The effect of intravenous lidocaine on laryngeal and respiratory reflex responses in anaesthetised children

T. O. Erb,1 B. S. von Ungern-Sternberg,2 K. Keller3 and F. J. Frei1

1 Senior Consultant, 3 Nurse Specialist, Department of Anaesthesia, University Children’s Hospital Basel, Basel, Switzerland
2 Consultant, Department of Anaesthesia and Pain Management, Princess Margaret Hospital for Children and Chair, Paediatric Anaesthesia School of Medicine and Pharmacology, The University of Western Australia, Perth, Australia

Summary

We studied the effect of intravenous lidocaine on laryngeal and respiratory reflex responses in children anaesthetised with sevoflurane. We tested the hypothesis that the incidence of laryngospasm evoked by laryngeal stimulation is temporarily diminished after the administration of lidocaine. Forty children, aged between 25 and 84 months, were anaesthetised with sevoflurane and breathed spontaneously through a laryngeal mask airway. Respiratory reflex responses were elicited by spraying distilled water onto the laryngeal mucosa at three time intervals: (i) before lidocaine was administered (baseline); (ii) at 2 min and (iii) at 10 min following the intravenous administration of a bolus of lidocaine 2 mg.kg−1. A blinded reviewer assessed the evoked responses. The incidence of laryngospasm was reduced from 38% at baseline to 15% 2 min after lidocaine administration (p < 0.02) and 18% 10 min after lidocaine administration (p = 0.10). We conclude that intravenous lidocaine significantly reduced the incidence of laryngospasm but that the effect was short-lived.

Correspondence to: T. O. Erb
Email: thomas.erb@ukbb.ch

*Presented in part at the Annual Meeting of the European Society of Anaesthesiology, Copenhagen, Denmark, May 2008.
Accepted: 3 July 2012
This article is accompanied by Editorials. See pp. 1, 3, 5 and 6 of this issue

Protecting the lungs from aspiration is vitally important and is largely regulated by laryngeal and respiratory reflexes such as coughing, laryngospasm, expiration reflex, spasmodic panting and apnoea. However, exaggerated upper airway reflexes, particularly laryngospasm, have the potential to cause harm [1]. An increased incidence of laryngospasm and apnoea is observed in children compared with adults and complications resulting from hypoxaemia are more common and more severe in children [2–4].

Lidocaine has been demonstrated to reduce the incidence of laryngospasm in anaesthetised children [5, 6]; however, its effectiveness has been questioned [7, 8]. Uncertainty regarding its usefulness is partly explained by the fact that most clinical studies were underpowered to assess the relatively rare event of laryngospasm. Often more common adverse effects, such as stridor and the occurrence of hypoxaemia from whatever cause, were included in analyses assessing its incidence. Furthermore, studies examining the action of intravenous lidocaine on cough suppression during tracheal intubation revealed that the effect may only last a few minutes [9]. The potentially transient nature of this effect might make evaluation in the clinical setting difficult.
The purpose of this study was to characterise the changes in laryngeal and respiratory reflex responses following intravenous lidocaine when the larynx was stimulated during sevoflurane anaesthesia and to determine whether these effects were transient. We tested the hypothesis that the incidence of laryngospasm induced by laryngeal stimulation is reduced 2 min after the intravenous administration of lidocaine but that this effect is less pronounced after 10 min.

Methods
The study protocol was approved by the local research ethics committee and written informed consent was obtained from the parents of all patients. Children weighing 12–35 kg, aged between 25 and 84 months, of ASA physical status 1 or 2 and who were scheduled for elective surgery in which airway management with a laryngeal mask airway would be appropriate, were enrolled in the study. Patients were excluded if they had clinical evidence of cardiopulmonary disease, cerebral dysfunction or neuromuscular disease. In addition, children with a history of respiratory infection during the preceding 2 weeks, those receiving medical treatment for asthma or children with a positive family history of neuromuscular disease or malignant hyperthermia were excluded from the study.

Midazolam 0.3 mg.kg\(^{-1}\) was administered rectally or orally 10 or 20 min, respectively, before induction of anaesthesia. Routine monitoring included pulse oximetry, capnography, electrocardiography and non-invasive blood pressure measurements. Real-time bispectral index score (BIS) data were obtained via electroencephalograph (EEG) electrodes (BIS sensor; Aspect Medical Systems, Natick, MA, USA) applied in a frontotemporal montage. The EEG was recorded using a BISx Power Link\textsuperscript{TM} (Philips, Bo¨blingen, Germany), and averaged values were stored using a computerised data recording system.

Inhalational induction of anaesthesia was performed using sevoflurane in a mixture of 50% nitrous oxide and 50% oxygen via a facemask. After induction of anaesthesia and obtaining intravenous access, nitrous oxide was discontinued and, for the remainder of the study, the fresh gas flow rate was set at oxygen 6 L.min\(^{-1}\) administered via a semi-closed breathing system. All patients were breathing spontaneously throughout the study. As soon as a sufficient level of anaesthesia was achieved (no response to a jaw trust manoeuvre), an appropriately sized non-lubricated Laryngeal Mask Airway Classic\textsuperscript{TM} (LMA; The Laryngeal Mask Company, Mahe, Seychelles) was inserted. For the remainder of the study period, the vaporiser settings were adjusted to maintain an end-tidal sevoflurane concentration of 2.5%.

The experimental design has been described previously [10]. End-tidal sevoflurane concentration was continuously measured from a sampling line located 1 cm down the LMA shaft using a calibrated side stream gas monitor (Avance S/5; Datex Ohmeda, Helsinki, Finland). A mainstream capnography adapter (Philips) and a dual-hotwire anemometer (Florian; Acutronic Medical Systems AG, Hirzel, Switzerland) was placed adjacent to the elbow connector to measure airflow and airway pressures. A flexible fibreoptic bronchoscope (BF3C30; Olympus Optical Company, Tokyo, Japan) connected to a video camera was passed through the diaphragm of the elbow connector. The tip of the bronchoscope was positioned to show the laryngeal inlet. All data, including video images, were stored simultaneously in digital format using Labview\textsuperscript{TM} (version 8.1; National Instruments, Austin, TX, USA).

A 20-gauge epidural catheter was advanced through the suction channel of the bronchoscope, and the tip of the catheter placed above the laryngeal inlet. Laryngeal and respiratory reflex responses were elicited by spraying 0.25 ml sterile distilled water through the catheter onto the laryngeal mucosa surrounding the vocal cords. Laryngeal and respiratory reflex responses and endoscopic images were recorded continuously before, during and after each stimulation.

An experienced paediatric anaesthetist (TOE) performed all the studies before the start of surgery in collaboration with research staff. In addition, a paediatric anaesthetist independent of the study team was responsible for the overall care of the patient.

In each patient, the larynx was stimulated on three consecutive occasions: (i) baseline under sevoflurane anaesthesia; (ii) 2 min; and (iii) 10 min after delivery of an intravenous bolus of 2 mg.kg\(^{-1}\) lidocaine administered over 60 s using a pre-filled infusion pump (Asena\textsuperscript{®} PK; Alaris Medical Systems, Basingstoke, UK).

Safety measures included a laryngospasm rescue protocol; if laryngospasm exceeded 10 s, then jaw thrust
and continuous positive airways pressure of 10 cmH₂O were applied. If this manoeuvre did not relieve laryngospasm or if oxygen saturation decreased to 90% or less, 1 mg.kg⁻¹ suxamethonium and 0.01 mg.kg⁻¹ atropine were administered intravenously and a tracheal tube was inserted into the patient’s trachea.

The laryngeal and respiratory reflex responses elicited by laryngeal stimulation were classified into the following categories, which have been adapted from previous descriptions [10, 11]: (i) laryngospasm, defined as complete closure of the glottis (at the level of the vocal and/or false cords) on video images lasting more than 10 s; (ii) central apnoea, defined as apnoea without complete closure of the glottis lasting more than 10 s; (iii) cough reflex, defined as a forceful expiration following inspiration; (iv) expiration reflex, defined as a forceful expiration without a preceding inspiration; and (v) spasmodic panting, defined as rapid shallow breathing (respiratory frequency greater than 60 breaths.min⁻¹) lasting more than 10 s. The time interval between stimulation of the laryngeal mucosa and re-establishment of a stable breathing pattern was measured to evaluate the duration of laryngeal and respiratory reflex responses [12]. All events that occurred within 3 min following laryngeal stimulation were evaluated. Analyses were performed offline; data containing video sequences were clipped and presented in random order to a blinded reviewer who was not present during data acquisition.

Blood samples were withdrawn from an intravenous catheter inserted into the patient’s arm opposite to that in which the lidocaine bolus was administered. Two blood samples (each consisting of 2 ml) were taken at 2 and 10 min after administration of lidocaine. The samples were centrifuged immediately after conclusion of the experiment, stored at −70 °C and analysed simultaneously using an enzyme immunoassay (Cobas Mira; Roche, Basel, Switzerland) to ascertain serum lidocaine concentrations.

This study was designed to detect the benefits of administration of intravenous lidocaine. Using McNemar’s test for the equality of a paired proportion, a sample size of 36 subjects has an 80% power to detect a difference in proportions of 0.20, when the proportion of discordant pairs is expected to be 0.23 with a 0.05 two-sided significance level. Computation was performed using nQuery Advisor 4.0 statistical package (Statistical Solutions Ltd, Cork, Ireland). Forty patients were included in the study to allow for a 10% dropout rate. Continuous data were analysed for normal distribution using the Shapiro–Wilk test. Repeated measurements of continuous variables were analysed with regression techniques using PROC MIXED procedures in SAS software version 9.1 (SAS Institute, Cary, NC, USA). Comparison of proportions was performed using McNemar’s test. Based on the a priori statement of performing two comparisons (baseline vs 2 min and baseline vs 10 min), no correction for multiple comparisons was performed. A p value of < 0.05 was considered statistically significant.

Results
The parents of 128 patients aged between 25 and 84 months and scheduled for elective surgery were invited to participate and the parents of 88 children declined their child’s participation (Fig. 1). One patient was excluded from analysis because a recheck revealed that his age (of 90 months) exceeded the upper age range for inclusion in the study. The results for 39 children were included in the study. Patients’ characteristics are presented in Table 1. One patient had to be withdrawn from the study following the second stimulation due to prolonged laryngospasm and was treated according to the rescue protocol.

The respiratory and haemodynamic indices and depth of anaesthesia are shown in Table 2. After administration of a lidocaine bolus, the mean minute ventilation decreased, resulting in a mean increase in end-tidal carbon dioxide levels, which was significant at 10 min following the lidocaine bolus. The mean arterial blood pressure was lower than baseline at both 2 min and 10 min following the lidocaine bolus.

The mean (SD) serum lidocaine concentration 2 min following intravenous bolus administration was 3.2 (0.8) µg.ml⁻¹, which was significantly higher than the mean (SD) serum lidocaine concentration of 2.0 (0.4) µg.ml⁻¹ 10 min after termination of the bolus administration (p < 0.0001). The relationship between lidocaine concentration and laryngospasm is shown in Fig. 2.

Table 3 summarises laryngeal and respiratory reflex responses observed after the three stimulations.
Compared with baseline, the incidence of laryngospasm lasting greater than 10 s was reduced by 60%, from 15 patients to 6 patients (p = 0.011) during the second stimulation, 2 min after the intravenous administration of lidocaine. Compared with baseline, the incidence of laryngospasm was not significantly reduced following the third stimulation 10 min after lidocaine administration.

Compared with baseline, the incidence of central apnoea lasting more than 10 s was significantly reduced 2 min after the intravenous administration of lidocaine. During central apnoea, various vocal cord movements were observed, ranging from a widely open glottic aperture to a small opening at the level of the pars intercartilaginea of the vocal cords. There were varying degrees of laryngeal narrowing, which often showed dynamic changes during an apnoeic episode. There were

Table 1 Baseline characteristics of the 39 patients studied. Values are median (IQR [range]) or number.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (IQR [Range])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; months</td>
<td>61 (48–72 [25–83])</td>
</tr>
<tr>
<td>Male/female</td>
<td>24/15</td>
</tr>
<tr>
<td>Height; cm</td>
<td>113.5 (105.0–119.0 [91.0–122.0])</td>
</tr>
<tr>
<td>Weight; kg</td>
<td>19.0 (17.7–22.5 [12.0–35.0])</td>
</tr>
<tr>
<td>ASA physical status; 1/2</td>
<td>37/2</td>
</tr>
</tbody>
</table>

Compared with baseline, the incidence of laryngospasm lasting greater than 10 s was reduced by 60%, from 15 patients to 6 patients (p = 0.011) during the second stimulation, 2 min after the intravenous administration of lidocaine. Compared with baseline, the incidence of laryngospasm was not significantly reduced following the third stimulation 10 min after lidocaine administration.

Compared with baseline, the incidence of central apnoea lasting more than 10 s was significantly reduced 2 min after the intravenous administration of lidocaine. During central apnoea, various vocal cord movements were observed, ranging from a widely open glottic aperture to a small opening at the level of the pars intercartilaginea of the vocal cords. There were varying degrees of laryngeal narrowing, which often showed dynamic changes during an apnoeic episode. There were

Table 2 Details of respiratory and haemodynamic variables and anaesthetic depth. Data are mean (SD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stimulation 1 (baseline) (n = 39)</th>
<th>Stimulation 2 (2 min after lidocaine) (n = 39)</th>
<th>Stimulation 3 (10 min after lidocaine) (n = 39)</th>
<th>p value (baseline vs lidocaine at 2 min)</th>
<th>p value (baseline vs lidocaine at 10 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate; breaths.min⁻¹</td>
<td>34.5 (7.1)</td>
<td>33.8 (8.2)</td>
<td>33.6 (8.2)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Minute ventilation; ml.kg⁻¹.min⁻¹</td>
<td>156 (36)</td>
<td>140 (42)</td>
<td>147 (41)</td>
<td>&lt;0.0001</td>
<td>0.0016</td>
</tr>
<tr>
<td>End-tidal carbon dioxide levels; kPa</td>
<td>5.7 (0.8)</td>
<td>5.8 (0.8)</td>
<td>5.9 (0.8)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Oxygen saturation; %</td>
<td>99.9 (0.2)</td>
<td>99.9 (0.3)</td>
<td>99.9 (0.5)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Heart rate; beats.min⁻¹</td>
<td>110 (11)</td>
<td>110 (11)</td>
<td>109 (11)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mean arterial pressure; mmHg</td>
<td>55.6 (8.4)</td>
<td>52.6 (6.2)</td>
<td>51.4 (6.1)</td>
<td>0.001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bispectral index values</td>
<td>41.9 (10.2)</td>
<td>36.2 (8.8)</td>
<td>36.8 (8.8)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>End-tidal sevoflurane concentration; %</td>
<td>2.5 (0.1)</td>
<td>2.5 (0.1)</td>
<td>2.5 (0.1)</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>
no differences in the incidence of cough reflex, expiration reflex or spasmodic panting.

Compared with baseline, the mean (SD) duration of apnoea was shorter 2 min after administration of lidocaine at 21.7 (34.7) s vs 30.8 (28.5) s, whilst apnoea duration 10 min after lidocaine administration was similar to baseline at 30.8 (34.9) s. These differences were not statistically significant.

The mean (SD) duration of laryngeal and respiratory reflex responses until the re-establishment of normal breathing following laryngeal stimulation was significantly reduced 2 min after administration of lidocaine compared with baseline (28.8 (37.4) s vs 45.8 (41.5) s, respectively, p = 0.04), whereas there were no differences between stimulation 10 min after lidocaine administration and baseline.

Applying jaw thrust and continuous positive airway pressure of 10 cmH₂O in patients with laryngospasm lasting more than 10 s effectively relieved laryngospasm without desaturation in all but one patient who was managed by administration of suxamethonium, atropine and tracheal intubation. In this patient, the lowest recorded oxygen saturation was 66% and there was no associated bradycardia.

**Discussion**

Stimulation of the larynx in children aged between 25 and 84 months undergoing sevoflurane anaesthesia

---

**Figure 2** Serum concentration of lidocaine at stimulations 2 min and 10 min after administration of 2 mg.kg⁻¹ lidocaine with (yes) or without (no) laryngospasm.

**Table 3** Details of laryngeal and respiratory reflex responses to laryngeal stimulation. Data are number (proportion).
caused various laryngeal and respiratory reflex responses both before and after intravenous administration of lidocaine.

Although of great clinical relevance, comprehensive characterisation of laryngeal and respiratory reflex responses is still lacking [13]. A clinical model using laryngeal stimulation originally developed in adults [11] and adapted to the paediatric setting was applied as we have done in previous studies [10, 14]. This model permits detailed analysis of reflex responses under consistent and safe examination conditions.

The major finding of this study was that the incidence of laryngospasm was significantly decreased after the intravenous administration of a lidocaine bolus in children anaesthetised with sevoflurane. However, this effect appears to be short-lived because the impact was less pronounced 10 min following lidocaine administration compared with the effect at 2 min after lidocaine administration.

This result is in agreement with previous studies performed in children anaesthetised with halothane undergoing ear, nose and throat surgery who received intravenous lidocaine in a dose of 1.5 or 2 mg.kg$^{-1}$ between 1 and 5 min before tracheal extubation [5, 6]. In both these studies, laryngospasm or stridor was assessed by clinical observation as a combined outcome and was found to occur in approximately 20% of children. However, as the risk of developing hypoxaemia under the clinical condition of ‘stridor’ (narrowing of the laryngeal aperture) vs ‘laryngospasm’ (complete closure of the laryngeal aperture) is considerably different, this combined assessment has important limitations. The true incidence of laryngospasm is unknown; Leicht et al. [8] could show no effect of intravenous lidocaine on the incidence of laryngospasm; however, they defined laryngospasm as stridor during inspiration, occlusion (no airflow) or the presence of cyanosis. In their study, true laryngospasm, i.e. occlusion, occurred in only one patient who happened to be in the lidocaine group, making firm conclusions on the effects of lidocaine impossible. In contrast, the present study utilised a clinical model that allows consistent and precise assessment under stable conditions. Our results suggest that the intravenous administration of lidocaine reliably blunts laryngeal and respiratory reflex responses induced by laryngeal irritation.

Another important finding was that the protective effect appears to be short-lived. This is in agreement with studies assessing the effect of lidocaine on tracheal intubating conditions in adults. Yukioka et al. [9] found that coughing was best suppressed by 2 mg.kg$^{-1}$ intravenous lidocaine when administered between 1 and 5 min before tracheal intubation. This resulted in a mean peak serum concentration of lidocaine that was greater than 3 μg.ml$^{-1}$ and an effect that wore off after approximately 10 min. In our study, there was no protective effect of lidocaine 10 min after administration compared with baseline, and analysis of serum lidocaine concentrations demonstrated that serum levels declined considerably over this 10-min period.

The administration of lidocaine resulted in a significant increase in the depth of anaesthesia as assessed by BIS monitoring. This is in agreement with studies by both Kim et al. [15] and Gaughen and Durieux [16] in which administration of lidocaine resulted in a reduction in BIS values. Furthermore, intravenous lidocaine, when plasma concentrations exceeded 3.5 μg.ml$^{-1}$, reduced the MAC value of nitrous oxide and halothane [17]. Although the mechanism by which intravenous lidocaine suppresses laryngeal and respiratory reflex responses is unknown, possible effects include general anaesthesia, direct blockade of noxious stimuli and depression of motor function. However, a reflex response to laryngeal irritation is mediated at subcortical levels and therefore a cortical effect may be inadequate to reduce the response to laryngeal irritation [15]. We found that laryngeal and respiratory reflex responses elicited 10 min after the administration of intravenous lidocaine were different from those elicited 2 min after administration, even though BIS values were similar at these two time intervals, and we believe that a direct anaesthetic effect of lidocaine does not sufficiently explain how it reduces the response to laryngeal irritation.

No adverse reactions were observed when a lidocaine bolus of 2 mg.kg$^{-1}$ was administered intravenously over a period of one minute. The highest recorded serum concentration of lidocaine (5.3 μg.ml$^{-1}$) in this study is unlikely to cause side effects in anaesthetised patients [18]. A lidocaine dose–response relationship was observed in a study by Yukioka et al. [9], who reported complete suppression of cough when...
plasma levels were above 3 μg.ml⁻¹ when tracheal intubation was attempted in adults. These data are in broad agreement with our study whereby laryngospasm was not observed in any patient when the serum lidocaine concentration exceeded 3.6 μg.ml⁻¹.

Several limitations exist with this study. First, midazolam administered as a premedicant may have affected the results of this study by altering laryngeal and respiratory reflex responses to some extent. However, it is a commonly used premedicant and represents current standard practice in children in many institutions. Second, the results should not be extrapolated when using other anaesthetic drugs such as propofol because laryngeal and respiratory reflex responses have been demonstrated to be different when propofol is administered compared with sevoflurane [10]. Third, no control group was included in this study; however, the stability of the model over a specific time frame has been previously examined in a separate group of children anaesthetised with sevoflurane and exposed to three repeated laryngeal stimulations [19] in a similar manner to those in the present study. The laryngeal and respiratory reflex responses were remarkably constant in successive stimulations and the results were in agreement with the work of Tagaito et al. [11], who found no significant differences in the incidence of laryngeal and respiratory reflex responses that could be accredited to repeat stimulation. Given these circumstances, it was felt unnecessary to include a control group. A fourth limitation was the presence of an LMA when performing the stimulations. The insertion of an LMA may result in laryngeal injury such as oedema of the peripheral receptors of the afferent reflex arc [12]. Increased intracuff pressure, as well as the use of intermittent positive pressure ventilation, could affect laryngeal soft tissue [20, 21], and Tanaka et al. [12] have shown depression of defensive reflexes over a period of time when an LMA is in situ. However, the measurements in our study were performed immediately following induction of anaesthesia; care was taken to apply low cuff pressures [22] and all patients were breathing spontaneously.

There are particular ethical aspects to this kind of study, especially in children. To ensure compliance with research ethics committee requirements, we liaised with the committee at great length during the study’s design, although certain ethical issues may still remain. These are discussed further in the accompanying commentaries [23–26].

Exaggerated laryngeal or respiratory reflex responses resulting in laryngospasm or apnoea are significant complications during paediatric anaesthesia [2]. Experimental work in animals suggests that these reflexes might be developmentally dependent [27]. Reducing the incidence of these reflexes will potentially improve the safety of anaesthesia, and administration of lidocaine in this context has been advocated for many years, even though its exact impact remains unclear [13]. Although sevoflurane is widely used in children, not least because of its ability to obtund pharyngeal and laryngeal reflexes [28], laryngospasm occurs frequently [10, 19] and adjuvant medication to reduce its incidence is warranted. The results of our study suggest that the incidence of laryngospasm is decreased after the intravenous administration of lidocaine; however, the timing of administration, for example, before extubation, must be carefully planned to obtain optimum effects because it is short-acting. An example when it may provide protective effects is in a child undergoing ear, nose and throat surgery at emergence from anaesthesia.

In conclusion, we found that the intravenous administration of lidocaine significantly reduced the incidence of laryngospasm evoked by laryngeal stimulation in children anaesthetised with sevoflurane; however, the effect was short-lived and incomplete.

Acknowledgements
The authors express their gratitude to all the children and their families who participated in this study and to Allison Dwileski (Department of Anaesthesia and Intensive Care Medicine, University Hospital Basel, Basel, Switzerland) for her expert help with manuscript preparation.

Competing interests
This study was supported by the Swiss National Science Foundation (SNSF 3200B0-109322), the Department of Anaesthesia and Intensive Care Medicine, University Hospital Basel, Basel, Switzerland and the University Children’s Hospital Beider Basel, Basel, Switzerland. No other external funding or competing interests declared.
References


