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Respiratory Reflex Responses of the Larynx Differ between Sevoflurane and Propofol in Pediatric Patients

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Background: **The effects of anesthetics on airway protective reflexes have not been extensively characterized in children. The aim of this study was to compare the laryngeal reflex responses in children anesthetized with either sevoflurane or propofol under two levels of hypnosis using the Bispectral Index score (BIS). The authors hypothesized that the incidence of apnea with laryngospasm evoked by laryngeal stimulation would not differ between sevoflurane and propofol when used in equipotent doses and that laryngeal responsiveness would be diminished with increased levels of hypnosis.**

Methods: **Seventy children, aged 2–6 yr, scheduled to undergo elective surgery were randomly allocated to undergo propofol or sevoflurane anesthesia while breathing spontaneously through a laryngeal mask airway. Anesthesia was titrated to achieve the assigned level of hypnosis (BIS 40 ± 5 or BIS 60 ± 5) in random order. Laryngeal and respiratory responses were elicited by spraying distilled water on the laryngeal mucosa, and a blinded reviewer assessed evoked responses.**

Results: **Apnea with laryngospasm occurred more often during anesthesia with sevoflurane compared with propofol independent of the level of hypnosis: episodes lasting longer than 5 s, 34% *versus* 19% at BIS 40 and 34% *versus* 16% at BIS 60; episodes lasting longer than 10 s, 26% *versus* 10% at BIS 40 and 26% *versus* 6% at BIS 60 (group differences $P < 0.04$ and $P < 0.01$, respectively). In contrast, cough and expiration reflex occurred significantly more frequently in children anesthetized with propofol.**

Conclusion: **Laryngeal and respiratory reflex responses in children aged 2–6 yr were different between sevoflurane and propofol independent of the levels of hypnosis examined in this study.**

WHILE laryngeal reflexes such as laryngospasm, coughing, expiration reflex, and apnea are important to protect the lower airway from aspiration, exaggerated upper airway reflexes, such as laryngospasm, can also cause severe harm.[1] Despite their obvious clinical significance, little quantitative and qualitative basic information on these reflexes is available, especially in anesthetized humans.[2] In children, exaggerated upper airway reflexes that develop into apnea and laryngospasm with consecutive hypoxemia are more common and also more severe compared with other populations.[3,4] Although sevoflurane and propofol are commonly and often interchangeably used anesthetic agents in pediatric anesthesia, their effects on airway reflexes, particularly exaggerated protective laryngeal reflexes, have not been compared in children.[5–7] The aim of the current study was to characterize laryngeal and respiratory responses in children, aged 2–6 yr, anesthetized with either propofol or sevoflurane in relation to the level of hypnosis by using a stimulation technique previously described in adults.[8,9] In a randomized controlled trial, we tested the hypothesis that the incidence of apnea with laryngospasm evoked by laryngeal stimulation does not differ between sevoflurane and propofol when used in Bispectral Index score (BIS)–controlled anesthesia and that laryngeal responsiveness is diminished with an increased level of hypnosis.

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Materials and Methods

Subjects

The local ethics committee (Basel, Switzerland) approved the protocol. In total, 131 patients were invited to participate; 61 parents declined their child's participation, whereas 70 parents approved their child's participation with written informed consent. Exclusion criteria included clinical evidence of cardiopulmonary disease, cerebral dysfunction, or neuromuscular disease. In addition, children with a history of a respiratory infection in the 2 preceding weeks, asthma under medial treatment, or a positive family history of malignant hyperthermia were also excluded from participation in the study. Per request of the local ethics committee, a physician independent of the anesthesia and research team confirmed these exclusion criteria in each patient. Blocked randomization was generated using a computer-generated random number, and randomization was concealed until used. Patients were randomly allocated to receive propofol or sevoflurane and to the order of level of hypnosis: BIS 40 followed by BIS 60 or BIS 60 followed by BIS 40.

Anesthesia and Preparation of the Subjects

Preanesthetic medication consisted of 0.3 mg/kg midazolam given either rectally or orally 10–20 min before induction of anesthesia. Routine monitoring included electrocardiography, noninvasive blood pressure measurements, capnography, and pulse oximetry. Real-time BIS data were obtained *via* electroencephalographic

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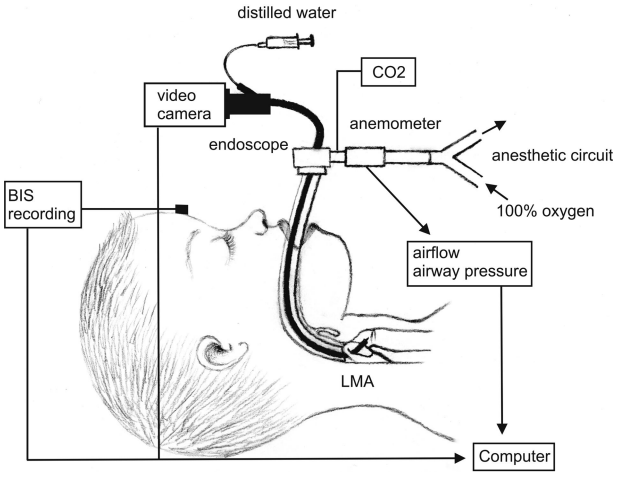

Fig. 1. Arrangement of experimental apparatus. BIS = Bispectral Index score; CO_2 = carbon dioxide; LMA = laryngeal mask airway.

electrodes applied in a frontotemporal montage (BIS® Sensor; Aspect Medical Systems, Natick, MA). The electroencephalogram was recorded using an Aspect A-2000 XP® (Aspect Medical Systems), and averaged values were recorded every 5 s using a computerized data recording system.

In all patients, anesthesia was induced with 70% nitrous oxide in 30% oxygen *via* facemask. As soon as peripheral venous access was established, nitrous oxide was discontinued, and the fresh gas flow was set to 6 l/min oxygen applied through a semiclosed anesthetic circuit for the remainder of the study. All patients were breathing spontaneously during the entire study. Anesthesia was deepened in the propofol group with an initial bolus of 3 mg/kg, followed by additional boluses (1 mg/kg) if necessary, and in the sevoflurane group, anesthesia was started with an inspiratory fraction of 8%. As soon as a sufficient level of anesthesia was achieved (no reaction to a jaw trust maneuver), an *LMA-Classic*™ (The Laryngeal Mask Company, Mahe, Seychelles) was inserted. Thereafter, maintenance of anesthesia (propofol infusion or sevoflurane inhalation) was adjusted to achieve the first randomly assigned level of hypnosis (BIS 40 ± 5 or BIS 60 ± 5).

An elbow connector with a self-sealing diaphragm was attached to the distal end of the *LMA*™. *Via* the elbow connector, end-tidal carbon dioxide was continuously measured using a calibrated sidestream capnometer (Avance S/5; Datex Ohmeda, Helsinki, Finland). A dual–hot wire anemometer (Florian; Accutronic Medical, Hirzel, Switzerland) was placed next to the elbow connector to measure ventilatory airflow (fig. 1). The same equipment was also used to measure airway pressure next to the anemometer. A fiberoptic endoscope (BF3C30; Olympus Optical Company, Tokyo, Japan) connected to a video camera (Olympus OTV-S5C; Olympus Optical Company) was passed through the diaphragm of the elbow connector. The tip of the bronchoscope was positioned to allow for visualization of the laryngeal aperture. All data including video images were stored simultaneously in digital format using Labview (version 6.1; National Instruments, Austin, TX) customized in our laboratory.

Laryngeal Stimulation

An epidural catheter (20 gauge) was advanced through the suction channel of the endoscope, and the tip of the catheter was placed above the glottic level. To elicit airway reflexes, 0.2 ml distilled water was injected through the catheter onto the laryngeal mucosa around the vocal cords. The respiratory responses and the endoscopic images were continuously registered before, during, and after the stimulation.

Experimental Procedures

An experienced pediatric anesthesiologist (T. O. E. or F. J. F.) in collaboration with research staff performed all studies before the start of surgical interventions. In addition, a pediatric anesthesiologist independent of the study team was responsible for the monitoring of the patient.

In each patient, the larynx was stimulated under two different levels of hypnosis of which the order was randomly assigned: superficial level of hypnosis with BIS 60 ± 5 or a deeper level of hypnosis with BIS 40 ± 5. Laryngeal stimulations were performed at least 5 min after ensuring that respiratory parameters were stable and BIS values were stable within the range of the assigned level.

Safety measures included a laryngospasm rescue protocol: in case laryngospasm exceeding 10 s occurred, jaw thrust and continuous positive airway pressure of 10 cm H_2O were applied.[10,11] If this measure did not relieve laryngospasm or pulse oximeter peripheral oxygen saturation (Spo_2) decreased to 90% or lower, 1 mg/kg succinylcholine and 0.01 mg/kg atropine were administered intravenously.

Respiratory Parameter Analyses

The respiratory responses elicited by the laryngeal stimulation were classified into the following categories (adapted from previous descriptions by Tagaito *et al.*):[8] (1) apnea with laryngospasm, defined as a complete closure of the glottis on the video images lasting longer than 5 s; (2) apnea with laryngospasm, defined as a complete closure of the glottis on the video images lasting longer than 10 s; (3) central apnea, defined as apnea without complete closure of the glottis lasting longer than 5 s; (4) central apnea, defined as apnea without complete closure of the glottis on the video images lasting longer than 10 s; (5) cough reflex, defined as a forceful expiration with previous inspiration; (6) expiration reflex, defined as a forceful expiration without a preceding inspiration; and (7) spasmodic panting,

defined as a rapid, shallow breathing (respiratory frequency > 60 breaths/min) lasting longer than 10 s. Furthermore, episodes of apnea interrupted by one or several expiration reflexes were identified and their cumulative time without inspiration was determined, and the time interval between the stimulation of the laryngeal mucosa and reestablishment of a stable breathing pattern was measured to evaluate the duration of respiratory reflex responses.[9] All events that occurred within 3 min after laryngeal stimulation were evaluated. All analyses were performed off-line by a reviewer blinded to the patient's group and level of hypnosis.

Statistical Analysis

Sample size calculation was based on detecting equivalence between the treatments with apnea; laryngospasm was the outcome variable of primary interest. Because the α error was set at 0.05 and the β error was set at 0.2, a sample size of 33 patients per group was needed, assuming that the expected difference in proportions was 0.0, the equivalence limit difference in proportions was 0.3, and the proportions in the treatment groups were 0.6 (expected for the airway reflex "apnea with laryngospasm" based on data by Tagaito *et al.*).[8] Computation was performed using nQuery Advisor 4.0 (Statistical Solutions Ltd., Cork, Ireland). For nonadherence to the protocol (*e.g.*, *LMA*™ could not be placed to allow for the full glottic opening to be visualized, or stable depth of hypnosis before laryngeal stimulation), which was expected in 5% of the subjects, 2 additional patients per group were included.

Demographic and procedural data were analyzed for normal distribution by the Shapiro-Wilk test, and data are reported as mean ± SD or median (interquartile range). Repeated measurements of continuous or categorical variables were analyzed with regression techniques using PROC MIXED or CATMOD® procedures in SAS software version 9.1 (SAS Institute, Cary, NC). The regression model used the patient's group assignment, the repeated-measures factors (level of hypnosis), and the interactions between the two as independent variables. Because of the low incidence of the spasmodic panting outcome, this variable was analyzed using the Fisher exact test. All analyses were performed based on an intention-to-treat approach. A *P* value less than 0.05 was considered statistically significant.

Results

Seventy healthy children, aged 2–6 yr, scheduled to undergo elective surgery or dental procedures during general anesthesia, were studied. Demographic data are shown in table 1; the baseline characteristics were similar, with a predominance of male subjects in both groups.

Table 1. Demographic Data and Administered Drugs

	Propofol Group	Sevoflurane Group
Demographic data		
Age, yr	4.6 (3.6, 5.4)	4.7 (3.2, 6.0)
Male/female, n	27/8	27/8
Height, cm	109 (102, 114)	109 (98, 120)
Weight, kg	18.9 (16.0, 21.0)	18.5 (15.0, 22.0)
Administered drugs		
Propofol infusion, $\mu g \cdot kg^{-1} \cdot min^{-1}$		
BIS 40	223 (206, 258)	0
BIS 60	134 (121, 145)	0
ET sevoflurane, %		
BIS 40	0	2.4 (1.9, 2.7)
BIS 60	0	1.3 (1.1, 1.5)

Data are presented as median (25th, 75th percentiles).

BIS = Bispectral Index score; ET = end-tidal.

In the sevoflurane group, laryngeal stimulations could be performed according to the protocol in 34 of 35 patients. In one case, the study had to be stopped after the first stimulation because of prolonged laryngospasm, which resolved immediately after the administration of succinylcholine. In the propofol group, stable clinical conditions could not be achieved before the first stimulation in three patients (persistent cough in one patient, recurrent short self-limiting laryngospasms in one patient, no stable hypnotic level in one patient); therefore, no laryngeal stimulations were performed in these patients. In one additional patient, digital data were not available for analysis because of failures of the data storage system leaving 31 subjects for detailed video analysis in the propofol group.

The administered drugs (table 1) resulted in similar BIS values in both groups (BIS 40: 39 ± 3 in both groups; BIS 60: 58 ± 4 in both groups and an electromyogram activity of 32 ± 1 dB on all occasions). Characteristics of the respiratory and hemodynamic status are shown in table 2. All measured variables were different within groups between the two levels of hypnosis applied, whereas respiratory rate, minute ventilation, and heart rate were all significantly greater in the sevoflurane group compared with the propofol group. The measured end-tidal carbon dioxide was not statistically different between the groups.

Effects of Sevoflurane and Propofol on Respiratory Reflexes

Figure 2 summarizes the types and incidences of analyzed reflex responses observed in the two groups (propofol *vs.* sevoflurane) under the two levels of hypnosis (BIS 40 *vs.* BIS 60).

Complete closure of the glottic aperture occurred significantly more often in the sevoflurane group independent of the level of hypnosis. This difference between the propofol and sevoflurane groups was more prominent in the category specifying episodes of laryngo-

Table 2. Respiratory and Hemodynamic Variables

	Group	BIS 40	BIS 60	*P* Value, Group (PRO *vs.* SEV)	*P* Value, Level of Hypnosis (BIS 40 *vs.* BIS 60)	*P* Value, Interaction (Group × Level)
RR, breaths/min	SEV	32.4 ± 6.6	26.5 ± 6.7	0.0038	0.001	0.0003
	PRO	25.5 ± 7.2	23.5 ± 7.2			
V_E, ml · kg^{-1} · min^{-1}	SEV	138 ± 32	157 ± 28	0.01	<0.0001	0.53
	PRO	123 ± 25	138 ± 29			
$ETco_2$, mmHg	SEV	50 ± 5	44 ± 5	0.23	<0.0001	0.34
	PRO	51 ± 6	46 ± 5			
Spo_2, %	SEV	100	100			
	PRO	100	100			
HR, beats/min	SEV	107 ± 13	100 ± 13	0.016	<0.0001	0.01
	PRO	97 ± 14	94 ± 14			
MAP, mmHg	SEV	53 ± 6	54 ± 8	0.51	<0.0001	0.01
	PRO	52 ± 8	57 ± 9			

BIS = Bispectral Index score; $ETco_2$ = end-tidal carbon dioxide; HR = heart rate; MAP = mean arterial pressure; PRO = propofol (n = 32); RR = respiratory rate; SEV = sevoflurane (n = 35); Spo_2 = pulse oximeter peripheral oxygen saturation; V_E = minute ventilation.

spasms lasting longer than 10 s. Video analysis revealed that closure of the glottic aperture was predominantly visible at the level of the false cords rather than restricted to the vocal cords in both groups. The incidences of shorter and longer lasting central apnea differed neither between the two groups nor between the levels of hypnosis, whereas various simultaneous laryngeal responses were observed having a continuum spectrum from widely open glottic aperture to a small opening at the level of the pars intercartilaginea of the vocal cord. Furthermore, grades of laryngeal narrowing often showed a dynamic change over an apneic episode.

In contrast, cough and expiration reflexes occurred significantly more frequently in the propofol group, with a significant predominance of the latter under a superficial level of hypnosis. In all these analyses, the interaction coefficient between the patient's group assignment and level of hypnosis did not differ from zero, indicating that the group effect did not depend upon the level of hypnosis. Spasmodic panting was not observed in the sevoflurane group and occurred only very rarely in the propofol group (5%). This difference could have been due to chance.

Cumulative time of episodes of apnea interrupted by one or several expiration reflexes lasted longer in the sevoflurane group than in the propofol group (13.7 ± 18.2 s *vs.* 6.7 ± 7.8 s, respectively; $P = 0.017$), whereas there were no differences between the hypnotic levels in both groups ($P = 0.70$). The duration of respiratory responses until reestablishment of normal breathing af-

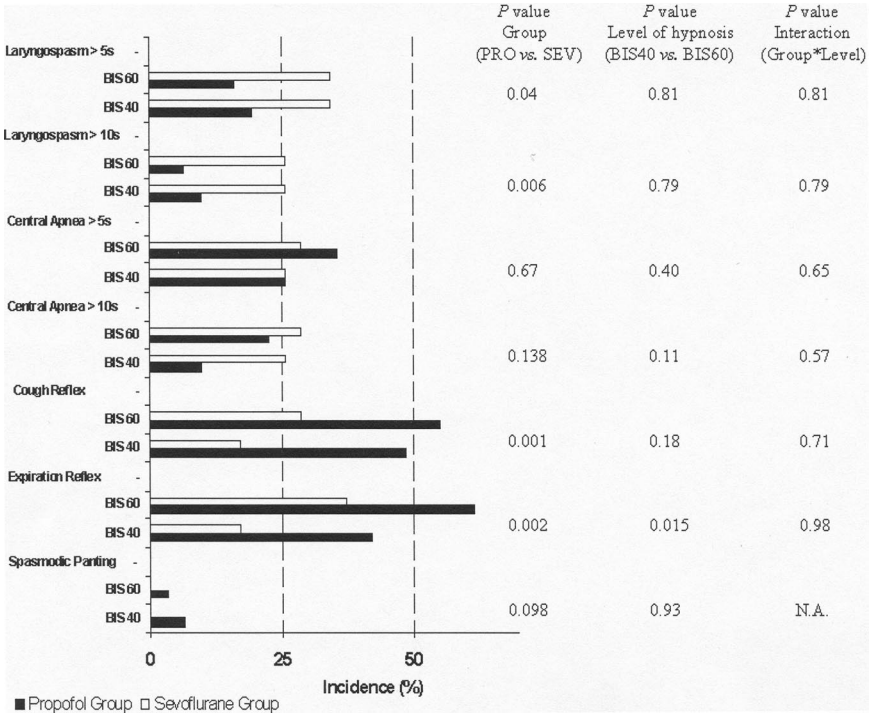

Fig. 2. Incidences of various types of laryngeal and respiratory responses to laryngeal stimulation in the propofol (PRO) and sevoflurane (SEV) groups. Statistical analyses examined effects of the anesthetic drug, the level of hypnosis, and their interaction (Group * Level). For the reflex "spasmodic panting," the interaction could not be calculated. BIS = Bispectral Index score.

ter laryngeal stimulation differed depending on the level of hypnosis in both groups and was shorter after stimulation at BIS 40 compared with BIS 60 (propofol group: 31 ± 29.3 s *vs.* 57.1 ± 57.8 s; sevoflurane group: 22.4 ± 35.9 s *vs.* 37.5 ± 55.7, respectively; $P = 0.002$), whereas there were no differences between the groups ($P = 0.19$).

Applying jaw trust and continuous positive airway pressure of 10 cm H_2O in patients with laryngospasms lasting longer than 10 s effectively relieved the laryngospasm on 18 of 19 occasions, except for 1 patient in the sevoflurane group in whom laryngospasm had to be treated with the administration of succinylcholine. Desaturation ($Spo_2 \leq 90\%$) occurred in 3 patients in the sevoflurane group and in 4 patients in the propofol group. On all occasions, the desaturations were short lasting, without bradycardia, and were associated with coughing except for the patient with prolonged apnea with laryngospasm. Gross limb movement after stimulation occurred in 11 patients in the sevoflurane group and in 22 patients in the propofol group.

Discussion

This study showed that stimulation of the larynx in children aged 2–6 yr undergoing propofol or sevoflurane anesthesia caused various types of reflex responses, including apnea with laryngospasm, central apnea, expiration reflex, cough reflex, and spasmodic panting. In contrast to our hypothesis, there were significant differences in the incidence of laryngeal and respiratory reflex responses after stimulation of the larynx. The parameter of primary interest, apnea with laryngospasm, was more frequent with the use of sevoflurane, whereas the incidences of cough and expiration reflex were greater with the use of propofol. Furthermore, the incidences of apnea with laryngospasm, central apnea, and cough reflex were independent of the level of hypnosis (BIS 40 *vs.* 60).

Comparison of Laryngeal and Respiratory Reflex Responses

To characterize respiratory reflex responsiveness in anesthetized patients, a model using laryngeal stimulation was developed by Tagaito *et al.*[8] and Tanaka *et al.*[9] in adults, and the elucidated responses were classified in consistent categories. However, when this model is applied to children, the assessment of reflex responses should be based on definitions that are of potential relevance for the population under investigation. Because the normal range of respiratory rates differs between children and adults (probably because of differences in body size and metabolism), physiologic implications of the time of cessation of breathing might differ, and apnea of short duration (> 5 s), as shown in children with obstructive sleep apnea, may be relevant.[12,13] Accordingly, analysis of the data in the current study also included apnea with laryngospasm and central apnea lasting longer than 5 s as well as episodes lasting longer than 10 s, the definition commonly applied in adult studies.

The major finding of this study was that the outcome of primary outcome apnea with laryngospasm occurred more frequently in patients anesthetized with sevoflurane and that this difference was more marked between the study groups when the longer lasting events (> 10 s) rather than short lasting events (> 5 s) were considered. Therefore, although laryngospasms of various durations occurred in patients anesthetized with either drug, the proportion of longer lasting events, which is of special interest from a clinical point of view, was greater in children anesthetized with sevoflurane.

In both groups, apnea without complete closure of the larynx as judged from analyses of the video images was observed similarly after laryngeal stimulation. Although the presence or absence of central respiratory drive *per se* is of minor clinical importance as long as the passage of the larynx is open, the impact of concomitant laryngeal narrowing can be critical for the maintenance of oxygenation.

Because this is the first study in children using a laryngeal stimulation technique, for comparative purposes, only studies performed in adult patients anesthetized with sevoflurane[9,14] or propofol[8] are available that assessed laryngeal and respiratory reflex responses using a similar model. Incidences as well as the pattern of respiratory reflex responses observed in our study differ from those reported in these studies. The incidences of apnea with laryngospasm, expiration reflex, and spasmodic panting were considerably lower in both groups of our study; however, the incidence of cough was greater in our patients anesthetized with propofol. Several factors, such as differences in the end-tidal carbon dioxide concentration,[15] the use of atropine[16] and/or midazolam as a preanesthetic medication, and the magnitude of laryngeal stimulation, might account for these marked differences.

Effects of Level of Hypnosis

Defensive airway reflexes seem to be more active during light anesthesia, leading to the common practice of deepening the anesthesia in their presence.[10,17] Therefore, it is reasonable to expect a reduced laryngeal responsiveness with increasing amounts of anesthetic agents. However, except for expiration reflex, the incidences of the examined laryngeal and respiratory reflex responses were not different for the two levels of hypnosis (BIS 40 *vs.* BIS 60; fig. 2). This finding might be explained by the fact that the difference between the two levels of hypnosis was too small to elicit different laryngeal and respiratory reflex responses. One of the purposes of this study was to examine conditions that

occur during the induction and emergence of anesthesia. In a previous study in pediatric patients anesthetized with sevoflurane, the outcome "closure of the vocal cords" after spraying the larynx with lidocaine during laryngoscopy did not correlate with BIS.[18] Furthermore, the incidences of various laryngeal and respiratory reflex responses were similar in a study comparing 1.2 *versus* 1.8 minimum alveolar concentration of sevoflurane.[14] However, the duration of respiratory responses until reestablishment of a normal breathing pattern was significantly shorter in patients anesthetized at a deeper level of hypnosis (*i.e.*, BIS 40 *vs.* BIS 60); this might have accounted for the general clinical impression that increasing the depth of anesthesia obtunds laryngeal and respiratory reflex responses.

Limitations of the Study

The current study was designed to compare propofol and sevoflurane at doses adjusted to achieve a BIS value (within a stable range) rather than comparing fixed dosing regimens used in clinical practice. This might be considered to be a limitation of the study. However, BIS as a pharmacodynamic endpoint provided a basis for rational clinical comparisons between an inhalational and an intravenous agent.[19] Although still less comprehensively evaluated in children, the electroencephalographic effects of general anesthetics in children older than 1 yr seem comparable to those observed in adults.[20] BIS is a good predictor of the hypnotic state for both drugs examined in this study.[21,22] Furthermore, the electromyographic activity measured by the BIS monitor was low and similar in both groups and at both levels of hypnosis, suggesting that electromyographic activity did not produce a systematic bias with the BIS reading in our spontaneously breathing patients.[23]

A limitation of this model was the use of an *LMA*™ when the laryngeal stimulations were performed. It has been speculated that the insertion of an *LMA*™ might result in immeasurable minor injuries, including edema of the receptors at the peripheral site of the afferent reflex arc.[9] In addition, increased intracuff pressure by the use of nitrous oxide and also the use of intermittent positive-pressure ventilation possibly interfered with the laryngeal soft tissue.[24,25] The results of the experiment by Tanaka *et al.*[9] show a depression of the defensive reflexes over time with the *LMA*™ *in situ*. However, the measurements in our experiment were performed immediately after induction of anesthesia, no nitrous oxide was used with the *LMA*™ *in situ*, and the patients were breathing spontaneously all the time. Moreover, the comparison between the two drugs should not be influenced by these factors because laryngeal stimulations were performed under the same conditions.

Midazolam was administered to all of the children in the current study and might have modified the results, because midazolam alone or through its interaction with the study drugs might alter respiratory reflex responses to an unknown extent. However, the use of midazolam as a preanesthetic medication is common and represents the current standard of practice in children.

Implications

In pediatric anesthesia, exaggerated laryngeal or respiratory reflexes leading to laryngospasm or breath holding represent significant complications.[3] Reduction of the incidence of these reflexes will potentially enhance the safety of anesthesia in this population, and knowledge regarding the impact of different drugs and dosages is therefore of paramount importance.[2] Because sevoflurane and propofol are widely used for pediatric anesthesia, these agents are of primary interest. However, experimental work performed in animals showed a pattern of laryngeal defensive reflexes that may be developmentally dependent, with a more vigorous response in young animals compared with neonatal or adult animals, suggesting that results in children might be age dependent.[26]

Sevoflurane and propofol obtund pharyngeal and laryngeal reflexes,[27,28] which partially accounts for their widespread use for induction of anesthesia in pediatric patients. It is common practice at many pediatric centers to use sevoflurane for inhalation induction mainly to facilitate the insertion of intravenous access. In this situation, defensive laryngeal reflexes, especially laryngospasm, are highly undesirable, and an increased understanding of laryngeal defensive reflexes during light states of anesthesia is of particular importance in children.

We found that laryngeal defensive reflexes differ in children anesthetized with either sevoflurane or propofol. Laryngospasm occurred more frequently during sevoflurane anesthesia, whereas cough and expiration reflexes occurred more often during propofol anesthesia. This suggested that the anesthetic agent might have major effects on the pattern of potentially harmful defensive airway reflexes.

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