Comparison of the Effects of Etomidate, Propofol, and Thiopental on Respiratory Resistance after Tracheal Intubation

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Background: Tracheal intubation frequently results in reversible bronchoconstriction. Propofol has been reported to minimize this response in healthy patients and in asthma patients, but may be unsuitable for hemodynamically unstable patients for whom etomidate may be preferable. The current study examined respiratory resistance after tracheal intubation after induction with either thiopental, etomidate, or propofol. A supratherapeutic dose of etomidate was used to test the hypothesis that the bronchoconstrictive response could be minimized by deep intravenous anesthesia.

Methods: Seventy-seven studies were conducted in 75 patients. Anesthesia was induced with either 2.5 mg/kg propofol, 0.4 mg/kg etomidate, or 5 mg/kg thiopental. Respiratory resistance was measured at 2 min after induction.

Results: Respiratory resistance at 2 min was 8.1 ± 3.4 cmH₂O·L⁻¹·s (mean ± SD) for patients receiving propofol versus 11.3 ± 5.3 for patients receiving etomidate and 12.3 ± 7.9 for patients receiving thiopental (P < 0.05 for propofol vs. either etomidate or thiopental).

Conclusions: Respiratory resistance after tracheal intubation is lower after induction with propofol than after induction with thiopental or after induction with high-dose etomidate.

(Key words: Anesthetics, intravenous: etomidate; propofol; thiopental. Intubation: intratracheal. Lungs: bronchial hyperreactivity.)

WHETHER performed in the awake patient or after induction of anesthesia, tracheal intubation often causes bronchoconstriction with a measurable increase in resistance of the respiratory system.¹⁻³ This constrictive response presumably is initiated by activation of abundant laryngeal and tracheal receptors with reflex constriction of the peripheral airways.

A recent study using wheezing as an end point found that tracheal intubation after induction of asthmatic patients with propofol did not produce any cases of wheezing compared with a 27% incidence after induction with a thiobarbiturate and 13% with an oxybarbiturate,⁴ suggesting that propofol might be a better choice than a barbiturate for limiting bronchoconstriction.

We assessed respiratory resistance (Rₚ₀) in a nonasthmatic patient population with a high incidence of smoking, and compared thiopental, etomidate, and propofol. Etomidate was studied for several reasons. It often is the drug of choice for hemodynamically unstable patients, it has been suggested as a useful induction agent for asthmatic patients⁵ and it is advertised as "the choice for your patients compromised by asthma and other reactive airway disease."⁶

We hypothesized that Rₚ₀ after induction of anesthesia with a thiobarbiturate would be greater than Rₚ₀ after induction with propofol. We also hypothesized that using high-dose etomidate would result in a lower Rₚ₀ than when a thiobarbiturate was used.

To test these hypotheses, anesthesia was induced with either propofol, etomidate, or thiopental, and Rₚ₀ was measured after intubation.

Methods

The protocol was approved by the Human Subjects Committee of the University of Washington School of Medicine and the Seattle Veterans Affairs Medical Center and informed consent was obtained from patients un-
dergoing general anesthesia and tracheal intubation for elective, noncardiac surgery. Two patients were studied twice. Reasons for patient exclusion were unstable cardiac or pulmonary disease, current treatment with corticosteroids, bronchodilator use within 12 h of induction, or if the protocol was otherwise deemed unsuitable by the primary anesthesiologist.

Patients were randomized to receive either thiopental (n = 31), etomidate (n = 23), or propofol (n = 23) by random envelope withdrawal. Two patients who had previously been randomized were studied a second time with the original drug excluded from the randomization envelope. This resulted in 75 patients who underwent 77 total studies. Five additional patients were excluded before the first measurement because of difficult intubation (>5 min delay) or other violation of protocol.

Before surgery, the peak expiratory flow was measured while the patient was sitting upright. Three successive efforts were observed and the best result recorded. Peak expiratory flow was not measured in five patients who either were unable to cooperate because of abdominal pain or could not form a mouth seal around the tube. Normalized peak expiratory flow was calculated as a percentage of the predicted value based on age and height. Anesthetic premedication and bronchodilators were excluded with the exception of 2 μg/kg fentanyl, which was given shortly before induction. Anesthesia was induced with 5 mg/kg thiopental, 0.4 mg/kg etomidate, or 2.5 mg/kg propofol, and patients were paralyzed with 1.5 mg/kg succinylcholine. Vecuronium (0.1 mg/kg) was used in two patients for whom succinylcholine was contraindicated. Before injection of propofol, up to 20 mg lidocaine was injected into the vein with proximal occlusion of the vein to minimize injection pain.

Tracheal intubation was accomplished with a 7.5-mm (n = 5) or 8-mm (n = 74) uncut endotracheal tube. The ventilator was set for eight breaths/min at a tidal volume of 10 ml/kg with I:E ratio of 1:3, and inspiratory flow of 0.5–0.7 l/s. The resistance measurement was made immediately after intubation (2 min after induction). Mean blood pressure and pulse were noted (Dinamap, Critikon, Tampa, FL). Postintubation whooping was assessed for the final 58 of the 77 studies by auscultation by the primary anesthesiologist, who was not blinded to the induction agent.

Respiratory resistance was measured by the isovolume method7 at 500 ml above functional residual capacity. Before each study, a Datex Ultima Capnomac spirometer (Datex Instrumentation, Helsinki, Finland) was calibrated for volume using a 1-l syringe (Hans Rudolph, Kansas City, MO). The ventilatory flow and pressure curves were sampled at 10-ms intervals, output to a personal computer, and the volume curve then determined by integration of the flow curve. The pressure drop across the endotracheal tube was excluded by first constructing a pressure-flow curve for both the 7.5-mm and 8-mm endotracheal tubes. For each measurement, the pressure drop across the tube for the flow noted was subtracted from the pressure measurements used during calculation, resulting in a value for Rn exclusive of the endotracheal tube. The isovolume method of resistance measurement is a technique applicable to mechanically ventilated patients and is based on measuring airway pressure and flow at identical volumes during inspiration and exhalation. Inspiratory pressure (Pi) is a function of respiratory compliance (C), inspiratory flow (Fi), and resistance (R). Expiratory pressure (Pe) is a function of respiratory compliance (C), expiratory flow (Fe) and resistance (R). Using V to represent lung volume above functional residual capacity, the equations are:

\[ Pi = V/C + R\cdot Fi \]
\[ Pe = V/C - R\cdot Fe \]

Subtracting these two equations yields:

\[ Pi - Pe = R\cdot (Fi + Fc) \text{ or } R = (Pi - Pe)/(Fi + Fc) \]

This method measures a value of \( R_n \) that reflects a mean resistance at a given lung volume during both inhalation and exhalation.

Comparisons among the three patient groups were made with analysis of variance plus post hoc testing with the Student-Newman-Keuls multiple comparison test. If the data failed normality tests, the Kruskal-Wallis analysis of variance for nonparametric data was applied with between group comparisons performed using the Mann-Whitney U test.

A level of \( P \leq 0.05 \) was chosen for rejection of the null hypothesis for all tests. Data are presented as mean ± SEM in figures and as mean ± SD in tables.

**Results**

Patient demographics are shown in table 1. There were no significant differences among the three groups in age, sex, weight, height, normalized peak expiratory flow, proportion of smokers, or pack-years smoked. Smokers’ and nonsmokers’ peak expiratory flow as a percent of normal did not differ significantly (89 ± 20% vs. 81 ± 25%, \( P = 0.24 \)). Former smokers were
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Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Propofol (n = 23)</th>
<th>Thiopental (n = 31)</th>
<th>Etomidate (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54 ± 14</td>
<td>55 ± 14</td>
<td>54 ± 15</td>
</tr>
<tr>
<td>Female/male</td>
<td>2/21</td>
<td>3/28</td>
<td>2/21</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>180 ± 8</td>
<td>177 ± 6</td>
<td>177 ± 8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83 ± 19</td>
<td>85 ± 16</td>
<td>85 ± 19</td>
</tr>
<tr>
<td>Smokers/nonsmokers</td>
<td>16/6</td>
<td>22/8</td>
<td>18/5</td>
</tr>
<tr>
<td>Smoking (pack/years)</td>
<td>42 ± 25</td>
<td>35 ± 31</td>
<td>44 ± 29</td>
</tr>
<tr>
<td>Peak expiratory flow (% predicted)</td>
<td>84 ± 21</td>
<td>87 ± 21</td>
<td>77 ± 29</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

classified as smokers. Pack-years did not differ between current and former smokers (42 ± 32 vs. 36 ± 20). Heart rate and blood pressure were similar in the three groups, with the exception of a higher blood pressure in the etomidate group compared to the thiopental or propofol groups at the time of the postintubation measurement (table 2).

Figure 1 shows the resistance measured for each patient after induction. The propofol group showed significantly lower mean Rns (8.1 ± 3.4 cmH2O·l−1·s; mean ± SD) than either the etomidate (11.3 ± 5.3, P = 0.05) or thiopental (12.3 ± 7.9, P < 0.01) groups. Clinically wheezing patients among those examined within the first 10 min after induction are highlighted in figure 1 with 2 of 22 (thiopental), 3 of 18 (etomidate), and 0 of 18 (propofol) in each group (P = 0.14 by Fisher’s exact test for propofol vs. thiopental and etomidate groups combined).

Of the two patients who were each studied twice, one received propofol and thiopental, and one propofol and etomidate. There was no difference in Rns after intubation between the propofol and etomidate trials.

The patient who received propofol and thiopental developed Rns of 5.7 cmH2O·l−1·s with propofol and 11.8 cmH2O·l−1·s with thiopental.

Normalized peak expiratory flow correlated with postinduction Rns in the etomidate (r = −0.61, P = 0.002) and thiopental (r = −0.40, p = 0.03) groups but did not correlate in the propofol group (r = −0.14, P = 0.56).

Table 2. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Propofol (n = 23)</th>
<th>Thiopental (n = 31)</th>
<th>Etomidate (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mmHg), baseline</td>
<td>101 ± 13.4</td>
<td>102 ± 17.2</td>
<td>106 ± 15.3</td>
</tr>
<tr>
<td>Heart rate (beats/min), baseline</td>
<td>71 ± 12</td>
<td>67 ± 11</td>
<td>64 ± 8</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg), 2 min</td>
<td>96 ± 26*</td>
<td>108 ± 25*</td>
<td>129 ± 27</td>
</tr>
<tr>
<td>Heart rate (beats/min), 2 min</td>
<td>81 ± 16</td>
<td>80 ± 16</td>
<td>76 ± 15</td>
</tr>
</tbody>
</table>

Data are mean ± SD.* P < 0.05 versus etomidate.

Fig. 1. Respiratory resistance of all subjects after tracheal intubation. The solid squares represent the four patients in whom audible wheezing was present. Auscultation was performed in only 58 of the 77 studies.

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Figure 2 shows $R_e$, at 2 min with the study population divided into nonsmokers ($n = 20$) and smokers (present or past, $n = 57$). Smokers showed a greater $R_e$, overall with a clear difference between propofol and etomidate or thiopental. There were no significant differences among nonsmokers.

Discussion

The important finding of this study is that tracheal intubation with propofol anesthesia produces lower $R_e$ than when thiopental or a relatively high dose of etomidate is used. Because we do not have measurements of $R_e$ before intubation, we cannot rule out the possibility that etomidate and thiopental increased resistance whereas propofol left resistance unchanged. The different techniques required to measure resistance in the awake versus the anesthetized patient prevent direct comparisons of preintubation and postintubation $R_e$.

Our findings confirm the findings of Pizov et al., who found less wheezing after induction with propofol than with an oxybarbiturate or thiobarbiturate. Our study extends their findings to a group of patients that included 74% smokers. Our study included more than 90% males whereas Pizov et al. studied primarily women, with a high number of asthmatic patients.

We also studied etomidate for several reasons. Unlike the barbiturates, etomidate has never been reported to have any bronchoconstricting activity. It actually has been suggested as a suitable drug for asthmatic patients based on in vitro studies showing that althesin but not etomidate produced histamine release from basophils of asthmatic patients and is advertised by the manufacturer as a drug of choice for patients with reactive Airways. Etomidate also is frequently a drug of choice in patients with impaired ventricular function for whom hemodynamic stability may be especially important. Finally, etomidate can be safely administered at higher doses than routinely used for induction in an effort to maximize anesthetic depth and thus, hopefully, minimize bronchoconstriction. A dose of 0.4 mg/kg will produce plasma concentrations in excess of those required for induction of surgical anesthesia. However, our results show no difference from thiopental, even with a relatively large dose.

Our study also supports the study of Prien, who reported that for 36 patients under general anesthesia, respiratory impedance measured before and after placing patients in lithotomy position increased with thio-
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We gave 2 ml 1% lidocaine before propofol injection to minimize pain on injection. While lidocaine has been reported to limit airway reactivity as measured by cough, the dose required was a minimum of 1.5 mg/kg, suggesting that lidocaine was not a major contributor to the difference among groups.

The mechanism of propofol’s relative bronchodilating effect is unknown. Our study argues against the hypothesis previously put forward that the effect is simply related to the sedative effects of propofol because a high dose of etomidate did not achieve the same effect. Another hypothesis proposes that propofol may interfere with calcium flux. However, in vitro, the concentrations of propofol required exceed those seen clinically and propofol and thiopental are both capable of interfering with calcium flux, making this an inadequate explanation for the differing effects of the two drugs. The mechanism thus remains to be elucidated.

References