Upper airway reactivity and upper respiratory tract infection: effect of nebulized lidocaine†

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Patients presenting for elective anaesthesia and surgery may be suffering with, or recovering from, a recent upper respiratory tract infection. Airway reflexes are heightened and these individuals may be more likely to suffer airway complications on administration of general anaesthesia. We have examined the effect of nebulized lidocaine on upper airway reflexes in such subjects. Using dilute ammonia as a chemical stimulus to the upper airway, we measured upper airway reactivity in 15 volunteers (aged 22–43 yr) with symptoms of an upper respiratory tract infection for 4 days or less. The threshold concentration of ammonia producing a brief reduction in inspiratory flow was determined. Measurements were made before and after administration of a nebulized solution of 4% lidocaine 4 ml or saline. After a 2-h interval the procedure was repeated with the alternative solution. The order of administration was randomized. The observer was blind to the solution given. Ammonia threshold was found to increase in subjects after nebulized lidocaine, from a median value of 327 (range 76–878) ppm to 878 (251–1620) ppm (P = 0.0007, Wilcoxon); there was no significant change after nebulized saline. After a convalescence period of at least 4 weeks, with no return of symptoms in the preceding 2 weeks, ammonia threshold was reassessed. It was found to be increased in all 15 subjects. Comparison of the five different times of measurement showed a highly significant difference (P < 0.001, Friedman). Subsequent analysis showed significant differences (P < 0.05, W ilcoxon) between convalescent ammonia threshold and both baseline and post-saline nebulizer values. There was no significant difference between convalescent and post-lidocaine ammonia threshold. We conclude that in adult subjects, nebulized lidocaine attenuated the heightened airway reflex sensitivity associated with symptoms and signs of upper respiratory tract infection.

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We have developed a portable device by which airway reactivity may be quantified. Using ammonia vapour diluted in air as a chemical stimulus, the threshold concentration required to produce a brief reduction in inspiratory flow is determined. This is a decrease in inspiratory flow rate of greater than 25% of peak inspiratory flow. Using this technique, it has been shown that upper airway reflexes are increased during upper respiratory tract infection and decreased by application of topical local anaesthetic in healthy subjects.

The aim of this study was to examine the effect of nebulized lidocaine on upper airway reflexes in volunteers with symptomatic respiratory infections.

Subjects and methods
After obtaining approval from the Ethics Committee and written informed consent, we studied 15 volunteers with symptoms suggestive of viral upper respiratory tract infection. They were aged 22–43 yr; all were non-smokers and not receiving medications. Exclusion criteria included a history of asthma and a respiratory tract infection in the previous 4 weeks. Upper respiratory infection was defined by criteria used previously in our laboratory and originally by Tait and Knight. Symptoms were classified into three categories: nasal—discharge, obstruction, sneeze; throat—soreness, non-productive cough; systemic—malaise, myalgia, pyrexia (≤38°C).

Inclusion criteria required at least one symptom from each category. Subjects were excluded if they had a temperature greater than 38°C, productive cough or evidence of lower respiratory tract infection.

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Airway reflex response was assessed using a challenge of ammonia in inspired air to assess the threshold concentration producing a reduction in inspiratory flow, as described below. A baseline ammonia threshold was determined. This was followed by a 4-ml solution of either 4% lidocaine or saline nebulized in air. A second determination of ammonia threshold was then made within 5 min of completion of the nebulizer. After a 2–3-h interval, the procedure was repeated with the alternative nebulizer; the order of presentation was randomized. The observer was blind to the solution given.

After a convalescent period of at least 4 weeks, with no return of symptoms in the preceding 2 weeks, ammonia threshold was reassessed to provide a ‘normal’ comparison.

Measurement technique
Measurement of airway reflex sensitivity was made using a previously described method which uses low concentrations of ammonia vapour as an irritant chemical stimulus to the airway during inspiration.1 Briefly, the subject was asked to breathe through a close-fitting mouthpiece while wearing a noseclip and to exhale to atmosphere via a one-way valve. The mouthpiece was attached to a pneumotachograph which recorded airflow onto a chart recorder. A pneumatic two-way balloon valve allowed the investigator to rapidly switch between room air and dilute ammonia vapour. Subjects were unaware of the switching of the pneumatic valve. In this way the subject’s airway was exposed to single intermittent breaths containing small concentrations of ammonia vapour. We recorded the threshold concentration required to elicit a rapid decrease in inspiratory flow, by at least 25% of peak inspiratory flow, followed by a swift recovery; the whole event lasted less than 0.5 s.1 Reduced ammonia threshold is associated with increased sensitivity of the airway; increased values represent depression of airway reflex sensitivity.

Ammonia was introduced via a Rotameter, from a 3% ammonia in nitrogen cylinder (British Oxygen Company). This was added to room air at a flow rate of 10 litre min⁻¹ to deliver accurate concentrations of ammonia vapour in the range 0–3500 ppm. Calibration of the system has been described previously.1 By altering the flowmeter settings in increments of 50 ml min⁻¹, corresponding to mean changes in ammonia concentration of 171 (range 125–235) ppm, we were able to determine the minimum concentration of ammonia vapour required to elicit the ammonia threshold.

Statistical analysis
Statistical analysis was performed using SPSS for Windows 95. The Wilcoxon’s test for paired non-parametric data was used to assess the effect of each nebulized solution. Friedman’s test (ANOVA) was used to compare acute and convalescent data.

Results
Seven of the volunteers received the lidocaine nebulizer first. Ammonia threshold for each subject before and after both nebulized lidocaine and saline is shown in Figure 1. After nebulized lidocaine, ammonia threshold increased in all instances although to a variable extent. The increase was significant (P=0.0007, Wilcoxon). After nebulized saline there was no obvious change and no significant difference. Data for the four measurements are shown in Table 1.

Subjects were reassessed 4–5 weeks later; none had symptoms or signs of infection within the preceding 2 weeks. Ammonia threshold increased in all 15 subjects to a median value of 878 (range 327–1620) ppm. Figure 2 shows box and whiskers plots for ammonia threshold at the five measurement times. Analysis showed a highly significant difference (P<0.001, Friedman). Subsequent analysis showed significant differences (P<0.05, Wilcoxon) between convalescent ammonia threshold and both baseline and post-saline nebulizer values. There was no statistically significant difference between convalescent and post-lidocaine ammonia threshold.

Discussion
The decision to anaesthetize a patient with symptoms and signs, or a very recent history, of respiratory infection is a common clinical dilemma. Most adults suffer at least one upper respiratory infection per year; the incidence is greater (5–6 episodes per year) in children. Therefore, many patients presenting for elective surgery and anaesthesia may either be suffering with, or recovering from, a recent respiratory infection. Postponement of planned anaesthesia and surgery may have medical, social and financial consequences. There have been relatively few studies investigating this important clinical area. These studies have focused on the incidence of adverse respiratory events associated with anaesthesia in children. In a large prospective study, Cohen and Cameron studied 1283 children with symptoms of a respiratory infection and 20 876 children without any symptoms who were undergoing elective surgery.5 They found that children suffering from an infection were three times more likely to suffer an adverse respiratory event; the risk increased 11-fold if tracheal intubation was performed. In 1992, Levy and colleagues6 reported that children with an acute or recent upper respiratory infection have an increased likelihood of transient hypoxaemia in the perioperative period. There has also been a well documented case of laryngospasm resulting in death in a child recovering from a recent respiratory infection.7 It has been suggested that an anaesthetist may be negligent for anaesthetizing a child while suffering from an upper respiratory tract infection.8

There are few studies of adult patients with symptoms of an upper respiratory tract infection undergoing anaesthesia. However, there is evidence of increased bronchial reactivity in such adults. Empey and colleagues demonstrated a
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Fig 1 Ammonia threshold concentration (NH₃TR) in volunteers with an upper respiratory tract infection before (pre) and after (post) administration of 4% lidocaine 4 ml and saline 4 ml, each nebulized in air. Bold lines represent two or three subjects (n=15). *P=0.0007 (Wilcoxon).

Table 1 Ammonia threshold concentration (NH₃TR) in volunteers with an upper respiratory tract infection before and after administration of 4% nebulized lidocaine 4 ml and saline 4 ml. Data are median (range) ppm (n=15). *P=0.0007 (Wilcoxon).

<table>
<thead>
<tr>
<th>NH₃TR (ppm)</th>
<th>Lidocaine</th>
<th>Saline</th>
</tr>
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<tbody>
<tr>
<td>Before nebulizer</td>
<td>327 (76–878)</td>
<td>327 (76–1000)</td>
</tr>
<tr>
<td>After nebulizer</td>
<td>878 (251–1620)*</td>
<td>327 (76–1000)</td>
</tr>
</tbody>
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Fig 2 Box and whiskers plot of ammonia threshold concentration (NH₃TR) in volunteers with an upper respiratory tract infection before (pre) and after (post) application of nebulized 4% lidocaine 4 ml (lid.) and saline 4 ml (sal.). Convalescent data are also shown. Boxes show median and 25th–75th centiles; whiskers indicate range (n=15). *P<0.05 from baseline (Wilcoxon).

200% increase in airway resistance in response to inhaled histamine in subjects with colds compared with a 30% increase in controls.9 However, Fennelly and Hall, in their editorial, could find little evidence to demonstrate that anaesthesia in adult patients with an upper respiratory tract infection leads to an increased incidence of respiratory complications.10

Nebulized lidocaine reduced the increased sensitivity of upper airway reflexes associated with the classic symptoms and signs of viral upper respiratory tract infection, the ‘common cold’. After administration of nebulized lidocaine, ammonia threshold was similar to that after convalescence, 4–5 weeks later, but we did not assess the duration of this effect.

Earlier work examined the degree and duration of effect of local anaesthesia on upper airway reflexes in healthy volunteers.3 Nebulized lidocaine 4% (4 ml) caused significant depression of upper airway reflexes for 25 min. It was more efficacious than two benzocaine lozenges (20 mg), lasting no more than 10 min. A direct spray of lidocaine 100 mg to the vocal cords caused the greatest depression of upper airway reflex sensitivity, an effect which lasted for 100 min.

Considerable inter-individual variation was evident which may be attributed in part to changes in upper airway reflex sensitivity with age.11 However, having achieved the diagnostic criteria, no attempt was made to grade severity or duration of illness (within 4 days). Also, diagnosis of viral respiratory infection is complicated by the fact that a particular clinical syndrome is not always associated with a specific pathogen. The rhinovirus, myxovirus and respiratory syncitial virus are most common. It is probable that a large spectrum of cause and severity existed among our subjects. Subjects acted as their own controls. We recruited on the basis of the presence of symptoms attributable to a viral infection. In everyday anaesthetic practice, such symptoms would be used to assess the need to postpone surgery.

Airway reflex activity is important to the anaesthetist because it is involved in both airway protection and complications such as cough and laryngospasm. Using this inhaled ammonia challenge technique, previous studies have shown that airway reflexes are depressed by administration of oral benzodiazepines.12 It has been shown that airway reactivity decreases with advancing age,11 which could lead to an increased incidence of postoperative pulmonary aspiration in the elderly.13 In comparison, chronic smokers have significantly greater airway reactivity than non-smokers,14 an effect that may last for up to 10 days of abstinence from cigarettes.

Our findings suggest that it may be possible to pharmacologically attenuate the heightened upper airway reflexes associated with upper respiratory tract infection and thus reduce the associated risk of airway complications in these patients. This may also apply to increased airway reflexes associated with smoking. However, attention should be given to the risk of pulmonary aspiration by anaesthetizing...
the larynx, thus probably contraindicating this technique in patients at particular risk. Not all risk associated with anaesthesia in patients with upper respiratory tract infection comes from increased upper airway reflex sensitivity. Accumulation of excessive tracheal secretions may be associated with postoperative pneumonia, and viral myocarditis could also be present.\(^\text{15}\)

In summary, we have shown that increased upper airway reactivity associated with the acute phase of an upper respiratory tract infection was attenuated by nebulized lidocaine, but the clinical significance of this technique is uncertain. The relationship between an increase in the sensitivity of airway reflexes and the incidence of airway problems during anaesthesia requires further investigation.

References

4 Tait AR, Knight PR. The effects of general anesthesia on upper respiratory tract infections in children. Anesthesiology 1987; 67: 930–5
5 Cohen MM, Cameron CB. Should you cancel the operation when a child has an upper respiratory tract infection? Anesth Analg 1991; 72: 282–8
7 Konarzewski WH, Ravindran N, Findlow D, Timmins PK. Anaesthetic death of a child with a cold. Anaesthesia 1992; 47: 624