Assessment of the cough reflex after propofol anaesthesia for colonoscopy

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Background. Dysfunction of the cough reflex as a result of the lingering effects of anaesthetics may lead to aspiration pneumonia or retained secretions after general anaesthesia. It is unknown whether low concentrations of propofol alter the cough reflex in the early period after anaesthesia. The objective of this study was to investigate the effect of low concentrations of propofol on the cough reflex sensitivity as assessed by the cough reflex threshold to an inhaled irritant.

Methods. Fifteen, ASA I–II, non-smoking patients undergoing elective colonoscopy were studied. Anaesthesia was induced and maintained with a blood target-controlled propofol infusion. Cough reflex threshold was measured with citric acid. Increasing concentrations of nebulized citric acid (2.5, 5, 10, 20, 40, 80, 160, 320, and 640 mg ml\(^{-1}\)) were delivered during inspiration until a cough was evoked. The citric acid concentration eliciting one cough (C1) was defined as the cough reflex threshold. C1 was log transformed for statistical analysis (Log C1). Log C1 was measured before anaesthesia and during the recovery period with estimated decreasing propofol concentrations of 1.2, 0.9, 0.6, and 0.3 mg ml\(^{-1}\).

Results. Log C1 (median; interquartile range) measured with propofol concentrations of 1.2, 0.9, 0.6, and 0 \(\mu\)g ml\(^{-1}\) were 1.9 (0.6), 1.9 (1.0), 1.9 (1.1), 1.9 (0.6), and 1.9 (0.7) mg ml\(^{-1}\) (NS), respectively. However, light sedation was observed with propofol concentrations of 1.2 and 0.9 \(\mu\)g ml\(^{-1}\).

Conclusion. This study indicates that residual sedation after propofol anaesthesia for colonoscopy does not adversely affect the cough reflex.


Keywords: anaesthetics i.v., propofol; citric acid; colonoscopy; complications, aspiration; complications, pneumonia; cough

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Cough reflex is the main mechanism of airway defence. It protects the lungs from inhalation of foreign particles and clears the airways of retained secretions. However, residual concentration of anaesthetics and residual sedation observed after general anaesthesia may depress this reflex.1–3 This impairment may lead to adverse respiratory events like aspiration pneumonia or retained secretions.

Propofol is often used in general anaesthesia for day-case surgery. In this setting, early recovery of airway reflexes is essential to allow safe resumption of fluid intake before hospital discharge. However, propofol is a potent depressant of airway reflexes at hypnotic concentrations,4,5 but the effects of low concentrations of this drug, such as those observed during recovery from general anaesthesia, have not been assessed. We therefore conducted this study to assess the effect of the low propofol concentrations observed during recovery from general anaesthesia on the cough reflex sensitivity assessed by the cough reflex threshold to an inhaled irritant.

Methods

The study was conducted in the Anaesthesia Department of Bichat Hospital, a 1200-bed University Hospital. It was approved by the Ethics Committee of Saint-Antoine Hospital and written informed consent was obtained from each patient.

ASA I–II non-smoking patients undergoing elective colonoscopy under general anaesthesia were scheduled for the study. Any of the following excluded the patient from the
Cough reflex after propofol for colonoscopy

The initial blood target for induction was 6 \( \mu \)g ml\(^{-1}\). Anaesthesia was induced and maintained with a blood target controlled propofol infusion (Diprifusor\textsuperscript{®} device, Astra-Zeneca Laboratory, France). The software running the device uses the Marsh pharmacokinetic model.\textsuperscript{6} It has a precision of 18.2\% (median absolute prediction error) and a bias of 7\% (median prediction error).\textsuperscript{2}

The initial blood target for induction was 6 \( \mu \)g ml\(^{-1}\). Thereafter, the target was modified according to the depth of anaesthesia as assessed by the motor response to endoscopic stimulation and arterial pressure and heart rate variations. During anaesthesia, patients were spontaneously breathing with supplemental oxygen administered through nasal prongs to keep pulse oxygen saturation above 95\%. Airway management was limited to manual jaw thrust and mandibular advancement. After anaesthesia, the patient was transferred to the post anaesthesia care unit while the propofol infusion was maintained with a blood target concentration of 1.2 \( \mu \)g ml\(^{-1}\).

The cough reflex threshold was determined by delivering increasing concentrations of nebulized citric acid (2.5, 5, 10, 20, 40, 80, 160, 320, and 640 mg ml\(^{-1}\)) during inspiration until cough was evoked. The concentration eliciting one cough (C1) was defined as the cough reflex threshold\textsuperscript{1} provided that cough was also elicited by the immediately greater concentration.\textsuperscript{3} The order of administration of citric acid solutions was always the same, from the lowest to the highest concentration. No saline was interspersed with increasing concentrations of citric acid. If cough was not evoked with the concentration of 640 mg ml\(^{-1}\), C1 was arbitrarily defined as 1280 mg ml\(^{-1}\). All measurements were performed in the morning to minimize the diurnal variation of the cough reflex, as the threshold is increased in the afternoon.

For the challenge, the patient was in the sitting position and wore a nose-clip and was asked to exhale to functional residual capacity and then inhale to total lung capacity through a mouthpiece (single-breath inhalation technique). Each concentration of tussive agent was inhaled five times with a 30-s pause between each inhalation. A breath-activated jet nebulizer was used (Nebulizer dosimeter MEDIPRON F.D.C. 88, MEDIPROM, Paris, France) which delivered a constant volume of solution (8 mg breath\(^{-1}\)). Citric acid solutions were prepared by the Pharmacy of Bichat Hospital. Normal saline was used as solvent. Solutions were used no more than 48 h after their preparation.

C1 was measured before anaesthesia (blood propofol concentration of 0 \( \mu \)g ml\(^{-1}\)) and during the recovery period with decreasing blood target propofol concentrations of 1.2, 0.9, 0.6, and 0.3 \( \mu \)g ml\(^{-1}\). Blood concentrations were estimated with the Diprifusor\textsuperscript{®} software, but were not measured. Each measurement at a given concentration was performed once and was started 5 min after the blood and brain propofol concentrations had reached equilibrium.

Before each challenge, sedation was assessed with the Observer’s Assessment of Awareness/Sedation Scale (OAA/S).\textsuperscript{10} It is a five point scale, which takes into account responsiveness, speech, facial expression, and eyes (see Appendix). It ranges from 5 to 1, a score of 5 corresponding to an alert state and a score of 1 to a deep sleep state. The same unblinded investigator assessed the OAA/S score and conducted the cough challenge.

Fifteen subjects were required to show a 50\% increase of Log C1 at a propofol concentration of 1.2 \( \mu \)g ml\(^{-1}\) when compared with the preoperative value (nQuery Advisor software, Statistical Solutions Company, Saugus, MA, USA). C1 was Log transformed for statistical analysis (Log C1). A Wilcoxon sign rank test was used for comparisons. Results were expressed as the median (interquartile range).

## Results

From July 2001 to October 2002, 17 patients were included. Two patients withdrew their consent on the day of colonoscopy. So, 15 patients were studied and their characteristics are presented in Table 1.

OAA/S scores measured before colonoscopy and with propofol concentrations of 1.2, 0.9, 0.6, 0.3, and 0 \( \mu \)g ml\(^{-1}\) were 4 (2), 5 (1), 5 (0), 5 (0), and 5 (0), respectively. Scores measured at 1.2 and 0.9 \( \mu \)g ml\(^{-1}\) were significantly different from the score measured at 0 \( \mu \)g ml\(^{-1}\) (\(P<0.002\) and \(P<0.016\), respectively).

Log C1 measured with estimated propofol concentrations of 1.2, 0.9, 0.6, 0.3, and 0 \( \mu \)g ml\(^{-1}\) were 1.9 (0.6), 1.9 (1.0), 1.9 (1.1), 1.9 (0.6), and 1.9 (0.7) mg ml\(^{-1}\), respectively. Log C1 value measured at 1.2 \( \mu \)g ml\(^{-1}\) did not differ from that measured at 0 \( \mu \)g ml\(^{-1}\) (\(P=0.10\)). Individual variations of Log C1 values are presented in Figure 1. One patient was not able to cough with the highest concentration tested (640 mg ml\(^{-1}\)) at each of the five challenges.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and anaesthetic characteristics of the 15 patients. Results are expressed as median (interquartile range) unless otherwise stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40 (19)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64 (14)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167 (12)</td>
</tr>
<tr>
<td>Male patients</td>
<td>6/15 (40%)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>25 (17)</td>
</tr>
<tr>
<td>Dose of propofol received (mg)</td>
<td>290 (232)</td>
</tr>
</tbody>
</table>
Discussion

Despite residual light sedation observed after discontinuation of propofol anaesthesia, the cough reflex threshold measured with increasing concentrations of an inhaled irritant was not modified during the early postoperative period compared with the pre-anaesthetic period. Sensitivity of the cough reflex therefore did not appear to be modified by estimated propofol concentrations less than 1.2 \( \mu \text{g ml}^{-1} \).

Previous studies have suggested that postoperative impairment of the cough reflex may lead to aspiration pneumonia or retained secretions. Indeed, an increase of the cough reflex threshold was observed in medical patients who developed aspiration pneumonia or recurrent pneumonia.\(^{11,12}\) Moreover, a decrease of the cough threshold induced by ACE inhibitors may be protective against aspiration pneumonia.\(^{13}\) Consequences of cough reflex depression after general anaesthesia may be worse in patients with pulmonary disease like COPD patients. Indeed, cough contributes to up to 60% of total pulmonary clearance in COPD patients but only to 8% in healthy patients.\(^{14}\)

Little is known about the effects of anaesthetics on the cough reflex and especially the effect of subhypnotic concentrations of anaesthetics like those observed in the recovery period. Nishino and Tagaito reported that enflurane and propofol depress the cough reflex.\(^{2,3}\) However, both studies addressed the effects of high, hypnotic concentrations of these drugs, that is 0.7 MAC enflurane and 3 \( \mu \text{g ml}^{-1} \) propofol concentrations. Dilworth and colleagues reported an increase of the cough reflex threshold elicited by citric acid and capsaicin until the first day after upper abdominal surgery. Drugs administered during anaesthesia may have been responsible for that increase.\(^{8}\)

In the present study, we investigated the effect of lingering concentrations of propofol and the associated residual sedation observed in the post anaesthesia care unit, in view of the high risk of adverse respiratory events during the early postoperative period.\(^{15,16}\) We observed a small but significant decrease of the OAA/S score indicating light levels of sedation with blood propofol concentrations of 1.2 and 0.9 \( \mu \text{g ml}^{-1} \). However, we did not observe any effect of low propofol concentration on the cough reflex threshold. The cough reflex appears more resistant to the effect of anaesthetic agents than pharyngeal reflexes. Indeed, venous blood propofol concentration of 0.9 \( \mu \text{g ml}^{-1} \) deeply impairs pharyngeal reflexes.\(^{14}\) Differential sensitivity of both reflexes towards the same anaesthetic drug seems to be related to a differential sensitivity of each neural pathway in the brain.\(^3\) However, we cannot rule out that our negative results were related to a type II statistical error. Since the number of subjects included in the study was calculated to demonstrate a 50% increase in Log C1, a smaller Log C1 change may not have been detected.

Preservation of the cough reflex after propofol anaesthesia may be clinically relevant for the management of ambulatory patients. It may allow early and safe resumption of oral fluid intake before hospital discharge, that is without aspiration of fluid into the trachea. Colonoscopy is the most frequent procedure conducted under general anaesthesia in France. More than 800 000 procedures are performed each year in France accounting for 10% of all anaesthetics.\(^{17}\) Owing to the number of cases and the ambulatory nature of the procedure, safety is a primary concern. So, knowing that the concentrations of propofol observed in the recovery period do not impair airway protective reflexes is rather reassuring for the management of the patient. These results could also be extended to all procedures conducted under propofol sedation with or without topical anaesthesia or local anaesthetic infiltration, that is with no or little systemic resorption of local anaesthetics (cataract and ocular surgery, dental extractions, extracorporeal shock-wave lithotripsy, angiography, cosmetic surgical procedures, \textit{in vitro} fertilization procedures, etc.).

In this study, patients only received propofol without upper airway instrumentation. Our findings can therefore not be extrapolated to other anaesthetic protocols using different anaesthetic agents or airway manipulation, as opioids, volatile agents, and muscle relaxants impair upper airway function.\(^{18}\) Similarly, upper airway reflexes are depressed after tracheal intubation or laryngeal mask airway insertion.\(^{19,20}\) We chose not to insert a laryngeal mask airway or a tracheal tube because that is not the usual practice in our Institution. The patients in this study were young non-smoking patients and the procedure was a colonoscopy, which does not interfere with lung function. In contrast, patients with abnormal upper airway function, for example diabetic patients, smokers or elderly, may have a different postoperative course.\(^{21,23}\) However, these conditions are associated with an increase of the cough reflex threshold. If we had included these patients, we may have overlooked an increase of the cough reflex threshold caused by low propofol concentrations because of the high basal threshold of the patients. The surgical procedure may also influence the cough threshold, as described after upper abdominal surgery.\(^8\)
Measurement of the cough threshold evoked by a tussive agent like citric acid is the gold standard for assessing the cough reflex sensitivity. It has been used to assess the effect of many conditions on this reflex, for example asthma,24 smoking,22 chronic obstructive lung disease,25 or diabetes.21 It is also routinely used to test the efficacy of anti-tussive drugs.9 Capsaicin is the other tussive agent used in cough challenge. Theoretically, the results may have been different if capsaicin had been used instead of citric acid. However, this is probably not the case. Indeed, dose–response curves to citric acid and capsaicin are similar in humans.26 Moreover, studies that have used both citric acid and capsaicin as tussive agent in serial cough challenges have shown similar evolution of the cough reflex threshold whatever the tussive agent used.8

In conclusion, propofol concentrations observed during recovery from general anaesthesia for colonoscopy and associated sedation do not appear to adversely affect the cough reflex.

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References

Appendix
Assessment categories included in the OAA/S.10

<table>
<thead>
<tr>
<th>Score</th>
<th>Reactivity</th>
<th>Speech</th>
<th>Face expression</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Response readily to name spoken in normal tone</td>
<td>Normal</td>
<td>Clear, no ptosis</td>
<td>Glazed and marked ptosis</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to name spoken with a normal tone</td>
<td>Mild slowing or thickening</td>
<td>Glazed or mild ptosis</td>
<td>Glazed and marked ptosis</td>
</tr>
<tr>
<td>3</td>
<td>Responds only after name is called loudly and/or repeatedly</td>
<td>Slurring or prominent slowing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Response after gentle hand stimulation</td>
<td>Mild relaxation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Responds only after mild prodding or shaking</td>
<td>Few recognizable words</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Does not respond to mild prodding or shaking</td>
<td></td>
<td></td>
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</tbody>
</table>