Heart Rate Response to Intravenous Landiolol during Propofol Anesthesia

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Summary

Propofol suppresses both the sympathetic and parasympathetic nervous systems. There have been no clinical studies examining the infusion rate-related hemodynamic interaction between propofol and landiolol, an ultra-short acting β1-blocking agent. Twenty-four patients were divided into two groups. Patients in the P-1.25 group (n = 12) received intravenous (IV) propofol (1.25 mg/kg) over 1 min followed by continuous infusion of propofol at 5 mg/kg/h. Tracheal intubation was facilitated with IV rocuronium, and anesthesia was maintained with propofol at 5 mg/kg/h and 67% nitrogen in oxygen. Patients in the P-2.5 group (n = 12) received IV propofol (2.5 mg/kg) over 1 min followed by propofol at 10 mg/kg/h. All other protocols were identical to those in the P-1.25 group. Fifteen minutes after tracheal intubation, patients in both groups received IV landiolol at incremental infusion rates (40, 50, 60, 70, 80, 90, and 100 µg/kg/min for 2 min at each dose). Changes in heart rate (HR) were greater in patients in the P-1.25 group than the P-2.5 group. The landiolol infusion at 40, 50, or 60 µg/kg/min caused HR changes of −6±4, −9±6, and −13±6 beats/min (bpm) in the P-1.25 group, while the HR in the P-2.5 group decreased by −1±3, −4±2, and −6±4 bpm (mean±SD, P<0.05). When landiolol was infused at a rate of 90 µg/kg/min, HR decreased by more than 15 bpm in all patients in the P-1.25 group, but only 40% of patients in the P-2.5 group. We conclude that the HR response to IV landiolol is attenuated at higher propofol infusion rates.

Key words: Anesthetics, propofol, heart, heart rate, landiolol

Introduction

Propofol attenuates both the sympathetic and parasympathetic nervous systems and reduces sympathetic tone to a greater degree than parasympathetic tone or parasympathetic tone to a greater degree than sympathetic tone. On the other hand, meta-analysis has shown that propofol significantly increases the incidence of bradycardia when compared with other anesthetics. Pharmacologically, propofol induces changes in myocardial β adrenoceptor binding and responsiveness, and attenuates β adrenoceptor-mediated signal transduction.

Landiolol hydrochloride, an ultra-short acting β-selective blocking agent, was developed by modifying the chemical structure of esmolol to produce higher cardioselectivity and greater potency without increasing its duration of action. To the best of our knowledge, there have been no clinical studies that have investigated the alteration of heart rate response when landiolol is co-administered with propofol. To examine the hypothesis that the heart rate (HR) response to intravenous (IV) landiolol would be altered dose-dependently during propofol anesthesia, we studied the infusion rate-related hemodynamic interaction between propofol and landiolol in humans.

Materials and Methods

Twenty-two adult patients, ASA physical status 1, aged between 20 and 48 years, and undergoing a variety of general surgical procedures were studied. The study protocol was approved by the human history of cardiovascular, pulmonary or neurological
research committee of Akita University School of Medicine (No. 138), and written informed consent was obtained from each patient. Subjects with a disorders, or those who had taken any medication that affects cardiovascular function were excluded. All patients received 10 mg of lafutidine (H2 receptor antagonist, UCB Japan Co., Ltd., Tokyo, Japan) orally as preanesthetic medication 90 min before the arrival in the operating room (OR).

On the arrival in the OR, a 20-gauge IV cannula was inserted, and bicarbonated Ringer’s solution was administered at a rate of 10 mL/kg/h throughout the study. Standard lead II electrocardiography (ECG) was initiated and an automated blood pressure (BP) cuff (Dynascope, DS 5300, Fukuda Denshi Co., Ltd., Tokyo, Japan) was applied on the contralateral arm. HR was determined as averaged data at 4-sec intervals on the ECG monitor, and mean BP was measured via the oscillometric method.

The patients were randomly assigned to one of two groups. After pre-oxygenation, patients in the P-1.25 group \((n = 12)\) received IV propofol (Maruishi Pharmaceutical, Osaka, Japan) at 1.25 mg/kg over 1 min, followed by continuous infusion of propofol at 5 mg/kg/h without the infusion of analgesic drugs. Intubation of the trachea was facilitated with IV rocuronium (0.6 mg/kg), and anesthesia was main-tained with propofol at 5 mg/kg/h and 67% N2 in oxygen. Mechanical ventilation was adjusted to maintain Et-CO2 at approximately 35 mmHg. Patients in the P-2.5 group \((n=12)\) received IV propofol at 2.5 mg/kg over 1 min followed by continuous infusion of propofol at 10 mg/kg/h. The remaining protocol was identical to the P-1.25 group.

We obtained a stable hemodynamics at 15 min after tracheal intubation in both groups. Patients with a baseline HR of less than 65 were excluded. Patients in both groups received IV landiolol (Ono Pharmaceutical Co., Ltd., Osaka, Japan) at incremental infusion rates \((40, 50, 60, 70, 80, 90, \) or 100 \(\mu g/kg/min\) for 2 min at each dose) via a controlled infusion pump (TE 312, Terumo Co., Ltd., Tokyo, Japan), until HR decreased by more than 15 beats/min \(\) (bpm) from baseline values before surgical stimulation. Landiolol hydrochloride was diluted with normal saline to a concentration of 2.5 mg/mL. HR and BP (systolic, mean, diastolic) were measured at 1-min intervals until the end of each infusion period, while ECG was monitored continuously. At the end of each infusion period, values for HR and BP were subjected to data analyses. When systolic BP fell below 80 mmHg or HR below 50 bpm, rescue treatment with ephedrine or atropine was administered, respectively, and the patient was excluded from subsequent data analysis. Changes in HR were plotted against landiolol infusion rates of 40, 50, or 60 \(\mu g/kg/min\). The cumulative percentage of patients whose HR decreased by more than 15 bpm was also plotted against landiolol infusion rate.

Power analysis based on our pilot study revealed that at least 6 patients in each group had 80% power to detect differences between mean decrease in HR with a significance level \((\alpha)\) of 0.05 (G*Power, version 3.1.9.2, Heinrich-Heine University). Statistical analysis was performed using two-way analysis of variance to compare changes in hemodynamic variables between groups. When a significant difference was identified, this was followed by unpaired Student’s \(t\)-test with Bonferroni’s correction. Intergroup differences in demographic data were also compared by unpaired Student’s \(t\)-test or chi squared analysis. Changes in hemodynamic variables over time within each group were analyzed by repeated-measures analysis of variance, followed by paired Student’s \(t\)-test. Testing for significance in the incidence of negative HR responses after landiolol infusion between the two groups was accomplished by chi-squared analysis. Data were expressed as means \pm SD and a \(P\) value \(< 0.05\) was considered to be the minimum level of significance.

**Results**

There were no significant differences between the groups with respect to age, weight, height or gender (Table 1). One patient in each group was excluded from the study, because the baseline HR (after induction of anesthesia and just prior to landiolol infusion) was less than 65; a patient in the P-1.25 group was going on a diet and a patient in the P-2.5 group had an athlete’s heart. Before the induction of anesthesia and baseline in HR remained unchanged (Table 2). There were also no significant differences

**Table 1** Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>P-1.25 group</th>
<th>P-2.5 group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / female</td>
<td>4/7</td>
<td>4/7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>41(\pm)9</td>
<td>37(\pm)11</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>150(\pm)9</td>
<td>159(\pm)6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58(\pm)10</td>
<td>59(\pm)10</td>
</tr>
</tbody>
</table>

Values are numbers or mean \(\pm\) SD
in the decrease in HR and mean BP after infusion of propofol between the P-1.25 and P-2.5 groups (−1 ± 10, −2± 8 bpm, and −9± 8, −16± 14 mmHg, respectively). No patients’ systolic BP fell below 80 mmHg or HR below 50 bpm during the study.

Changes in HR were greater in patients in the P-1.25 group, in whom landiolol infusion at 40, 50, or 60 µg/kg/min resulted in HR changes of −6±4, −9±6, −13±6 bpm, as compared to changes of −1±3, −4±2 and −6±4 bpm in the P-2.5 group, respectively (P<0.05, Fig. 1). When landiolol was infused at a rate of 90 µg/kg/min, HR decreased by more than 15 bpm in all patients of the P-1.25 group, but in only 40% of patients of the P-2.5 group (P<0.0001 vs. the P-2.5 group, Fig. 2).

There were no significant differences in systolic, diastolic, and mean BP between the groups (Table 2). No patient in either the P-1.25 or P-2.5 group developed arrhythmias after landiolol infusion. There were no other adverse effects related to landiolol infusion or propofol-landiolol interactions.

### Discussion

Our main finding is that the HR response to IV landiolol was attenuated at a higher propofol infusion rate. The decreased heart rate response to IV landiolol at a higher propofol infusion rate was contrary to our expectations.

Although the mechanisms for this finding remain unclear, autonomic nervous system changes due to propofol are of concern. Propofol anesthesia reduces parasympathetic tone to a lesser degree than sympathetic tone when using HR variability (HRV) analysis. By contrast, there have been reports that propofol anesthesia decreases parasympathetic tone to a lesser degree than sympathetic tone when using HRV analysis. But in only 40% of patients of the P-2.5 group (P<0.0001 vs. the P-2.5 group, Fig. 2).

### Table 2 Heart Rate and Blood Pressure at Each Dose of Intravenous Landiolol Infusion Rate

<table>
<thead>
<tr>
<th>Group</th>
<th>Before anesth</th>
<th>Baseline</th>
<th>Landiolol infusion rate (µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>HR</td>
<td>79±8</td>
<td>78±12</td>
<td>71±10†</td>
</tr>
<tr>
<td>P-1.25</td>
<td></td>
<td></td>
<td>80±11†</td>
</tr>
<tr>
<td></td>
<td>124±22</td>
<td>116±17†</td>
<td>106±11†</td>
</tr>
<tr>
<td>P-2.5</td>
<td>140±19</td>
<td>115±16†</td>
<td>110±10†</td>
</tr>
<tr>
<td>sBP</td>
<td>85±13</td>
<td>76±11†</td>
<td>70±8†</td>
</tr>
<tr>
<td>P-1.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95±14</td>
<td>78±8†</td>
<td>75±6†</td>
</tr>
<tr>
<td>P-2.5</td>
<td>67±8</td>
<td>60±13†</td>
<td>56±11†</td>
</tr>
<tr>
<td>dBP</td>
<td>76±9</td>
<td>64±10†</td>
<td>58±5†</td>
</tr>
</tbody>
</table>

Values are mean±SD. Baseline=after induction of anesthesia and just before landiolol infusion; HR=heart rate (beats/min); sBP=systolic blood pressure (mmHg); mBP=mean blood pressure (mmHg); dBP=diastolic blood pressure (mmHg). *p<0.05 versus baseline; †p<0.05 versus before anaesthesia; §p<0.05 versus P-1.25

![Table 2](image1)

![Figure 1](image2)

**Figure 1**

Heart rate responses to intravenous landiolol infusion at 40, 50, or 60 µg/kg/min in patients in the P-1.25 group (n=10) and P-2.5 group (n=10). Means±SD, * P<0.05 between groups.

![Figure 2](image3)

**Figure 2**

Cumulative percentage of patients whose heart rate decreased by more than 15 bpm/min from baseline values after intravenous landiolol infusion in patients in the P-1.25 group (n=10) and P-2.5 group (n=10).
reduces cardiac parasympathetic tone to a greater degree than sympathetic tone, depending on the depth of anesthesia when HRV analysis was employed. Therefore, the effects of propofol on cardiac autonomic nervous system remain controversial may be situation-specific.

In our study protocol, induction and maintenance of propofol anesthesia (before infusion of landiolol) did not cause a reduction in HR, as has been described previously. Though both sympathetic and parasympathetic tone might be suppressed by propofol according to the previous study, the balance between sympathetic and parasympathetic tone would have been maintained when we induced and maintained anesthesia with propofol.

Landiolol exerts its β-blocking action by competing with catecholamines at β-adrenoceptor sites, and is not thought to suppress sympathetic nerve activity. Propofol can decrease cardiac β-adrenoceptor binding and responsiveness. These previous reports may indicate that landiolol, which competes with catecholamines at β-adrenoceptor sites, exhibits dose-dependent decreases in cardiac β-adrenoceptor binding with propofol, and thus a weaker HR response to IV landiolol is seen at higher infusion rates of propofol.

Landiolol is rapidly hydrolyzed to an inactive form by both carboxylesterase in the liver and pseudocholinesterase in the plasma, resulting in an elimination half-life of about 4 min. In the low-dose escalation regimen (1 min loading infusion at 30 µg/kg/min, followed by 10 min continuous infusion at 10 µg/kg/min), the blood concentration of landiolol changed within a constant range from 2 min after starting administration. Therefore, it is reasonable that the patients received IV landiolol at an incremental infusion rate every 2 min in our protocol.

We recognize a few limitations to our study. First, we examined patients of ASA physical class 1, aged between 20 and 48 years. In elderly patients, and patients with cardiovascular disease or arrhythmias, our results might not apply because both sympathetic and parasympathetic activity may differ in these patients. Secondly, patients in our protocol received IV landiolol at incremental infusion rates. In clinical settings, however, patients are given IV landiolol at an appropriate infusion rate after a loading dose.

In conclusion, the HR response to IV landiolol was attenuated at a higher propofol infusion rate. The reduced HR response to IV landiolol at a higher infusion rate of propofol is possibly due to propofol-induced dose-dependent changes in autonomic nervous system activity or in the β-adrenoceptor affinity of landiolol. Further study is warranted to determine infusion rate-related hemodynamic interactions between propofol and landiolol in patients with tachycardia or tachyarrhythmias, as such patients exhibit modulation of basic autonomic nervous system balance.

Disclosures

We declare no conflicts of interest. This study was supported solely by institutional or departmental sources.

References

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