Effect of prophylactic bronchodilator treatment with i.v. carperitide on airway resistance and lung compliance after tracheal intubation

Z. Wajima¹*, T. Shiga¹, K. Imanaga¹, T. Inoue¹ and R. Ogawa²

¹Department of Anaesthesia, Chiba-Hokusoh Hospital, Nippon Medical School, 1715 Kamagari, Inba-mura, Inba-gun, Chiba 270-1694, Japan. ²Department of Anaesthesiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan

*Corresponding author. E-mail: HFB01245@nifty.com

Background. Lung resistance increases after induction of anaesthesia. We hypothesized that prophylactic bronchodilation with i.v. carperitide before tracheal intubation would decrease airway resistance and increase lung compliance after placement of the tracheal tube in both smokers and nonsmokers.

Methods. Ninety-seven adults aged between 24 and 59 yr were randomized to receive i.v. normal saline (0.9% saline) (control) or carperitide, 0.2 µg kg⁻¹ min⁻¹ throughout the study. The 97 patients included smokers and nonsmokers. Thus the patients were allocated to one of the four groups: smokers who received normal saline (n=21), nonsmokers who received normal saline (n=27), smokers who received carperitide (n=19) or nonsmokers who received carperitide (n=30). Thirty minutes after starting normal saline or carperitide infusion, we administered thiamylal 5 mg kg⁻¹ and fentanyl 5 µg kg⁻¹ to induce general anaesthesia and vecuronium 0.3 mg kg⁻¹ for muscle relaxation. Continuous infusion of thiamylal 15 mg kg⁻¹ h⁻¹ followed anaesthetic induction. Mean airway resistance (Rₐₚ), expiratory airway resistance (Rₑₚ) and dynamic lung compliance (Cₑₚ) were determined 4, 8, 12 and 16 min after tracheal intubation and compared between the four groups.

Results. At 4 min after intubation, Rₐₚ and Rₑₚ were higher and Cₑₚ lower in smokers than in nonsmokers in the control group. Rₐₚ and Rₑₚ were lower and Cₑₚ higher in smokers in the carperitide group than in smokers in the control group. Rₐₚ and Rₑₚ were lower in nonsmokers in the carperitide group than in nonsmokers in the control group.

Conclusions. Marked bronchoconstriction occurred in the control groups (smokers and nonsmokers) 4 min after tracheal intubation. Prophylactic treatment with carperitide before induction of anaesthesia and tracheal intubation was advantageous, particularly in smokers.

Br J Anaesth 2006; 96: 660–9

Keywords: anaesthetic techniques, tracheal intubation; complications, bronchospasm; pharmacology, carperitide

Accepted for publication: January 23, 2006

After induction of anaesthesia, tracheal intubation often causes increased lung resistance (bronchoconstriction).¹⁻³ This response is presumably initiated by activation of abundant laryngeal and tracheal receptors with reflex constriction of the peripheral airways.² We hypothesized that prophylactic bronchodilator treatment with i.v. carperitide, a recombinant form of α-human atrial natriuretic peptide (α-hANP), with a bronchodilating effect in animals,⁴ asthmatic patients⁵⁻⁷ and healthy individuals,⁸ before tracheal intubation would result in decreased airway resistance and increased lung compliance after placement of the tracheal tube. Atrial natriuretic peptide (ANP) is a 28-amino-acid hormone secreted by the cardiac atria and isolated lung tissue that has vasodilator, natriuretic and diuretic properties.⁹

In previous studies, we used thiamylal and fentanyl to facilitate bronchoconstriction.¹⁰⁻¹² In addition, we believe any case involving anaesthesia induction with thiamylal and fentanyl and tracheal intubation to be at risk of bronchoconstriction.¹³ In the present study, we used this ‘model of
bronchoconstriction' to examine the effects of pretreatment with carperitide in both smokers and nonsmokers.

**Methods**

After obtaining approval from the local institutional review board and written informed consent from patients, 97 ASA I or II adult patients undergoing minor elective surgery were enrolled in the study. Patients with a clinical or radiological abnormality of respiratory system or suspected (history of atopy) or overt (history of wheezing) bronchial hypersensitivity and those under treatment with a β-blocker were excluded from the study. Numbers generated by a software program (Microsoft Office Excel 2003) were used to randomly assign the patients to receive either normal saline (control) \((n=48)\) or carperitide \((n=49)\). The 97 patients included smokers and nonsmokers. Thus, the study involved four groups of patients: smokers who received saline \((n=21)\), nonsmokers who received saline \((n=27)\), smokers who received carperitide \((n=19)\), and nonsmokers who received carperitide \((n=30)\).

The patients in control groups received continuous i.v. infusion of normal saline \((0.9\% \text{ saline}, 20 \text{ ml h}^{-1})\), and those in the carperitide groups received continuous i.v. infusion of carperitide \((\text{HANP Injection 1000; Daichi Pharmaceutical Co., Ltd, Tokyo, Japan}) 0.2 \text{ µg kg}^{-1} \text{ min}^{-1} \text{ (20 ml h}^{-1})\) during the study period. Thirty minutes after starting the infusion, we administered thiopental 5 mg kg\(^{-1}\) and fentanyl 5 µg kg\(^{-1}\) for induction of general anaesthesia and vecuronium 0.3 mg kg\(^{-1}\) for muscle relaxation to facilitate tracheal intubation using a disposable tracheal tube (internal diameter, 8 mm). The tracheal tube was inserted 2 min after vecuronium injection.

Continuous infusion of thiopental 15 mg kg\(^{-1}\) h\(^{-1}\) was continued after the induction of anaesthesia. The lungs were ventilated with a mixture of oxygen and air (fraction of inspired oxygen, 0.5) delivered by means of a semi-closed circle system \((\text{Ohmeda Modulus® CD Anesthesia System, Ohmeda, Madison, WI, USA})\) at a fresh gas flow rate of 6 litre min\(^{-1}\). The ventilatory system was set to maintain a tidal volume of 8 ml kg\(^{-1}\), an inspiratory:expiratory ratio of 1:2 and a ventilatory frequency of 10 bpm. The mean airway resistance \((R_{awm})\), expiratory airway resistance \((R_{awe})\) and dynamic lung compliance \((C_{dyn})\) were determined 4, 8, 12 and 16 min after tracheal intubation. These three respiratory variables were measured and analysed using a CP-100 pulmonary function monitor \((\text{Bicore, Irvine, CA, USA})\) attached to a flow transducer \((\text{VarFlex®, Bear Medical Systems, Inc., Palm Springs, CA, USA})\) and an oesophageal balloon catheter \((\text{SmartCath®, Bear Medical Systems, Inc.})\).\(^{10–13}\)

The arterial blood sample was obtained to measure plasma epinephrine and norepinephrine just before infusion of saline or carperitide (baseline) and 30 min later (just before induction of anaesthesia). The study ended before the start of the surgery. Data were collected by an investigator who was unaware of the treatment allocation, and the subjects and the investigators performing intubation were also unaware of the treatment allocation.

**Statistical analysis**

A computer-generated randomization list was used for randomization technique. Data were analysed using JMP for Windows software (release 5.1: SAS Institute Inc., NC, USA) and SamplePower® 2.0 for Windows software (SPSS Inc., IL, USA). Previously collected \((\text{Wajima Z, Shiga T, 2001, unpublished})\) data for patients at our institution were analysed to establish the appropriate sample size for this study, and from this analysis, statistical power calculations suggested that a group size of 19 patients would have 80% power \((\alpha=0.05)\) to detect a difference in \(R_{awe}\) at 4 min for 3.0 cm H\(_2\)O litre\(^{-1}\) s\(^{-1}\) or greater between nonsmokers in the control group and those in the carperitide group.

Values are expressed as mean \((SD)\). Within group differences in systolic and diastolic arterial pressure, and heart rate were assessed by two-way ANOVA with repeated measures and paired \(t\)-tests with Bonferroni’s correction. Inter-group differences in values between the various time points were analysed by unpaired \(t\)-test. Differences in \(R_{awm}\), \(R_{awe}\) and \(C_{dyn}\) after tracheal intubation between the four groups were analysed by one-way ANOVA followed by the Tukey–Kramer post hoc test for multiple comparisons. Paired and unpaired \(t\)-tests were used to analyse differences in plasma epinephrine and norepinephrine concentrations. A \(P\)-value of <0.05 was considered statistically significant.

**Results**

Patient characteristics of different study groups are shown in Table 1. Preoperative pulmonary function test results did not differ between the groups (data not shown).

Arterial blood pressure did not change after treatment compared with baseline values in patients who received saline; however, arterial blood pressure decreased after treatment comparison with baseline values in patients

<p>| Table 1 Patient characteristics in different study groups. Data are expressed as mean ((SD)) unless otherwise indicated |
|----------------------------------|-----------------|-----------------|------------------|------------------|
| Normal saline ((n=48))         | Carperitide ((n=49)) |</p>
<table>
<thead>
<tr>
<th>Smokers</th>
<th>Nonsmokers</th>
<th>Smokers</th>
<th>Nonsmokers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>9/12</td>
<td>5/22</td>
<td>7/12</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>41 (24–59)</td>
<td>43 (34–56)</td>
<td>41 (24–55)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>63 (16)</td>
<td>55 (9)</td>
<td>62 (9)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>167 (8)</td>
<td>161 (8)</td>
<td>164 (7)</td>
</tr>
<tr>
<td><strong>Smoking (cigarettes/day)</strong></td>
<td>18 (11)</td>
<td>0</td>
<td>17 (9)</td>
</tr>
<tr>
<td><strong>Smoking duration (yr)</strong></td>
<td>21 (13)</td>
<td>0</td>
<td>19 (8)</td>
</tr>
</tbody>
</table>
who received carperitide (Fig. 1A). After induction of anaesthesia, arterial blood pressure decreased compared with baseline values in both the groups (Fig. 1A). Systolic and diastolic arterial pressures were significantly lower after treatment and after induction of anaesthesia in patients who received carperitide compared with those who received saline (Fig. 1A).

Although heart rate increased after carperitide infusion, it did not change after normal saline infusion (Fig. 1B). Heart rate after anaesthesia induction decreased compared with baseline values in patients who received saline, however, it remained elevated in patients who received carperitide (Fig. 1B), and it was significantly higher after carperitide treatment than after saline treatment and after induction of anaesthesia (Fig. 1B).

Overall, $R_{awm}$, $R_{awe}$ and $C_{dyn}$ after tracheal intubation differed between smokers and nonsmokers in patients who received normal saline (Table 2); at 4 min after intubation, $R_{awm}$ and $R_{awe}$ values were higher and $C_{dyn}$ value was lower in smokers compared with nonsmokers.

At 4 min after intubation, $R_{awm}$ and $R_{awe}$ values were lower and $C_{dyn}$ value higher in patients who received carperitide compared with smokers who received saline (Table 2). At 4 min after intubation, $R_{awm}$ and $R_{awe}$ were lower in nonsmokers who received carperitide compared with those who received saline (Table 2).

The baseline and post-treatment concentrations of plasma epinephrine were similar after treatment with normal saline or carperitide (Table 3). Baseline concentrations of plasma norepinephrine were also comparable. Plasma norepinephrine concentrations increased after medication with carperitide but not after saline (Table 4).

**Discussion**

If $R_{awm}$ or $R_{awe}$ increases, or $C_{dyn}$ decreases, bronchoconstriction must occur. Although each of these three changes can be associated with asthma, anaphylactic histamine release, and other respiratory abnormalities, according to our results, $R_{awm}$ and $R_{awe}$ may be more sensitive than $C_{dyn}$ to such respiratory abnormalities. Marked bronchoconstriction occurred especially in our normal saline groups (smokers and nonsmokers) 4 min after tracheal intubation. At this point, smokers in the carperitide group had lower $R_{awm}$ and $R_{awe}$ and higher $C_{dyn}$ than smokers who received saline. Also at 4 min after intubation, $R_{awm}$ and $R_{awe}$ were lower in nonsmokers in the carperitide group than in nonsmokers in the control group. These findings suggest that pretreatment with carperitide before induction of anaesthesia and tracheal intubation is advantageous for smokers and also, as a new discovery, that it may be beneficial even for nonsmokers. Our previous study did not indicate that pretreatment with colforsin daropate, which has a bronchodilating effect, was advantageous for nonsmokers when given before induction of anaesthesia and tracheal intubation.

Carperitide is an effective bronchodilator in humans. It is well known that ANP, which activates guanylyl cyclase, relaxes airway smooth muscle with increased concentration of intracellular cyclic guanosine monophosphate (cGMP). The surface of tracheal smooth muscle cells is densely occupied by large conductance Ca$^{2+}$-activated K$^+$ (BKCa) channels; these may be involved in the relaxation of tracheal smooth muscle by β-agonists and forskolin, which elevate intracellular cyclic adenosine monophosphate (cAMP). Single channel recordings have shown that application of ANP augments BKCa channel activity and that these channels are activated by cGMP in smooth muscle cells. Isometric tension recordings have also indicated that application of ANP results in relaxation of tracheal smooth muscle with augmentation of BKCa channel activity, a response similar to that with agents that elevate the intracellular concentration of...
Table 2 Mean airway resistance ($R_{awm}$), expiratory airway resistance ($R_{awe}$) and dynamic compliance ($C_{dyn}$) after tracheal intubation in smokers and nonsmokers per study group. Data are expressed as mean (sd). *P<0.05, **P<0.01 and ***P<0.005 vs 4 min; †P<0.05 and ‡P<0.01 vs nonsmokers after tracheal intubation (Table 2). These results suggest that i.v. carperitide before intubation is beneficial for smokers. Kil and colleagues1 also showed that post-intubation lung resistance was lower in nonsmokers than in smokers after treatment with ipratropium bromide, an anticholinergic bronchodilator, and albuterol, a β2-adrenergic agonist. Our results show that with pretreatment with i.v. carperitide, $R_{awm}$, $R_{awe}$ and $C_{dyn}$ were very similar for smokers and nonsmokers after tracheal intubation (Table 2). These results suggest that i.v. carperitide before intubation is beneficial for smokers. Kil and colleagues' comment that ‘The lesser response to bronchodilators in smokers was surprising in that smokers are often said to have reactive airways. However, this result may reflect a higher fixed resistance in smokers than in nonsmokers. The airway response to tracheal intubation may be a normal reflex response that may even be blunted in smokers by the presence of chronic irritation and inflammation. However, this remains speculation.’ The differences in study groups noted above may account for this difference in response to intubation.

Kil and colleagues1 administered inhaled ipratropium bromide and albuterol to their patients, and we administered i.v. carperitide. I.V. administration for 30 min may not be the best method; inhalational administration may be an alternative or better method. We believe that a suitable method of carperitide inhalation needs to be developed. In this study, we chose 0.2 μg kg$^{-1}$ min$^{-1}$ for the carperitide dosage because the accepted clinical dosage of i.v. carperitide for acute heart failure ranges from 0.1 to 0.2 μg kg$^{-1}$ min$^{-1}$.22 However, we could not determine whether this was

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>After injection</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline (ng ml$^{-1}$)</td>
<td>0.08 (0.04)</td>
<td>0.07 (0.04)</td>
<td>NS</td>
</tr>
<tr>
<td>Carperitide (ng ml$^{-1}$)</td>
<td>0.07 (0.05)</td>
<td>0.07 (0.04)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3 Plasma epinephrine levels. Data are expressed as mean (sd)

Table 4 Plasma norepinephrine levels. NS, not significant. Data are expressed as mean (sd)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>After injection</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline (ng ml$^{-1}$)</td>
<td>0.29 (0.13)</td>
<td>0.29 (0.12)</td>
<td>NS</td>
</tr>
<tr>
<td>Carperitide (ng ml$^{-1}$)</td>
<td>0.28 (0.13)</td>
<td>0.42 (0.20)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

cAMP.19 Moreover, measurement of intracellular Ca$^{2+}$ concentrations by fura-2 loading methods has indicated that suppression of Ca$^{2+}$ influx mediated by increasing BK$_{Ca}$ channel activity is involved, at least in part, in the cGMP-induced relaxation in tracheal smooth muscle.20 Recently, Mikawa and colleagues21 found that external application of ANP and 8-brom cGMP results in a concentration-dependent inhibition of the spontaneous tone in human tracheal smooth muscle and that the inhibitory effects of these agents are suppressed in the presence of BK$_{Ca}$ channel inhibitor. Their results indicated that an increase in the concentration of intracellular cGMP leads to relaxation of human tracheal smooth muscle and that BK$_{Ca}$ channel activity is involved in cGMP-induced relaxation in the tissues.

Kil and colleagues' reported no difference in lung resistance after tracheal intubation between smokers and nonsmokers given placebo. In contrast, 4 min after tracheal intubation in our study, $R_{awm}$ and $R_{awe}$ were higher and $C_{dyn}$ lower in smokers than in nonsmokers in the control group (Table 2). We speculate that differences in the study groups may be responsible for the contradictory results. In
the optimal dose for our purposes, and further investigation is needed.

Plasma epinephrine concentrations remained unchanged in our study after i.v. carperitide treatment, and plasma norepinephrine concentrations increased significantly. But we consider this change to be very small and not clinically relevant. As reported previously,13 these results show that catecholamines were not involved in the lower R awm and R awe values and higher C dyn values in the carperitide group after intubation compared with the control group.

Rapid adrenergic down-regulation can occur in many tissues. Therefore, β2-agonists might have a rapidly decreasing effect over time, which is a potential problem in the treatment of bronchial asthma.23 Carperitide may be effective in patients with bronchial asthma who fail to respond to β-stimulants because the action of this drug is not mediated through β-adrenoreceptors. However, further clinical investigation is required to confirm such speculation.

In summary, our results suggest that prophylactic treatment with carperitide before anaesthesia induction and tracheal intubation minimizes increases in airway resistance associated with tracheal intubation; this effect is advantageous for middle-aged smokers, and it may also be beneficial for nonsmokers. Carperitide has a potent bronchodilating effect, and further dose–response investigation is needed.

Acknowledgement
A part of this work was supported by the Japan Society for the Promotion of Science (JSPS) [Grant-in-Aid for Scientific Research (C) 16591569].

References
3 Kim ES, Bishop MJ. Endotracheal intubation, but not laryngeal mask airway insertion, produces reversible bronchoconstriction. Anesthesiology 1999; 90: 391–4
22 Society of Japanese Pharmacopoeia (1997), Yakuii Nippo, Ltd, Tokyo, Japan (Summary Basis of Approval (SBA) No.5: Carperitide (Genetical Recombination) [HANP Injection 1000]). Tokyo, Japan: Yakuii Nippo, Ltd, 1997