Original contribution

Dose-dependent hemodynamic effects of propofol induction following brotizolam premedication in hypertensive patients taking angiotensin-converting enzyme inhibitors☆,☆☆

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Abstract

Study Objective: To determine a propofol dose that minimizes hemodynamic changes on induction of anesthesia in patients chronically taking angiotensin-converting enzyme inhibitors (ACEIs).

Design: Prospective, randomized trial.

Setting: Operating room of a university-affiliated general hospital.

Patients: 88 ASA physical status II and II hypertensive patients chronically taking ACEIs, scheduled for elective abdominal surgery with general anesthesia.

Interventions: Patients were premedicated with brotizolam and anesthesia was induced with propofol, fentanyl, and rocuronium; anesthesia was then maintained with isoflurane. Patients were randomly assigned to undergo anesthetic induction with propofol in doses of 1.3, 1.6, 2.0, or 2.3 mg/kg.

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1. Introduction

Perioperative administration of angiotensin-converting enzyme inhibitors (ACEIs) may be beneficial as they attenuate the adrenergic response to stressful stimuli in a variety of patients undergoing cardiac [1], gynecological [2], vascular [3], and cerebrovascular [4] surgeries and in patients with impaired left ventricular (LV) function [4]. Patients taking ACEIs may require more vasopressors to maintain adequate blood pressure (BP) [5,6], and are reportedly at special risk of intraoperative hypotension, especially after anesthetic induction [7,8]. Profound bradycardia and hypotension have been described following spinal anesthesia in a patient receiving an ACE inhibitor [9].

Some investigators recommend that ACEIs be continued [1,10] before anesthesia while others advise that they be discontinued [7]. Hypotension resistant to pressors, especially during induction of general anesthesia, is the most feared potential complication of continuing ACEI administration.

The most probable mechanism for post-induction hypotension associated with perioperative continuation of chronic ACEI treatment is increased cardiovascular sensitivity to anesthetic induction agents [11]. To the extent that this mechanism applies, it may simply be sufficient to reduce induction agent doses in patients taking ACEIs. The hemodynamic and heart rate (HR) responses to various induction doses of propofol in patients taking ACEIs were evaluated to determine the induction dose of propofol with the lowest frequency of hemodynamic changes.

2. Materials and methods

With approval of the Institutional Review Board of the Edith Wolfson Medical Center, a total of 88 hypertensive patients with well-preserved LV function [ejection fraction (EF) > 45%] who were taking ACEIs for at least 6 weeks were enrolled in the study [10]. Ancillary antihypertensives, including beta-blockers, were permitted. All patients were ASA physical status II or III, aged 40 to 65 years, and scheduled for elective abdominal surgery with general anesthesia. Patients were excluded from the study if they had a history of congestive heart failure, recent stroke (<6 wks), recent myocardial infarction (<one month), or if the attending anesthesiologist anticipated difficult laryngoscopy or intubation.

2.1. Protocol

Participating patients were allowed to continue the ACEI they routinely took until the day of surgery. All other chronic medications were continued through the morning of surgery. Patients were premedicated with sublingual 0.25 mg brotizolam (a short-acting benzodiazepine) and intravenous (IV) midazolam (one mg), which were given about 30 minutes before induction of anesthesia. Fentanyl (one μg/kg) was given 5 minutes before induction. A bolus of IV rocuronium (0.6 mg/kg) was given at the beginning of induction.

Patients were thus randomly assigned to anesthetic induction with propofol in doses of 1.3, 1.6, 2.0, or 2.3 mg/kg (22 pts/group). Randomization was based on computer-generated codes that were maintained in opaque envelopes and opened immediately before induction of anesthesia. Among the patients who consented to participate in the study and were randomized, 21 dropped out or were excluded on the morning of surgery. Reasons included failure to continue taking ACEIs, including on the morning of surgery; cancellation of their surgery for non-anesthetic reasons; or patient withdrawal of consent. The remaining 67 patients were treated per their assigned randomization as follows: the designated dose of propofol was injected over a 30-second period immediately after rocuronium administration. One and a half minutes later, the trachea was intubated with direct laryngoscopy. Mechanical ventilation was set to maintain an end-tidal PCO₂ (P₃₀CO₂) near 35 mmHg with a fresh gas flow of oxygen two L/min and nitrous oxide three L/min; inspired isoflurane concentration was set to 1%. Lactated Ringer’s solution was given at a rate of 5 mL/kg/min during the first 10 minutes of anesthesia.
Blood pressure and HR were evaluated at one-minute intervals during the first 10 minutes of anesthesia, detailed below. During this period, hemodynamic responses were treated per protocol: hypertension [systolic blood pressure (SBP) > 160 mmHg or more than 30% above the baseline value] was treated with 10-mg boluses of esmolol; tachycardia [HR > 100 beats per minute (bpm)] associated with normal or elevated BP was similarly treated; bradycardia (< 50 bpm) was treated with atropine 0.5 mg; and hypotension (SBP < 100 mmHg or more than 30% below the baseline value) was treated with phenylephrine 50 μg in patients with HRs exceeding 50 bpm and with ephedrine 5 mg in patients who were bradycardic.

The attending anesthesiologist was permitted to make any additional management changes deemed necessary for patient safety, including adjusting the isoflurane concentration or adding an opioid. The study concluded 10 minutes after induction of anesthesia and subsequent anesthetic management was at the discretion of the attending anesthesiologist.

2.2. Measurements

Demographic and morphometric characteristics were recorded. ASA physical status and chronic medications were also recorded. Baseline SBP was the mean of three oscillometric measurements performed the day before surgery after the patient rested comfortably in the supine position for at least 10 minutes [12]. Oscillometric BP and HR were recorded at one-minute intervals for 10 minutes after induction of anesthesia.

A 5-lead electrocardiogram was continuously monitored for ST-segment changes in lead V5. The number and type of hemodynamic interventions were recorded. End-tidal isoflurane concentration was also recorded at one-minute intervals for 10 minutes after anesthetic induction.

Table 1 Morphometric, demographic, and baseline characteristics; average number of hypotensive/bradycardic events; and average patient-specific mean end-tidal isoflurane concentration during the first 10 minutes of anesthesia, by propofol dose group

<table>
<thead>
<tr>
<th>Factor</th>
<th>Propofol dose</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.3 mg/kg</td>
<td>1.6 mg/kg</td>
</tr>
<tr>
<td></td>
<td>(n=15)</td>
<td>(n=18)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Mean end-tidal Iso %</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>End-tidal Iso % (SD)</td>
<td>14</td>
<td>0.10 ± 0.01</td>
</tr>
<tr>
<td>Men</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>B-blocker use</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Ca-channel blocker use</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>ASA physical status</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>status 0.73 †</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hypotensive/bradycardic events</td>
<td>15</td>
<td>18</td>
</tr>
</tbody>
</table>

BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, HR=heart rate, Iso %=isoflurane concentration, B-blocker=beta-blockers, Ca-channel blocker=calcium channel blockers.

⁎ Statistics are means ± SD for normally-distributed continuous variables (P-value from analysis of variance F-test), medians (first quartiles, third quartiles) for non-normally distributed continuous variables (Kruskal-Wallis Test), and percentages for categorical variables (chi-squared test).
† Fisher’s exact test was used due to low expected cell counts.

ASA physical status data unavailable.
Propofol induction and ACE inhibitors

2.3. Data analysis

Though patients were randomly assigned to undergo anesthetic induction with propofol in different doses, the potential existed that covariables would be somewhat unbalanced among the 4 groups due to the small sample sizes in each group. Thus, the analysis centered around assessing the relationship between the number of pharmacologic interventions and the propofol dose.

A multivariable negative binomial regression model was used to model a hypothesized linear relationship between propofol dose and the logarithm of the count response (referring to the fact that our primary outcome—the number of hypotensive/bradyincar interventions—is a count), and this served as our primary analysis; using the log-count as a response yielded a multiplicative interpretation of effects (ie, percent difference in means were estimated for a fixed increase in propofol dose). Secondary analysis centered on estimating the mean number of hypotensive/bradyincar events, assuming no such log-linear relationship between dose and response. The negative binomial model was preferred over the simpler Poisson regression model because the observed variability in the response was greater than that expected by assuming a Poisson distribution (the Poisson model assumes variance equal to the mean), a characteristic commonly known as over-dispersion.

Stepwise selection was used (with significance-to-enter and significance-to-stay thresholds set purposely conservative at 0.30 and 0.20, respectively) to select covariable main effects included in the model. Interaction effects between dose and those covariables selected using the stepwise procedure were not assessed, primarily due to the risk of overfitting, which is generally attributable to limited sample size. The procedure GENMOD in SAS 9.1.3 (SAS Institute, Cary, NC, USA) was used for building the Poisson and negative binomial regression models, while R software version 2.7.0 (The R Foundation for Statistical Computing, Vienna, Austria) was used to build the figures.

3. Results

Baseline characteristics and intraoperative outcomes are univariably summarized in Table 1; patients in the lower propofol dose groups were significantly taller and heavier, though body mass index (BMI) did not significantly differ among the groups. No patient complained of awareness during anesthesia.

Median (Q1, Q3) pharmacologic intervention counts were 0 (0,3), 2 (0,2), 1 (0,5), and 1 (1,3) for the 1.3, 1.6, 2.0, and 2.3 mg/kg propofol dose groups, respectively. Because not all covariables were adequately balanced, this univariable result was subject to potential confounding and our multivariable negative binomial model was used (Table 2).

Figs. 1 and 2 show no obvious differences in mean HR, minimum HR, mean arterial pressure (MAP), or minimum MAP among the 4 different propofol dose groups. The histogram in Fig. 3 shows that the observed count of hypotensive/bradyincar events in the initial 10 minutes of anesthesia roughly follows an exponential decay—a quantity that declines at a rate proportional to its value—from 28 (42%) patients with zero interventions down to one (1%) patient with 10 interventions.

Age and chronic medication entered our multivariable model via the stepwise procedure. After adjusting for these covariables in a model assuming a linear relationship between dose and log-response (Fig. 4), it was estimated that a propofol dose increase of 0.3 mg/kg was associated with a 31% increase in mean number of hypotensive/bradyincar interventions [95% confidence interval (CI) of +5% and +65%; P = 0.018].

The secondary model using a categorical dose predictor is shown in Fig. 4 (point estimates and CIs are shaded in gray). Based on our modeling, a dose of propofol 1.3 mg/kg resulted in the fewest estimated mean number of interventions.

4. Discussion

We evaluated the hemodynamic responses to various propofol induction doses in patients chronically taking ACEIs. Interestingly, mean and lowest HRs were generally similar over the range of induction doses spanning 1.3 to 2.3 mg/kg. Average and lowest MAPs also were generally similar over the tested dose range. Nonetheless, our model indicated that a propofol dose of 1.3 mg/kg—the lowest dose used in this study—requires the smallest number of interventions for hypotension or bradycardia during the first 10 minutes of anesthesia.

During emergency/urgent surgical procedures, there were significant univariately associations of cardiac death with the coexistence of any of the 3.5 (2.1, 6.0) - Yes vs. No (B-Blocker, Ca-channel blocker) - Yes vs. No (ACEI, phenylephrine showed a low efficacy in management of cardiac failure [13]. In patients treated chronically with ACEI, phenylephrine showed a low efficacy in management...
of intraoperative hypotension [11] while IV angiotensin II, a combination of terlipressin plus ephedrine, or terlipressin alone, were effective in the treatment of hypotension in such patients [12,14,15].

In contrast, use of ACEI during surgery may be beneficial as it attenuates the adrenergic response to stressful stimuli in cardiac surgical patients [1], in vascular surgery patients [3], in those undergoing cerebrovascular surgeries [4], and in patients with impaired LV function [16]. In a recent study of 149 ambulatory surgical patients, Griffin et al. [17] showed that discontinuation of ACEI treatment more than 10 hours versus less than 10 hours prior to surgery did not cause an increase in prevalence of preoperative hypertension. Furthermore, the degree of preoperative hypertension was comparable in each group.

We should stress the importance of the finding that 60% of the perioperative hemodynamic disturbances in our patients taking ACEI chronically required pharmacological support and the possibility to prevent these adverse effects by adapting the doses of hypnotic.

A limitation of our study is that about a quarter of our enrolled patients dropped out of the study or were eliminated before induction of anesthesia. Consequently, group sizes differed somewhat, as did group characteristics. However,
we used statistical methods (namely, multivariable analysis) in an attempt to compensate for these slight differences in baseline characteristics. It remains likely that other factors affect hemodynamics, including anxiety and patients’ intravascular volume status.

A second limitation is the implicit assumption that optimal hemodynamic control is synonymous with optimal anesthesia. This is certainly not exactly correct since anesthesia includes analgesia and amnesia along with control of hemodynamic responses. We assume that titrating the dose of propofol based on bispectral index (BIS) monitoring could also prevent perianesthetic hypotensive events. However, controlling hemodynamic responses is the most critical aspect of anesthetic induction since blunting the hypertensive and tachycardic response to laryngoscopy and intubation requires at least 4 times anesthetic concentration needed to prevent recall. It remains possible that continuing the ACEIs provoked problems after induction that were not evaluated in our study. We did not compare patients who continued taking ACEIs with those who stopped and therefore cannot answer definitively whether patients taking this class of medications should stop before surgery. However, our results suggest that stopping ACEIs is unnecessary, especially if a relatively low dose of propofol is used for anesthetic induction.

In summary, an induction dose of 1.3 mg/kg of propofol has the lowest expected number of pharmacologic interventions to maintain stable hemodynamics in patients receiving chronic ACEI medication.

References