal swallowing, that is, the start of pressure rise at the level of the base of the tongue "TB-start"; Bolus transit time (pharyngeal) = the interval between the times at which the bolus head passed the anterior faucial arches and the tail of the bolus passed the UES; C = swallowing maneuvers of contrast medium; contr. dur. = contraction duration; contr. Rate = contraction rate; Coordination = measured as the time between the start of pressure rise at the lower part of the pharyngeal constrictor "Ph Low-start" and the start of UES relaxation "UES relaxation-start"; Initiation = of the pharyngeal phase of swallowing, the interval between the times at which the head of the bolus passed the anterior faucial arches and the hyoid bone started to move forward; max. contr. = maximum contraction pressure; Mi = midazolam; Mi_{10min} and Mi_{30min} = recordings 10 and 30 min after infusion of midazolam was stopped; Ph Low = lower pharyngeal manometry transducer; S = spontaneous swallows of saliva; TB = tongue base; UES = upper esophageal sphincter; UES relaxation = residual mean UES pressure at relaxation during pharyngeal swallowing; UES resting tension = mean UES pressure during 10 s at resting conditions not swallowing.

UES pressure decreased later relative onset of expiration compared with baseline (baseline, 94 ± 71 ms; Mi_{10min}, 149 ± 88 ms; $P = 0.006$), whereas at Mi_{30min}, there was no change in the time between UES pressure decrease and onset of inspiration (132 ± 105 ms, $P = 0.21$).

Vital Parameters

Heart rate, noninvasive blood pressure, and peripheral oxygen saturation were stable throughout the study (table 4). End-tidal carbon dioxide increased at Mo_{10min} and Mo_{30min} and decreased at Mi_{10min} and Mi_{30min} compared with baseline (table 4).

Missing Data

Due to low spontaneous swallow frequency at Mo_{10min} and Mo_{30min}, the number of swallows occurring during the 10-min recording period was sometimes fewer than three, thus 11 of 48 and 10 of 48 spontaneous swallows of saliva were missing, respectively. In volunteers receiving midazolam, videoradiographic imaging malfunctioned in one female and at Mi_{10min} in one male, resulting in 6 of 48 and 4 of 48 swallows of contrast medium missing at Mi_{10min} and Mi_{30min}, respectively. Because of lower swallow frequency at Mi_{10min} or Mi_{30min} and technical problems at Mi_{30min} in one male and one female, 8 of 48 and 6 of 48 spontaneous swallows of saliva were missing, respectively. Moreover, due to technical problems, plasma concentrations of midazolam could not be determined in one female.

Discussion

This is the first study to describe the effects of morphine and midazolam on the interaction between swallowing and control of breathing. Young adults administered intravenous morphine or midazolam in doses that produce sedation, displayed pharyngeal dysfunction with impaired airway protection. Furthermore, both morphine and midazolam affected the coordination between breathing and swallowing, ultimately causing changes that may be associated with increased risk for aspiration.[4]

Morphine

Opioid effects on breathing are well documented,[17] whereas information about opioid effects on swallowing and integration with breathing is scarce.[18,19] Subanesthetic concentrations of general anesthetics increase the incidence of pharyngeal dysfunction, effects that correlate with levels of sedation.[9] Here, morphine increased pharyngeal dysfunction and changed the coordination with breathing (fig. 5A), but with poor correlation to level of sedation. This is noteworthy because detrimental effects will be difficult to predict with clinical evaluation. Pharyngeal dysfunction increased due to insufficient oral bolus control and penetration of contrast to the laryngeal vestibule (fig. 5A), events that may lead to aspiration. Morphine further profoundly reduced the frequency of spontaneous swallowing at rest (fig. 5A), abating this protective mechanism for continuous pharyngeal clearance.[12,20,21] Although pharyngeal dysfunction with misdirected swallowing increased, coughing did not. Such drug-induced attenuation of cough could aggravate consequences of pharyngeal dysfunction, a potentially hazardous combination previously described for anesthetics[9] and NMBAs.[10,11,13]

Furthermore, morphine prolonged the apneic period preceding swallowing. Preswallow apnea has been described as a safety mechanism to warrant the cessation of respiratory airflow before swallowing.[15,22,23] Prolonged apnea before swallowing could also reflect active breath-holding aiming to withhold sufficient lung volume to allow expiration after swallowing.[15] In animal models, opioids inhibit respiratory neurons active during inspiration,[17,24] reducing inspiratory tidal volumes. This could diminish the positive subglottic airway pressure and thereby obliterate expiration causing inspiration to follow swallowing. Alternatively, similar to anesthetic agents increasing latency to swallow,[12,14] morphine could cause delayed triggering of swallowing, thereby extending the period of preswallow apnea. Interestingly, intrinsic pharyngeal activity seemed more sensitive to morphine than pharyngeal coordination with respiratory phases because morphine caused a pronounced increase in pharyngeal dysfunction, whereas there was only a tendency toward an increase in swallows followed by inspiration.

Morphine had, in our study, little effect on pharyngeal muscle contraction duration and velocity. Furthermore, we found no effect on UES resting tension (fig. 5A), whereas others have shown opioids to influence esophageal motility[25] and lower esophageal sphincter pressure.[26–28] The UES pressure oscillates with breathing, increasing during inspiration to prevent aerophagia, reflux, and aspiration.[2,29] Morphine caused a delayed start of inspiration after the UES pressure increase. We speculate that, because UES resting tension was unaffected, this is an effect of altered signaling to respiratory motor neurons.

Midazolam

Midazolam markedly increased the incidence of pharyngeal dysfunction and disrupted coordination with breathing, impairing airway integrity (fig. 5B) similar to morphine and previously general anesthetics and NMBAs.[9–11,13] However, in contrast to general anesthetics, we found no association between pharyngeal dysfunction and sedation level, possibly because of a lesser degree of sedation in the current study. Compared with previous studies with general anesthetics, doses of midazolam were relatively lower yielding a mean VAS-sedation score of 5.4 at Mi_{10min}, whereas propofol, isoflurane, and sevoflurane yielded VAS-sedation scores of 4.8 to 4.9[9] (lower scores indicate deeper sedation). Midazolam caused pharyngeal dysfunction mainly through insufficient oral bolus control and impaired pharyngeal clearance after swallowing (fig. 5B), leaving bolus residues that may be aspirated with subsequent inspirations, resembling the effects

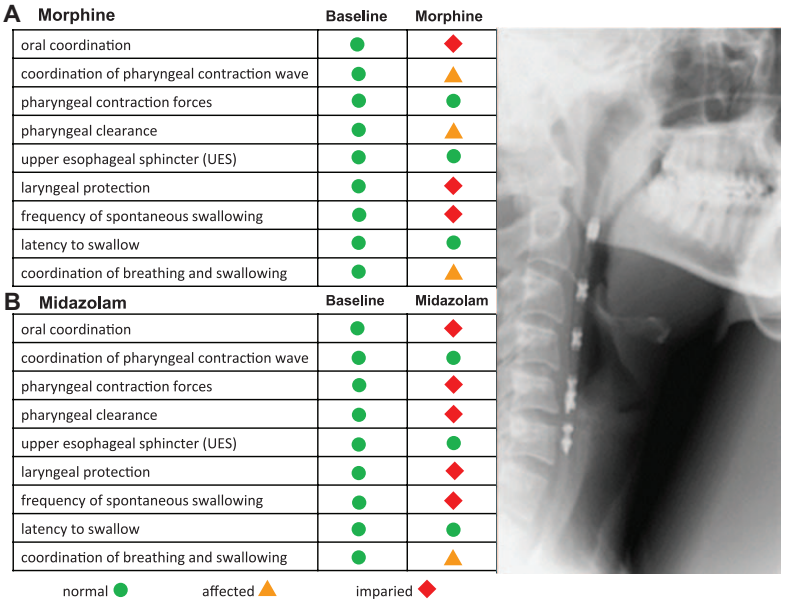

Fig. 5. Schematic presentation of key factors for normal pharyngeal function and airway protection and the impact of morphine (*A*) and midazolam (*B*). Oral coordination, (prevents premature leakage of oral contents into the pharynx); coordination of pharyngeal contraction wave (the propagation of contractions in the pharyngeal constrictor muscles into the UES); pharyngeal muscle contraction forces (increased pharyngeal pressures moves bolus caudally during swallowing); pharyngeal clearance (prevents retention of pharyngeal residue after completion of the pharyngeal contraction wave); UES (resting pressure in the UES contributes to airway protection by preventing aerophagia and regurgitation); laryngeal protection (prevents penetration of contents to laryngeal inlet and aspiration); frequency of spontaneous swallowing (prevents accumulation of bolus in the pharynx); latency to swallow (response time to initiate swallowing); coordination of breathing and swallowing (swallowing during expiration and normal duration and timing of apnea in relation to the pharyngeal phase of swallowing prevents aspiration). UES = the upper esophageal sphincter.

of propofol.[9] Interestingly, midazolam increased pharyngeal dysfunction without a corresponding increase in misdirected swallowing-associated coughing.

Midazolam reduced the swallowing frequency (Mi_{10min}), and there was a trend toward prolonged swallow latency similar to previous findings[12,14] (fig. 5B). In animal studies, activating γ-aminobutyric acid (GABA) receptors inhibits the swallowing reflex, increasing response latency and interval between swallows,[30] and tonic stimulation of GABA receptors in the central pattern generator for swallowing inhibits fictive swallowing,[31] proposing a possible molecular target for direct effects of midazolam on swallowing.

During midazolam sedation, swallows followed by inspiration increased. This risk pattern occurs more frequently in several neurological diseases[4,32,33] and is associated with aspiration in poststroke patients.[4] Normally, the larynx opens after swallowing, and positive subglottic airway pressure ensures expiratory airflow.[34,35] This is considered protective as expiratory airflow potentially expels bolus residues remaining after swallowing and thereby clears the laryngeal inlet.[1–3,36,37] However, if either subglottic pressure is too low or inspiration is prematurely initiated, inspiration will follow directly after swallowing. This may be a particularly hazardous pattern as midazolam also impaired the pharyngeal clearance of bolus residues after swallowing.

Although swallows followed by inspiration increased, respiratory phases and apneic periods before and after swallowing were unaffected. It has been suggested that neurons in the central pattern generators for breathing and swallowing collaterally affect each other because in the rat, swallowing cannot be triggered during inspiration,[38] and swallow apnea is preserved in patients after laryngectomy.[39] Although midazolam profoundly affected the pharynx, coordination of swallowing with respiratory phases was affected only for a short period of time (Mi_{10min}). Animal studies provide a rational for this observation in humans as anesthetic agents have been shown to influence neurons involved in swallowing to a greater extent than neurons involved in breathing.[40–42] Hence, we speculate that midazolam, *via* GABAergic stimulation, preferably reduce the activity in neurons engaged in swallowing; thereby moderating their inhibitory effect on respiratory neurons causing premature triggering of inspiration after swallowing.

Midazolam influenced the mechanical properties in the pharynx, causing reduced peak pressures, contraction velocity, and durations of contractions in pharyngeal muscles and reduced peak pressure in the UES similar to previously described effects of anesthetic agents.[9] However, the time course and coordination of the pharyngeal contraction wave and bolus transit time were unaffected (fig. 5B). Encumbered mechanical properties could contribute to the

impaired pharyngeal clearance seen after midazolam. Interestingly, we could not detect any effect of midazolam on UES resting tension, a finding in parallel with the effects of morphine and isoflurane, but in contrast to propofol and sevoflurane.[9] The timing of UES pressure changes related to breathing, however, was similar to morphine, altered by midazolam causing UES pressure increase to start earlier and decrease later in relation to onset of inspiratory and expiratory airflow.

Critique of the Study

The incidence of pharyngeal dysfunction at baseline was slightly higher than previously found in young adults.[9–11] All contrast medium swallows were analyzed by the same investigators (K.B. and A.I.H.C.); however, increased detection of signs of pharyngeal dysfunction over time cannot be ruled out. Moreover, no volunteer was excluded due to frequent uncontrolled swallowing at baseline as in former investigations.[9–11] Possible effects of administration of bolus through a syringe[13] would likely diminish over time, and therefore, effects of morphine and midazolam could be underestimated.

Dosage of drugs and timing of measurements were aimed to be clinically relevant, covering both effects directly after infusion of drug and after redistribution. Because the indications for and pharmacodynamic profiles of morphine and midazolam are different, no efforts to find eqiupotency or make comparisons were made. Deep sedation was avoided because forcing arousal could interfere with results.[14,43,44] Dose adjustment was required in one volunteer experiencing apnea during midazolam infusion. No other serious adverse events occurred.

The order of measurements was set to reflect clinical recovery, that is, the study was neither randomized nor placebo controlled. However, after sensory or voluntary initiation, the muscle contraction wave of pharyngeal swallowing is considered more reflexive and without voluntary control[45]; therefore, placebo effects should be minimal. The study was not designed to determine effects of gender.

Clinical Implications

Morphine or midazolam administered to young healthy adults in doses causing sedation but not anesthesia affected pharyngeal function and coordination of breathing and swallowing, ultimately impairing airway protection. Important from a clinical perspective, diminishing airway protection was not reflected in level of sedation. This is especially worth considering because morphine and midazolam commonly are regarded as safe for use in clinical settings with limited vital parameter monitoring. Moreover, in clinical anesthesia, patients are commonly exposed to multiple drugs and are thereby at risk for adverse effects from a combination of drugs lingering in the postoperative period.[46] Furthermore, elderly patients frequently experience age-related impairment of pharyngeal function[3,47,48] and may therefore be at increased risk for adverse effects compared with the young.[13]

Conclusion

Morphine and midazolam administered to young adults in clinically relevant subanesthetic doses cause pharyngeal dysfunction and affect coordination between breathing and swallowing, ultimately compromising airway protection and increasing the risk of aspiration. Although morphine mainly reduced the frequency of spontaneous swallows and prolonged the apneic period during swallowing, midazolam altered the mechanical properties of the pharynx and increased the incidence of inspiration immediately after swallowing. Pharyngeal dysfunction and concurrently reduced airway protection caused by morphine and midazolam cannot be safely predicted by monitoring the level of sedation.

Acknowledgments

The authors thank Jakob Bergström, M.Sc., and Fredrik Johansson, M.Sc. (Department LIME, Karolinska Institutet, Stockholm, Sweden), for statistical guidance, Ingeborg Gottlieb Inacio (Department of Physiology and Pharmacology, Section for Anesthesiology and Intensive Care Medicine, Karolinska Institutet) for IT assistance, and Anette Ebberyd, B.M.A. (Department of Physiology and Pharmacology, Section for Anesthesiology and Intensive Care Medicine, Karolinska Institutet), for skillful technical assistance during experiments.

Supported by the Swedish Research Council for Medicine, Stockholm, Sweden (grant no. K2011-52X-13405-12-3); Karolinska Institutet Funds, Stockholm, Sweden; Stockholm County Council, Stockholm, Sweden; Swedish Society for Anesthesia and Intensive Care Medicine, Gothenburg, Sweden; and Lena and Per Sjöberg's Foundation for Research, Ängelholm, Sweden.

Competing Interests

Dr. Hårdemark Cedborg has received lecture fees from Abbot Scandinavia AB and AbbVie AB (Stockholm, Sweden). Dr. Sundman has received lecture fees from Abbot Scandinavia AB (Stockholm, Sweden) and Schering-Plough, now Merck Inc. (Whitehouse Station, New Jersey). Dr. Eriksson has received lecture fees and advisory honorarium from Abbot Scandinavia AB and AbbVie AB and Merck Inc. None of the other authors has any financial relationship with a commercial entity that has an interest in the subject of this article.

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