Effects of EDTA- and Sulfite-containing Formulations of Propofol on Respiratory System Resistance after Tracheal Intubation in Smokers

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Background: The formulation of sulfite-containing propofol (SCP) has not been thoroughly investigated in patients with the extensive smoking history for the effects on the total respiratory system resistance after tracheal intubation. However adverse effects, including acute asthma and bronchospasm, have been reported with several other parenteral formulations of drugs containing sulfite as preservative. Therefore, the aim of this prospective randomized and double-blind study was to investigate the effects of EDTA-containing propofol (ECP) and SCP on the total respiratory system resistance (Rrs) in patients with the prolonged smoking history and undergoing propofol-based total intravenous anesthesia with tracheal intubation.

Methods: 40 patients scheduled for general anesthesia were enrolled into the study. Anesthesia was induced with either 2 mg/kg ECP, or 2 mg/kg SCP followed by vecuronium (0.1 mg/kg) to ensure complete neuromuscular relaxation for the time of the study. Maintenance anesthesia was continued with propofol infusion at 0.15 mg/kg/min for the first 15 min after intubation. Total respiratory system resistance (Rrs), was measured continuously for 10 min postintubation.

Results: The analysis of repeated Rrs measurements taken every minute for 10 min postintubation revealed trend consisting of higher Rrs in the SCP group when compared to the ECP group. The statistical analysis of the data performed using repeated measures analysis of covariance demonstrated statistically significant effect (P < 0.05) of the treatment group factor (SCP vs. ECP) and the time factor (time after intubation) on the postintubation Rrs.

Conclusion: The total respiratory system resistance measured repeatedly for 10 min after tracheal intubation in patients with smoking history is significantly elevated after induction with SCP than after induction with ECP. The preservative used for propofol formulation may alter the effects of propofol on the total respiratory system resistance in smokers.

Patients with the extensive smoking history and undergoing general anesthesia are at increased risk for reversible bronchoconstriction and bronchospasm in response to tracheal intubation.1–4 The formulations of propofol containing EDTA (ECP) or propofol without preservatives (widely available outside of US) have been reported previously to offer more protection against tracheal intubation-induced bronchoconstriction than other induction agents (i.e., thiopental and etomidate).5–11 Previous study using wheezing as an end point found that tracheal intubation after induction of asthmatic patients with propofol (with or without EDTA as preservative) did not produce any cases of wheezing compared with other induction agents suggesting that propofol might be a better choice for reducing postintubation bronchospasm.12

The effect of the formulation of sulfite-containing propofol (SCP) on the respiratory resistance after tracheal intubation in smokers has not been fully investigated. However, adverse reactions, including acute asthma and bronchospasm have been reported with several other drugs containing sulfite as preservative. Sulfite sensitivity in the form of bronchospasm is known to occur in the population of patients with reactive airways and bronchoconstriction was reported previously after inhalation, enteric or intravenous administration of sulfite containing products.13–25 Furthermore, a recent study investigating airway resistance in sheep after metacholine challenge and propofol anesthesia showed that SCP does not attenuate the induced airway constriction in contrast to EDTA-containing propofol.6 On the other hand, recent preliminary report by Navanni et al.,26 produced no evidence for the differences in attenuation of intubation-induced bronchoconstriction between limited number of patients induced with sodium thiopental, ECP, and SCP for anesthesia induction.

In view of these data, it seems reasonable to investigate the effects of ECP and SCP on post-tracheal intubation respiratory resistance in larger group of patients. The goal of the present study was to investigate in a prospective, randomized and double-blinded fashion the comparative effects of ECP and SCP anesthesia on the respiratory system resistance in patients at risk for intubation-induced bronchospasm and undergoing general anesthesia with tracheal intubation.

Methods

The Institutional Review Board at the Vanderbilt University Medical Center approved the study protocol and written informed consent was obtained from patients undergoing general anesthesia requiring tracheal intubation for elective surgery. The study population included patients classified as American Society of Anesthesiologists status 2–3. Only patients with reactive airways secondary to a long history of cigarette smoking (>1 pack/day, >5 yr) were enrolled into the study. All patients were actively smoking at the time of the investigation.
Patients with unstable cardiac or pulmonary disease, requiring rapid sequence intubation, patients under the age of 18 or geriatric patients above 80 yr of age, patients with sulfite allergy or treated with steroids or cholinolytics during the immediate perioperative period or in whom the protocol was otherwise deemed unsuitable by the primary anesthesiologists, were excluded from the study. After obtaining informed consent, the patients were assigned to receive 1% injectable emulsion of either ECP (Diprivan®, containing 0.005% of disodium edetate, manufactured for AstraZeneca Pharmaceuticals Ltd, Wilmington, DE, by AstraZeneca S.p.A., Caponago, Italy) (n = 20) or SCP (containing 0.25 mg/ml of sodium metabisulfite, manufactured for Baxter Healthcare Corporation, Deerfield, IL, by Gensia Sicor Pharmaceuticals, Irvine, CA) (n = 20). Propofol formulations (originally provided in 50 ml vials) were randomized, blinded, and dispensed in the opaque 50-ml syringes by the local hospital research pharmacy. Premedication with midazolam (0.04 – 0.05 mg/kg) was allowed. General anesthesia was induced with the investigated propofol 2 mg/kg bolus and fentanyl 0.002 mg/kg followed by vecuronium 0.1 mg/kg to accomplish muscle relaxation for the duration of the study. Intravenous injection of lidocaine (before or throughout propofol injection) was not used. Anesthesia was maintained with the same propofol formulation as used for induction at 0.15 mg · kg\(^{-1}\) · min\(^{-1}\) and supplemented by fentanyl (0.002 mg · kg\(^{-1}\) · h\(^{-1}\)).

Prior to tracheal intubation, complete muscle paralysis was confirmed using a nerve stimulation (train-of-four) of the ulnar nerve. All patients were intubated with a 7.5-mm endotracheal tube (ETT). The ETT was secured at 21 cm in women and at 23 cm in men. Correct placement of the ETT was confirmed by the presence of EtCO\(_2\) on the capnograph and auscultation of equal bilateral breath sounds. Mechanical ventilation was started immediately after intubation with 50% oxygen, using tidal volumes of 10 ml/kg at 10 breaths/min, inspiratory:expiratory ratio (I:E) 1:1.5, and using square form inspiratory flow from Ohmeda Anesthesia Ventilator (Datex-Ohmeda, Madison, WI). These settings were maintained for the duration of the study. The presence or absence of clinical signs of bronchospasm (by auscultation) was also noted preoperatively, pre- and postintubation by an anesthesiologist blinded to the investigated propofol formulation.

The respiratory measurements were obtained using the noninvasive cardiac output monitor NICO\(_2\)® System (Novametrix Medical Systems, Wallingford, CT) containing the respiratory profile module identical to the CO\(_2\)SMO® and VenTrak® lung mechanics analyzers from the same manufacturer, extensively investigated previously in the area of lung research.\(^{27}\) Measurements were obtained by inserting the disposable flow/pressure adapter probe between the ETT outlet and the ventilator Y tubing, and included total respiratory system resistance (Rrs), peak inspiratory pressure (PIP), and dynamic compliance (Cdyn) obtained from the continuously recorded flow-volume loops. Heart rate, noninvasive blood pressure, and pulse oximetry (SpO\(_2\)) were also recorded.

Flow and pressure measurements in the NICO\(_2\)® monitor are made by a fixed orifice differential pressure pneumotachometer. The NICO\(_2\)® monitor software compensations allow accurate flow and volume measurements, thus gas density and viscosity do not cause significant errors in flow measurement. The least-squares fitting method for calculating of Rrs has been used by the NICO\(_2\)® system and it is based on the measurement of patient airflow, volume and airway pressure, as specified by the manufacturer.\(^{28,29}\) Briefly, the least squares fitting method assumes a specific model for the respiratory system and fits the waveform data to that model expressed by equation:

\[
dP = RF + V/C
\]

where \(dP\) is the pressure difference, \(R\) is respiratory resistance, \(F\) is airway flow, \(V\) is volume sample and \(C\) is compliance term. The \(dP\) is the pressure relative to a baseline level. The pulmonary end-expiratory pressure (PEEP) of the prior breath is used as the baseline level. The least square method minimizes the sum of squares between the observed pressure (\(dP_{observed}\)) and the best fit curve, \(dP_{bestfit}\):

\[
S = \text{Sum}(dP_{bestfit} - dP_{observed})^2
\]

To minimize the error between the best fit and observed pressures, the partial derivatives of \(S\) respective to \(R\) and \(C\) are computed, set to 0 and solved for \(R\) and \(C\). This results in expressions for \(R\) and \(C\) consisting of cross-products of volume and flow, pressure and volume and flow themselves. The summations of these cross-products are accumulated throughout the inspiratory and expiratory portions of the breath from which dynamic compliance and resistance values are calculated. These calculations that are computationally intensive for a microprocessor-based system are computed real-time throughout the breath cycle using running summations.

The NICO\(_2\)® system was connected through the serial port to personal computer allowing data collection of all respiratory parameters at an average of 6 s. Means were calculated for every parameter by averaging 10 single data (60 s period) at 1 min through 10 min postintubation.

The primary outcome from this study includes Rrs after tracheal intubation in the investigated groups. The secondary outcomes include PIP, Cdyn and the incidence of wheezing after induction and intubation. The format of the study was expressed by two hypotheses: the null hypothesis (H0), which states that there is no statistically significant difference in the postintubation Rrs among the two groups and the alternate hypothesis (Ha), which states that there is a difference. A minimum
sample size of 20 patients in each group (40 patients total) was calculated as needed to be enrolled and analyzed to detect a clinically relevant difference in the primary outcome of Rrs according to the power analysis based on the following parameters: type II error rate ($\beta = 0.15$), type I error rate ($\alpha = 0.05$), difference in the population means ($\delta = 4$ mmHg $\cdot$ l$^{-1}$ $\cdot$ sec$^{-1}$), within group SD ($\sigma = 4$ mmHg $\cdot$ l$^{-1}$ $\cdot$ sec$^{-1}$). Categorical data were compared using Fischer exact test. A repeated measures analysis of covariance procedure was used to examine differences between the treatment groups over time. The analysis is an extension of a general linear model. The test statistics was adjusted for the repeated measures over subjects that introduce a new source of variability (within subject variability). This model allows for the formation of the variance-covariance matrices consisting of the within subject (repeated measures) and between subject sources of variance (treatment group). The model, as we specified it, fit an overall line for each treatment group including a term for treatment group, and a treatment group by time interaction term. Using this specification, the group by time interaction can be looked at as the slope of the response variable over time for each group, and the group term can be looked at as the intercept (also interpreted as the “mean of the outcome”) for each group. These analyses were performed using the SAS statistical package (SAS Institute, Cary, North Carolina) and utilized the mixed model procedure (Proc Mixed) described by Little et al. A $P$ value less than 0.05 was considered statistically significant and chosen for rejection of the null hypothesis.

Results

The patients’ demographics are shown in table 1. There were no significant differences between the two groups regarding age, sex, weight, height, ASA classification, proportion of smokers, pack-years (PPY) smoked, or any other analyzed demographic parameters. No statistically significant differences in the noninvasive blood pressure, heart rate, $SO_2p$, and temperature were noted between the study groups at any time during the study period (preoperatively, immediately after induction and for 10 min period after intubation, data not shown). The end-tidal carbon dioxide concentrations were similar before induction and did not differ between treatment groups during any recording period during the 10 min study period (average end-tidal carbon dioxide $30 \pm 4$ mmHg and $31 \pm 3.5$ mmHg for ECP and SCP induction, respectively). The duration of time from induction to intubation was similar in both treatment groups, $4.5 \pm 0.6$ and $4.3 \pm 0.5$ min, for ECP and SCP groups, respectively.

Figure 1 shows the mean airway resistance (Rrs) calculated for each study group at 1 min through 10 min postintubation. The repeated Rrs measurements for the next 10 min revealed trend consisting of higher Rrs for both groups over time ($P = 0.0294$) but the slopes are essentially equal ($P = 0.4991$), as determined by estimating and testing the group variable in the model. There was also significant decrease in mean Rrs for both groups over time ($P = 0.0437$); this was based on estimating and testing the group variable in the model. There was more variation between subjects in the SCP treatment group, compared with the ECP group. Figure 2 shows the generalized least squares fitted lines for the two treatments over time. The repeated measures analysis of covariance found that there is a statistically significant difference in intercepts between the two treatment groups ($P = 0.0013$); this was based on estimating and testing the group variable in the model. There was also significant decrease in mean Rrs for both groups over time ($P = 0.0294$) but the slopes are essentially equal ($P = 0.4991$), as determined by estimating and testing the group by time interaction. There was more variation between subjects in the SCP treatment group, compared with the ECP group ($\sigma_{B\text{-SCP}}^2 = 36.7111$ vs. $\sigma_{B\text{-ECP}}^2 = 47.7633$); the correlation of the measurements for individuals (that is, how similar were the measurements taken

Table 1. Summary of the Demographic Characteristics of the Patients

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Propofol-EDTA ($n = 20$)</th>
<th>Propofol–Sulfite ($n = 20$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>45.2 ± 13.7</td>
<td>47.8 ± 13.4</td>
</tr>
<tr>
<td>Sex (M/F), n</td>
<td>11/9</td>
<td>12/8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171.1 ± 9.7</td>
<td>174.1 ± 11.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84.8 ± 14.6</td>
<td>79.4 ± 16.2</td>
</tr>
<tr>
<td>ASA physical status (II/III), n</td>
<td>12/8</td>
<td>12/8</td>
</tr>
<tr>
<td>Medical history, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker &gt; 1 PPD</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>PPY smoking history (5–10/10–20/&gt;20/&gt;40)</td>
<td>2/5/9/4</td>
<td>1/4/10/5</td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Recent upper respiratory infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>COPD/bronchitis symptoms</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Seizure</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Albuterol/Combivent inhaler (as needed only), n</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; PPD = (cigarette) packs per day; PPY = (cigarette) packs per year.
on each subject over time) was very similar for both treatments ($\rho_{\text{SCP}} = 0.8987$ and $\rho_{\text{ECP}} = 0.9056$).

Postinduction wheezing was found (by auscultation during mask ventilation) in 3 patients, from which 2 were induced with SCP and 1 with ECP. Five patients showed wheezing postintubation, from which one patient remained wheezing in ECP group and 4 patients had wheezing in SCP group.

Despite statistically significant differences in the postintubation Rrs, only slight differences in the PIP values were recorded between the study groups (data not shown). The PIP values were about 10% higher in SCP group at 2 and 5 min after intubation, and these differences were not statistically significant ($P > 0.05$). No statistically differences ($P > 0.05$) in the Cdyn measurements were recorded in both investigated groups during 10 min after intubation (data not shown).

**Discussion**

Our results demonstrate that tracheal intubation in smokers after induction and maintenance of anesthesia with SCP produces higher postintubation Rrs than when ECP was used. This effect was found immediately (1 min) after intubation and lasted for at least 10 min. After statistical analysis of the data with repeated measures ANOVA it is concluded that both analyzed variables: treatment group factor (i.e., SCP vs. ECP) and time (i.e., time after intubation) significantly affected the overall Rrs in investigated subjects.

In the reported investigations we used the pneumotachometric technique to measure Rrs throughout the duration of the study. The measurement of Rrs includes, besides airway caliber associated resistance, components of resistance related to the chest wall, and addi-
tional components of lung resistance related to lung parenchyma. The inclusion of other components might make this parameter a less sensitive index to changes in airway caliber. Our measurements of respiratory resistance levels were however comparable with those of other studies and similar study populations.8,27,31 Our findings support the investigation of Brown et al.6 who showed that the change in the formulation of propofol abolishes the attenuation of induced bronchoconstriction in sheep model. In contrast to their study, our results revealed significant differences in the respiratory resistance after intubation and anesthesia induction with SCP compared to ECP, whereas Brown et al.6 found that SCP caused only a slight but not significant increase in Rrs to methacholine-induced bronchoconstriction; however, ECP attenuated methacholine-induced bronchoconstriction.

The effects of propofol on attenuation of airway muscle contraction induced by intubation or exposure to variety of physical and chemical factors have been confirmed in several in vitro studies,10,32 as well as studies in animals5,6 and humans.7–11 As shown in previous in vitro studies,10 propofol is able to inhibit Ca2+ release from intracellular stores and also attenuates Ca2+ influx via voltage dependent channels. In addition, in vitro propofol has been shown to produce relaxation of tracheal smooth muscle with spontaneous tone or contraction induced by acetylcholine, carbachol, histamine, prostaglandin F2α, and potassium.10,15 Our results are consistent with these previous studies in that they demonstrate that ECP, but not SCP, was able to attenuate intubation-induced bronchoconstriction.

Sulfite sensitivity in the form of bronchospasm and asthma is known to occur in the population of patients with reactive airways, and bronchoconstriction was reported previously after inhalation, enteric or intravenous administration of sulfite-containing products.13–25 The incidence of true sulfite allergy is estimated at 1/1000 patient.33 Sulfite-sensitive patients with asthma will not necessarily react after ingestion of sulfite containing food or drugs.22,23 However, it has also been shown that nonsulfite sensitive patients with asthma have a high incidence of bronchospasm after a metabisulfite challenge test.22

A number of studies have indicated that 5–10% of all chronic asthmatics are sulfite hypersensitive.17 Incidence of metabisulfite-induced bronchospasm in patients with reactive airways secondary to a long history of smoking has never been investigated. Eames et al.8 measured the airway resistance in response to intubation after induction with different anesthetics. The groups were subdivided into smokers and nonsmokers. Smokers showed a greater Rrs overall with a significant difference between propofol and other anesthetics. There was no significant difference among nonsmokers.

Based on the presented data we can consider that susceptibility to sulfite preservative in propofol is increased in at least some patients with previously altered tracheobronchial systems (e.g., asthma or history of smoking). The exact mechanism of sulfite-induced bronchoconstriction is unknown and might include: 1) IgE-mediated antigen reaction22; 2) Nonreaginic anaphylactoid reactions, caused when sulfite is combined with membranes of mast cells and basophiles22; and 3) Activation of tracheobronchial irritant receptors and stimulation of a cholinergic reflex.33 It is unclear at the present time which of the above mechanisms might be responsible (if any) for the increased total respiratory

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Fig. 2. The individual data points representing summarized interval total respiratory system resistance measurements (Rrs, in cm H2O · l-1 · sec-1) over 1 min period for each patient in groups obtaining EDTA-containing propofol (ECP) and sulfite-containing propofol (SCP). The lines represent fitted generalized linear least squares solution for ECP (dotted line) and SCP (solid line) treatment groups over time. The intercept is an overall mean for each treatment group.
system resistance after tracheal intubation in patients anesthetized with SCP. The other hypothesis implicates the adverse respiratory effects of some secondary products of propofol, metabisulfitite, and lipids present in the SCP preparation. It was reported previously that metabisulfitite content in the intralipid vehicle of propofol might promote formation various toxic oxidative metabolites of lipids, including malondialdehyde (MDA), and promote oxidative stress response. 54–56 The hypothetical role of the sulfitite and/or other potentially toxic compounds in the SCP solution in the mechanism of the observed adverse pulmonary effect remains to be elucidated.

In summary, SCP significantly increases intubation-induced bronchoconstriction in patients with a long history of smoking when compared to induction of general anesthesia with ECP. The clinical significance of this effect is uncertain and requires further investigations.

References
36. Baker MT: Thiobarbituric Acid reactive substances (Malondialdehyde) in metabisulfitite containing propofol emulsion (abstract). Anesthesiology 2001; 95(suppl):A503