Esmolol Reduces Anesthetic Requirement for Skin Incision during Propofol/Nitrous Oxide/Morphine Anesthesia

Jay W. Johansen, M.D., Ph.D.,* Ronald Flaishon, M.D.,† Peter S. Sebel, M.B., B.S., Ph.D. F.F.A.R.C.S.I.‡

Background: Although beta blockers have been used primarily to decrease unwanted perioperative hemodynamic responses, the sedative properties of these compounds might decrease anesthetic requirements. This study was designed to determine whether esmolol, a short-acting β1-receptor antagonist, could reduce the propofol concentration required to prevent movement at skin incision.

Methods: Sixty consenting patients were premedicated with morphine, and then propofol was delivered by computer-assisted continuous infusion along with 60% nitrous oxide. Patients were randomly divided into three groups, propofol alone, propofol plus low-dose esmolol (bolus of 0.5 mg/kg, then 50 μg·kg⁻¹·min⁻¹), and propofol plus high-dose esmolol (bolus of 1 mg/kg, then 250 μg·kg⁻¹·min⁻¹). Two venous blood samples were drawn at equilibration. The serum propofol concentration that prevented movement to incision in 50% of patients (Cₚ₅₀) was calculated by logistic regression.

Results: The propofol Cₚ₅₀ with nitrous oxide was 3.85 μg/ml. High-dose esmolol infusion was associated with a significant reduction in the Cₚ₅₀, to 2.80 μg/ml (P < 0.04). Propofol computer-assisted continuous infusion produced stable serum concentrations with a slight positive bias. Esmolol did not alter the serum propofol concentration. No intergroup differences in heart rate or blood pressure response to intubation or incision were found.

Conclusions: Esmolol significantly decreased the anesthetic requirement for skin incision. The components and mechanism of this interaction remain unclear. A simple pharmacokinetic interaction between esmolol and propofol does not explain the Cₚ₅₀ reduction. These results demonstrate an anesthetic-sparing effect of a β-adrenergic antagonist in humans under clinically relevant conditions. (Key words: Anesthetics, intravenous; propofol. Anesthetic techniques: computer-controlled infusion. β-receptor blockade: esmolol. Interactions (drug): esmolol-propofol.)

β-ADRENERGIC receptor antagonists have been in clinical use for more than 30 yr. These drugs have central nervous system depressant activity in animals¹⁻⁴ and anxiolytic effects in humans.⁵,⁶ More than 25 yr ago, Miller et al.⁷ suggested that drugs that affect central catecholamine release may alter anesthetic requirements. Sympathomimetic drugs that enter the central nervous system, such as ephedrine, mephentermine, and amphetamine, can increase halothane minimum alveolar concentration (MAC), whereas drugs that do not enter the central nervous system, such as isoproterenol, norepinephrine, and epinephrine, do not alter MAC directly.⁸⁻¹⁰ Antagonism of catecholamines in the brain or spinal cord might decrease anesthetic requirements.⁸ Although β-adrenergic receptor antagonists are used every day in the operating room, no published studies have examined the effect of these drugs on anesthetic requirements for skin incision in humans.

Minimum alveolar concentration of volatile agents is defined as suppression of movement to incision in 50% of patients.¹¹,¹² A similar definition has been proposed for intravenous anesthetics: the minimum effective plasma concentration, or Cₚ₅₀.¹³ Anesthetic drug interactions may be measured by reduction in MAC or Cₚ₅₀ of the primary anesthetic by a second drug. For example, intravenous opioids markedly decrease isoflurane and desflurane MAC.¹⁴⁻¹⁶ Measurement of drug interactions between intravenous anesthetic agents has proved difficult due to several technical issues. Steady-state plasma concentrations must be maintained for each drug. In addition, the individual rates of equilibration between the plasma and effect site compartments must be considered.¹⁷⁻²¹ Computer-assisted continuous infusion (CACI) devices can overcome several of these concerns by providing stable plasma levels of intravenous anesthetic agents that can be assumed to approach
steady-state conditions after a reasonable interval. Recently, Smith et al. used CACI to examined the reduction in propofol $C_{P0}$ by fentanyl.

Esmolol is an ultra-short-acting, cardioselective β1 adrenergic receptor antagonist that is effective in blunting adrenergic responses to several perioperative stimuli, including laryngoscopy with intubation, intraoperative events, emergence, and extubation. Its use has been promoted for minimizing the deleterious effects of intraoperative hypertension and tachycardia on myocardial oxygen consumption. Esmolol has been proposed as an alternative to alfentanil during propofol-nitrous oxide anesthetics in patients receiving neuromuscular blocking agents.

This study was designed to determine whether esmolol infusions could decrease the $C_{P0}$ of propofol under conditions approximating steady state.

Materials and Methods

Sixty consenting male and female patients, ages 18 to 70 yr, who were classified as American Society of Anesthesiologists physical status 1 to 3 and scheduled for elective surgery were studied. Exclusion criteria included a history of an allergic reaction to any study medication; advanced hepatic, renal, or cardiac dysfunction; long-term opioid, ethanol, sedative, or β-blocker use; poorly controlled asthma, diabetes, or hypertension; or weight more than 150% of ideal body weight.

After premedication with morphine sulfate (0.1 mg/kg to a maximum of 10 mg), patients were randomly assigned to one of three groups: propofol, propofol plus low-dose esmolol (bolus 0.5 mg/kg, then 50 μg·kg$^{-1}$·min$^{-1}$), or propofol plus high-dose esmolol (bolus 1 mg/kg, then 250 μg·kg$^{-1}$·min$^{-1}$). On arriving in the operating room, awake physiologic variables were noted. Continuous esmolol infusions by infusion pump (Baxter Model AS40A; Baxter Health Care, Deerfield, IL) were started before induction and continued at the given rate until the study was complete. After preoxygenation, anesthesia was induced by intravenous infusion of propofol using a CACI pump set at an initial effect-site target of 5.5 μg/ml. The CACI device used a three-compartment pharmacokinetic model with the kinetic data set of Smith et al. When patients lost consciousness, succinylcholine (1.5 mg/kg) was administered to facilitate endotracheal intubation. Mechanical ventilation to normocapnia with nitrous oxide (60%) was initiated. After intubation, the new predetermined target plasma propofol concentration was entered into CACI. Body temperature was maintained at more than 35.5°C.

Target propofol concentrations were assigned using a modification of Dixon’s method. Within each group, a concentration of propofol was estimated for the first patient. If that patient moved in response to skin incision, then the next patient in that group received a 10% increase in the target propofol concentration. If that patient did not move, then the next patient in that group received a 10% reduction in target propofol concentration. Using this method, the observer was not blinded to treatment group. Esmolol bolus and infusion rates were chosen to rapidly attain fivefold different plasma concentrations representing the upper and lower limits of the suggested therapeutic range.

Steady-state conditions were approximated by allowing at least 9 min to elapse before incision after the computer-predicted target propofol concentration had been reached. Full reversal of neuromuscular blockade was confirmed with a peripheral nerve stimulator. A skin incision of at least 2 inches was made. A positive response at incision was defined as movement of limbs, head, or body within 60 s. Coughing, chewing, or swallowing were not considered movement. Movement was not assessed until steady-state conditions had been met. However, spontaneous movements after equilibration were also considered positive.

Venous blood samples were drawn from the arm contralateral to the drug infusions 5 min after the predicted target propofol concentration had been reached and again at incision. Samples were immediately placed on ice, centrifuged as soon as possible, and frozen at −80°C until assay. Propofol plasma concentrations were determined by high-performance liquid chromatography, as described by Plummer, except that pentane was used as the extraction solvent. The coefficient of variation for analysis of known propofol concentrations was 6.2% in the range of 100 to 5,000 ng/ml. The lower limit of sensitivity of the assay was 2 ng/ml.

Data are represented as means ± SD, or as mean ± 95% confidence interval (CI). Statistical significance was set at a probability value less than 0.05. The $C_{P0}$ of propofol was calculated by two methods. First, the maximum likelihood solution to a logistic regression model (see appendix) was used. Second, the $C_{P0}$ was calculated from a limited data set consisting of only independent crossover pairs within each group by the up-down method of Dixon. The performance error,
median performance error, and median absolute performance error of the CACI infusion were calculated using the serum propofol concentration at skin incision, as previously described.\textsuperscript{22,34} One-way analysis of variance (ANOVA) was used to compare serum propofol concentrations and median performance error. Two-way repeated measures ANOVA was used to evaluate sequential physiologic data. When indicated, individual group means from ANOVA were compared with a post hoc Tukey’s Honestly Significant Difference test. A Kruskal-Wallis one-way ANOVA was used to analyze the median absolute performance error of the CACI device, which was not normally distributed.

**Results**

Of the sixty patients studied, 41 were women and 19 were men, with an average age of 42 ± 13 yr (range, 21–72 yr) and an average weight of 77 ± 17 kg (range, 48–120 kg). Ninety-five percent of patients were ASA physical status 1 or 2. There were no significant differences between groups with regard to demographic or surgical data. Most of the procedures were performed by general surgery (60%), with gynecological cases accounting for approximately 25%.

An average of 30 min elapsed between premedication and induction of anesthesia. The mean time from induction to incision or movement was 28 ± 11 min (range, 9–73 min). The mean time between the two blood samples was 11 ± 1 min (range, 3–39 min). Eight patients moved before incision after at least 9 min at the computer-predicted target propofol concentration. These patients were considered positive for movement. Incision was made at the first blood sample in three patients. With these 11 persons, the second blood sample was collected within 3 to 5 min. No significant differences in time from induction to incision, in time between blood samples, or in number of persons moving before incision were found among the three treatment groups.

The esmolol infusion rate and the natural log of serum propofol concentration at incision were significant factors in the logistic regression model for predicting movement to incision (fig 1). Age, height, weight, ASA physical status, and time from induction to incision were not significant factors. Based on the maximum likelihood solution to a logistic regression model, the \( \text{Cp} \) of propofol for skin incision was 3.85 \( \mu \text{g/ml} \) in the presence of 60% nitrous oxide and morphine premedication (table 1). Continuous high-dose esmolol infusion significantly reduced the propofol \( \text{Cp} \) by 26%, to 2.85 \( \mu \text{g/ml} \) \((P < 0.04)\) by logistic regression analysis. No significant change in propofol \( \text{Cp} \) (3.50 \( \mu \text{g/ml} \)) was seen after adding a low-dose esmolol infusion. Pre- and postincision heart rates were significant predictors of movement to incision in the logistic regression model. However, when mean heart rate in each group at each time point were included in the model, no significant change in the 50% response line was observed. Therefore, these two factors were eliminated from the logistic regression model and equation (Appendix 1).

Propofol \( \text{Cp} \) can also be computed by the method of

Anesthesiology, V 86, No 2, Feb 1997
Table 1. Reduction in Propofol Concentration Required to Suppress Movement to Incision (CP_{50}) by Esmolol

<table>
<thead>
<tr>
<th>Esmolol (µg·kg^{-1}·min^{-1})</th>
<th>Logistic CP_{50}</th>
<th>Dixon CP_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum (µg/ml)</td>
<td>CACI Target (µg/ml)</td>
<td>Serum (µg/ml)</td>
</tr>
<tr>
<td>0</td>
<td>3.85</td>
<td>3.89 ± 0.75</td>
</tr>
<tr>
<td>50</td>
<td>3.50</td>
<td>2.72 ± 0.28*</td>
</tr>
<tr>
<td>250</td>
<td>2.85*</td>
<td>1.95 ± 0.25*</td>
</tr>
</tbody>
</table>

* Significance compared with control within column, P < 0.05.  † Logistic regression analysis (appendix).  ‡ Up-and-down method of Dixon.  

Dixon using only independent crossover pairs within each group (table 1). By this method, an identical CP_{50} was found using either measured serum concentration or the computer-predicted target propofol concentration at incision. Both low- and high-dose esmolol infusions significantly reduced the propofol CP_{50} in a dose-dependent manner. Based on the CACI-target propofol concentrations, a 50% reduction in CP_{50} to 1.95 µg/ml was predicted in the presence of an infusion of 250 µg·kg^{-1}·min^{-1} esmolol.

The average percentage difference between the two plasma propofol samples in each patient was 0 ± 15% (range, +32% to −33%). The overall bias or median performance error of the CACI device was positive at 14% (mean, 17%; 95% CI, 8–27). The overall accuracy or median absolute performance error was 20% (mean, 27%; 95% CI, 20–34). Adding esmolol did not significantly alter the bias or the accuracy of the computer-controlled infusion (fig. 2, table 2). In this study, a power of 80% was achieved to detect a difference of 25% in the median performance error and 20% in median absolute performance error between control- and esmolol-treated groups. No significant correlation was observed between the bias or accuracy of CACI and movement within individual patients. Within the low-dose esmolol group, a statistically significant positive correlation was found between the bias and serum propofol concentration (y = 54x − 149, r = 0.86, P < 0.001) in patients who moved at incision (fig. 2b). No age-specific differences in the bias or accuracy of the CACI infusion were found by ANOVA with esmolol.

Figure 3 shows the physiologic response to endotracheal intubation and skin incision. Heart rate and mean arterial pressure at four specific times during surgery were normalized to each patient’s awake control value. A significant increase in heart rate (18–24%; P < 0.01) and mean arterial pressure (17–23%; P < 0.01) was found within each group after endotracheal intubation but not after incision. After equilibration at the target serum propofol concentration, mean arterial blood pressure decreased by 14% to 17% (P < 0.05) within each group. However, no change in baseline heart rate was seen under these conditions. Two-way repeated-measures ANOVA did not detect a significant difference among the three treatment groups with regard to any measured physiologic variable at any of the four time points.

Transient wheezing developed in one patient at incision.

Anesthesiology, V 86, No 2, Feb 1997

Fig. 2. Computer-assisted continuous infusion bias analysis. The percentage performance error for all propofol serum samples (Appendix 1) is plotted against the mean of the predicted and measured propofol serum concentrations. Each patient is represented by two serum samples. Patients who moved (open) or did not move (closed) are represented in each group: (A), control (○); (B) low dose + esmolol (△, ▢); and (C) high dose + esmolol (▽, ◇).
Table 2. Computer-assisted Continuous Infusion

<table>
<thead>
<tr>
<th>Esmolol (µg·kg⁻¹·min⁻¹)</th>
<th>Performance Error</th>
<th>Absolute Performance Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDPE Mean (95% CI)</td>
<td>MDAPE Mean (95% CI)</td>
</tr>
<tr>
<td>0</td>
<td>9</td>
<td>15 19 (13 to 25)</td>
</tr>
<tr>
<td>50</td>
<td>21</td>
<td>24 32 (20 to 44)</td>
</tr>
<tr>
<td>250</td>
<td>10</td>
<td>16 22 (13 to 31)</td>
</tr>
</tbody>
</table>

CI = confidence intervals; MDPE = median performance error; MDAPE = median absolute performance error.

Discussion

This study shows that esmolol, a β₁-adrenergic receptor antagonist, can reduce the Cₚ₅₀ of propofol for skin incision in the presence of 60% nitrous oxide and morphine premedication. A 26% reduction in the Cₚ₅₀ of propofol was demonstrated by logistic regression analysis at a clinically relevant esmolol infusion rate of 250 µg·kg⁻¹·min⁻¹. Logistic regression was selected as the primary method of analysis because all available data were used. Previous studies investigating control of adrenergic responses to perioperative stimuli have overlooked the anesthetic-sparing activity of esmolol. Many of these studies incorporated neuromuscular blocking agents into their study design, preventing detection of movement. A single bolus or noncontinuous drug administration also predominated throughout these studies.

No significant reduction in propofol Cₚ₅₀ was found at the lower esmolol infusion rate. The lack of significance at the lower esmolol infusion rate probably reflects the increased variability within this group and subsequent loss of statistical power. A larger sample size may have identified a significant difference. When the Cₚ₅₀ was calculated by the Dixon method with a more limited data set, esmolol produced a dose-dependent reduction that was significant at both infusion rates (Table 1). The control Cₚ₅₀ was constant regardless of the method of analysis.

In this study, the Cₚ₅₀ of propofol in tracheally intubated patients with 60% nitrous oxide after premedication with morphine was 3.85 µg/ml. This result corresponds closely with that of Shafer et al., who found a Cₚ₅₀ from venous samples of 3.40 µg/ml for propofol with nitrous oxide (70%) after meperidine premedication (1 mg/kg). Davidson et al. reported the propofol Cₚ₅₀ at 4.5 µg/ml using CAGI with nitrous oxide (67%).

Fig. 3. Physiologic response to intubation and skin incision. Maximum percentage changes from awake baseline in heart rate (A) and mean arterial blood pressure (B) are presented. Control (○), continuous esmolol infusions at 50 (●) or 250 (▼) µg·kg⁻¹·min⁻¹ are represented as the mean ± SD (n = 20 per group). Time points include postanesthetic induction (Ind), maximum postintubation (Int), precision baseline (plnc), and maximum postincision (Inc) values.

Anesthesiology, V 86, No 2, Feb 1997
in nontracheally intubated patients after temazepam
premedication. A wide discrepancy exists in reported
CP50 values for propofol/nitrous oxide anesthetic, with
values ranging from 1.55 to 5.36 µg/mL.35-39 Comparing
our results with other studies in the literature is difficult
because of differences in anesthetic technique, differ-
ences in endotracheal intubation, lack of computer-
controlled drug infusions, arterial versus venous sampling,
and measured response to skin incision. For example,
significantly lower CP50 values, 1.66 and 2.5 µg/mL,
were reported in nontracheally intubated patients recei-
ving a continuous propofol infusion and nitrous oxide
(67%), either with38 or without39 opioid premedica-
tion, respectively. Opioid premedication and nitrous
oxide were included in the experimental design to repli-
cate the clinical conditions under which this interaction
was first observed (Johansen JW, unpublished obser-
vations). The CP50 of propofol as the sole anesthetic for
skin incision has been reported to be 8.1 µg/mL in non-
tracheally intubated patients after a benzodiazepine pre-
medication40 and 15.2 µg/mL in tracheally intubated,
nonpremedicated patients.20

Computer-assisted continuous drug infusions provide
stable plasma drug concentrations so that intravenous
drug interactions can be explored. Equilibration be-
tween the plasma and effect-site approximating steady-
state conditions can be assumed after a reasonable inter-
val.20,22,40-42 Under these conditions, a plasma drug con-
centration should be equal to that in the effect site or
may represent a constant, stable fraction of that con-
centration. The half-time (t1/2, k,.) for equilibration between
the plasma and effect site for propofol has been reported
as 2.9 min.9 In each patient, the two venous
blood samples at equilibrium differed by 0 ≤ 15% from
their average. This suggests that stable propofol plasma
concentrations were achieved under our experimental
conditions. The first blood sample was taken at least 5
min after the computer-predicted target serum concen-
tration had been reached. An average of 11 min or at
least three time constants elapsed between the two
blood samples, suggesting that more than 94% equili-
bration between plasma and effect site had occurred in
most patients.

The overall CACI precision or median absolute perfor-
manee error was 20%, well within the 10-40% accuracy
reported by others using similar population pharmaco-
kinetic estimates.22,34,36,43,44 Adding esmolol did not af-
fect the precision or bias of propofol delivery by the
CACI system (table 2). Our study was designed to exam-
ine a pharmacodynamic interaction between esmolol
and propofol, not a pharmacokinetic interaction. How-
ever, this study had adequate power (80%) to detect a
difference of 25% in bias and 20% in accuracy between
control and esmolol-treated groups using measured se-
rum propofol concentrations. If esmolol altered the bias
or accuracy of propofol delivery by CACI and plasma
concentrations were stable, no change in CP50 would
have been found by our methods because only mea-
sured serum propofol concentrations were used in the
CP50 calculation.

The significance of the positive correlation between
an increasing bias and serum propofol concentration
in the low-dose esmolol group, predominately in the
patients who moved at incision, is unclear (fig. 2b).
This trend was not found in either control, high-dose
esmolol groups, or in patients who did not move within
the low-dose esmolol group. An example of increasing
CACI bias has been described during propofol and alfe-
tanil infusions.44

Venous propofol samples were used in this study.
These have been shown to be reliable after an initial
equilibration period.45 After a 20- to 25-min infusion,
differences between arterial and venous propofol con-
centrations were shown to be minimal.44 Increased vari-
ability in propofol measurements after venous sampling
has been reported in one study.46 However, subclinical
infusions of propofol were used in this study. Davidson
et al.46 found indirect evidence of incomplete venous
mixing or pulmonary sequestration during propofol
CACI propofol. A reduction in CACI bias from +21.4% to
-2% was found in this study after stopping the propo-
fol infusion for 90 s. Although arterial versus venous
blood sampling remains controversial, our results show
that reliable and consistent data can be obtained from
venous propofol samples. It remains possible that the
slight positive bias we observed in all groups may be an
artifact of venous sampling.

Esmolol infusions did not produce a significant
change at either infusion rate in heart rate or blood
pressure. Laryngoscopy and endotracheal intubation,
but not incision, caused a small increase in heart rate
and mean arterial pressure in all groups of patients.
Opioid premedication has been shown previously to
eliminate any clinically significant reduction in heart
rate or blood pressure associated with intubation when
a single bolus dose of esmolol was used.43 In this study,
no hemodynamically significant bradycardia was ob-

† Schuttler J, Schwilden H, Stoeckel H: Pharmacokinetic-dynamic

Anesthesiology, V 86, No 2, Feb 1997
served. Although one outpatient in the high-dose esmolol group was admitted overnight to the hospital, this was related to logistic and institution-specific concerns and not to medical necessity.

Twenty-seven years ago, animal studies with acute and chronic propranolol administration showed no change in halothane MAC in dogs and no change in brain content of biogenic amines in rats. Investigation of biogenic amines and anesthetic requirements stopped nearly 20 yr ago. In the current study, the mechanism by which esmolol decreased anesthetic requirements for skin incision is unknown. Our results show that esmolol does not alter plasma concentration of propofol by CACI, suggesting that a simple pharmacokinetic interaction between esmolol and propofol does not account for the CP50 reduction. However, the components of this interaction remain unclear. Esmolol could potentiate the effects of propofol, nitrous oxide, or opioid premedication. Esmolol has very little sedative effect, no analgesic activity, and, by itself, is not an anesthetic agent. The hemodynamic effects of esmolol are thought to be mediated by blockade at peripheral β-adrenergic receptors. The low-potency, low-lipid solubility and rapid metabolism within the blood stream do not exclude a central site for esmolol action. Some evidence for potentiation of the analgesic activity of opioids by β-blockers exists in the literature. Stanley et al. found a 25% decrease in the fentanyl dose for loss of consciousness in patients receiving long-term propranolol treatment. The significance and clinical utility of this drug interaction will depend on maximizing the CP50 reduction. Optimal conditions should be established with respect to essential components, sequence of interaction, time course, and dose response. It will also be necessary to determine whether the anesthetic-sparing effects of esmolol result from competitive antagonism at the β1 receptor or from a nonspecific drug effect.

We found that continuous esmolol infusions can significantly decrease anesthetic requirements for skin incision during balanced anesthesia with propofol, nitrous oxide, and morphine. Propofol CACI was accurate and stable, as measured by two venous blood samples. Esmolol did not affect the measured serum propofol concentration delivered by CACI, suggesting that esmolol does not significantly alter the pharmacokinetic properties of propofol. Adding esmolol to this balanced anesthetic technique resulted in no significant change in heart rate or blood pressure. β-adrenergic antagonists may represent a novel class of drugs that can modify anesthetic requirements in humans.

References

ESMOLOL DURING PROPOFOL/N₂O/MORPHINE ANESTHESIA


Appendix. A logistic regression model was used to solve the maximum likelihood equation for a 50% probability of movement in Figure 1. The equation is:

\[
\frac{a + b \ln(\text{propofol}) + c(\text{esmolol})}{a} = 0
\]

<table>
<thead>
<tr>
<th>a</th>
<th>b</th>
<th>c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient</td>
<td>-8.926</td>
<td>6.638</td>
</tr>
<tr>
<td>Standard error</td>
<td>2.84</td>
<td>2.03</td>
</tr>
<tr>
<td>P value</td>
<td>0.002</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Anesthesiology, V 86, No 2, Feb 1997