Reduction of the Minimum Alveolar Concentration of Isoflurane by Dexmedetomidine

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Background: α2-Adrenergic agonists have been shown to reduce anesthetic requirements of other anesthetics, and they may even act as complete anesthetics by themselves at high doses in animal models. The present study was designed to define the interaction of intravenous infusion of dexmedetomidine, an α2-adrenergic agonist, and isoflurane in patients having surgery by using the minimum alveolar concentration (MAC) of isoflurane as the measure of anesthetic potency.

Methods: Forty-nine women scheduled for abdominal hysterectomy were randomly allocated to receive either a placebo infusion (n = 16) or a two-stage infusion of dexmedetomidine with target plasma concentration of 0.5 ng/ml (n = 17) or 0.6 ng/ml (n = 16). The study drug infusion was commenced 15 min before induction of anesthesia with thiopental and alfentanil and was continued until skin incision. The end-tidal concentration of isoflurane for each patient was predetermined according to the “up-down” method of Dixon, and it was maintained for at least 15 min before the patient’s response to skin incision was assessed.

Results: The MAC of isoflurane was 0.85% end-tidal in the control group, 0.55% end-tidal with the low dose of dexmedetomidine, and 0.45% end-tidal with the high dose of dexmedetomidine.

Conclusions: The MAC of isoflurane in the control group was lower than that reported previously in similar patients having surgery, probably due to anesthesia induction with thiopental and alfentanil. Nevertheless, with the high dose of dexmedetomidine, the MAC of isoflurane was still 47% less than that withou dexmedetomidine. (Key words: Anesthetics, volatile; isoflurane, Minimum alveolar concentration, Sympathetic nervous system, α2-adrenergic agonists, Anesthesia.)

α2-ADRENERGIC agonists are being evaluated in anesthetic practice because of their sympatholytic, hemodynamic stabilizing, and analgesic and anesthetic sparing properties. Dexmedetomidine is a specific and selective α2-adrenergic agonist. In clinical studies, the anesthetic sparing effect of dexmedetomidine was demonstrated almost exclusively using hemodynamic criteria to assess anesthetic depth. However, because α2-adrenergic agonists are potent sympatholytic agents, autonomic nervous system reactions such as increases in heart rate or blood pressure may not be useful and reliable signs of insufficient anesthesia. Consequently concern has been raised regarding possible patient awareness during anesthesia when the sensitivity of hemodynamic variables as signs of anesthetic depth has been reduced.

The anesthetic potency of a volatile anesthetic is generally measured by the minimum steady-state alveolar anesthetic concentration required to suppress response in 50% of patients (MAC). This measure of potency can be used indirectly to assess the anesthetic effects of other agents by determining the effect of the agent in question on the MAC of the volatile anesthetic. The present study was designed to define the anesthetic interaction of isoflurane and an intravenous infusion of dexmedetomidine.

Materials and Methods

After local ethics committee approval and written informed consent, 49 women classified as American Society of Anesthesiologists physical status 1-2 (ages 31-55 yr) who were scheduled for abdominal hysterectomy under general anesthesia were included in this randomized parallel-group study (see table 1 for demographic characteristics). Exclusion criteria included breast-feeding, pregnancy, anemia, use of long-term medications or use of any medication within 1 week before surgery, a history of drug abuse, daily consumption of more than 30 g alcohol, and abnormal preoperative electrolyte concentrations. The patients were randomly allocated to three groups: The control group received physiologic
Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Low-dose Dexmedetomidine</th>
<th>High-dose Dexmedetomidine</th>
<th>Level of Significance (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>16</td>
<td>17</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>44.1 ± 1.14</td>
<td>45.4 ± 0.86</td>
<td>47.6 ± 0.93</td>
<td>0.049</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.8 ± 1.66</td>
<td>165.5 ± 1.74</td>
<td>164.7 ± 1.20</td>
<td>0.92</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.1 ± 2.50</td>
<td>66.9 ± 2.74</td>
<td>67.9 ± 2.43</td>
<td>0.96</td>
</tr>
<tr>
<td>Duration of study drug</td>
<td>17.4 ± 1.11</td>
<td>18.2 ± 0.90</td>
<td>18.5 ± 1.26</td>
<td>0.78</td>
</tr>
<tr>
<td>infusions before</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>induction (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of isoflurane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>administration before</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>skin incision (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction dose of</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>thiopental (mg)</td>
<td>20.1 ± 1.04</td>
<td>17.9 ± 0.92</td>
<td>18.0 ± 0.90</td>
<td>0.21</td>
</tr>
<tr>
<td>Data are mean ± SEM</td>
<td></td>
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</tr>
</tbody>
</table>

saline infusions, the low-dose dexmedetomidine group received a two-stage (loading and maintenance) infusion of dexmedetomidine targeted to achieve a steady-state plasma concentration of 0.3 ng/ml; and the high-dose dexmedetomidine group received a two-stage infusion of dexmedetomidine with a target concentration of 0.6 ng/ml. In the low-dose group, 75 μg/h dexmedetomidine was infused for the first 15 min and 60 μg/h was infused thereafter. In the high-dose group, 150 μg/h dexmedetomidine was infused for the first 15 min and 120 μg/h was infused thereafter. The study drug infusion was begun 15 min before induction of anesthesia, and a minimum period of 30 min was allowed to elapse before skin incision to ensure steady-state conditions between the plasma and brain effect compartment.

*Anesthesia*

The patients were not premedicated. When the patients arrived in the operating unit, an intravenous cannula was inserted for drug and fluid administration in one forearm, and another cannula was inserted in the contralateral forearm to obtain blood samples. The patients were connected to an electrocardiograph monitor, a pulse oximeter, and a noninvasive sphygmomanometer. Approximately 2 min before induction of anesthesia, 15 μg/kg alfentanil and 0.2 mg glycopyrrolate were administered intravenously. Anesthesia was induced initially with 2 mg/kg thiopental given intravenously supplemented with 25-mg intravenous boluses every 15 s until loss of eyelid reflex (determined every 15 s). The induction dose of thiopental was recorded. Succinylcholine (1.5 mg/kg given intravenously) was administered to facilitate endotracheal intubation. Muscle relaxation was monitored using a peripheral nerve stimulator. Immediately after intubation, administration of isoflurane was begun, and the inspired end-tidal concentration was adjusted to maintain the measured end-tidal concentration at the value predetermined for the patient. The patients were ventilated using a non-rebreathing system (Servo 900i; Siemens-Elema, Sweden) with oxygen in air (0.5 Fl.O.) and tidal volume approximately 10 ml/kg to maintain end-tidal carbon dioxide between 35 and 40 mmHg (± 7 - 5.3 kPa). End-tidal carbon dioxide and isoflurane concentrations were measured continuously with a multigas analyzer (Datex Capnomac; Instrumentarium, Finland) that was calibrated before each anesthesia dose was administered. The target end-tidal concentration of isoflurane was predetermined according to the "up-down" method described by Dixon and Mood. The first patient received 1.2% end-tidal isoflurane (approximately 1 MAC of isoflurane in patients ages 51 - 55 yr) in the control group, 0.7% end-tidal isoflurane (approximately 0.6 MAC) in the low-dose dexmedetomidine group, and 0.4% end-tidal (approximately 0.3 MAC) isoflurane in the high-dose dexmedetomidine group. These initial isoflurane concentrations were chosen based on previous studies in which similar dexmedetomidine doses decreased isoflurane requirements for anesthetic maintenance by 25% to 90%. If the pa-
REDUCTION OF THE MAC OF ISOFLURANE BY DEXMEDETOMIDINE

Fig. 1. The end-tidal isoflurane concentrations at which patients did (+) or did not (O) move in response to skin incision. (A) The control group. (B) The low-dose dexametomidine group. (C) The high-dose dexametomidine group.

tient moved in response to vertical skin incision, the assigned end-tidal concentration was increased by 0.1% end-tidal for the next patient in that group. If the patient did not move, the end-tidal concentration of isoflurane was decreased by 0.1%. The predetermined end-tidal concentration of isoflurane was maintained for at least 15 min to allow adequate time for alveolar and brain isoflurane partial pressures to equilibrate.5 Full recovery from succinylcholine-induced muscle relaxation was ensured and skin incision was performed. Movement was defined as gross purposeful movement of limbs, head, or body occurring within 60 s after skin incision. Coughing, chewing, or swallowing were not considered movement.4

After skin incision, the study drug infusion was discontinued and anesthesia was maintained with isoflurane in oxygen and nitrous oxide (FiO2, 0.3–0.4) supplemented with 1–2 μg/kg intravenous fentanyl bolus doses as deemed clinically appropriate. Muscle relaxation was achieved and maintained with vecuronium. Administration of isoflurane was discontinued at the time of fascial closure. On skin closure, neuromuscular block was reversed with a combination of 2.5 mg neostigmine and 0.5 mg glycopyrrolate given intravenously, and administration of nitrous oxide was discontinued.

Blood samples for determining plasma dexametomidine concentrations were obtained immediately before induction of anesthesia and at the time of skin incision. Blood samples for determining plasma thiopental and alfentanil concentrations were obtained at the time of skin incision. All samples were placed in prechilled tubes in ice and centrifuged as soon as possible (within 60 min), and the plasma was separated and stored at −70°C until assay. Plasma dexametomidine concentrations were analyzed using gas chromatography–mass spectrometry, plasma alfentanil concentrations were determined using capillary gas chromatography, and plasma thiopental concentrations were analyzed using high-performance liquid chromatography. The lower limits of detection were 10 pg/ml for dexametomidine, 2 ng/ml for alfentanil, and 10 ng/ml for thiopental. The respective intra-assay coefficients of variation were 3.3%, 3.1%, and 5.2% in the relevant concentration ranges.
Statistics

The anticipated number of move-no move pairs required for the present study was calculated with power analysis based on the results of Sebel et al.,16 in which the MAC of isoflurane was assessed in the presence of two different doses of fentanyl. Six pairs of patients in each group were analyzed to provide 80% power (1 − β = 0.80) with a 5% two-sided type I error (α = 0.05) in detecting at least a 20% difference in the MAC of isoflurane between two treatment groups.

The MAC of isoflurane was determined by two methods. The MAC for each group was estimated using the “up-down” method proposed by Dixon and Mood9 based on the sample conditional mean of the end-tidal isoflurane concentrations. Standard errors were calculated according to Dixon and Mood9 for the case in which the spacing between concentrations is sufficiently large compared with the standard deviation of the tolerance distribution. The relation between the MAC of isoflurane and the dexmedetomidine target plasma concentration was calculated, also using the maximum-likelihood solution to a logistic regression model.10,11 Analysis of variance was used to analyze continuous or semicontinuous variables (hemodynamics, drug doses, and so forth). The data are presented as means (SEM) unless stated otherwise.

Results

There were no important differences between the groups in the demographic data (table 1). The response to skin incision of each patient is presented in figure 1. The MAC of isoflurane was 47% smaller in the high-dose dexmedetomidine group and 35% smaller in the low-dose dexmedetomidine group than that in the control group, as calculated by the method described by Dixon and Mood (table 2). The MAC of isoflurane in the control group was significantly higher than that in the high-dose and low-dose groups (P = 0.022 and P = 0.025, respectively, in pairwise comparisons) as determined by the logistic regression model. The difference in the MAC between the dexmedetomidine groups was not significant (P = 0.47 in pairwise comparisons; table 2).

Patients in the low-dose dexmedetomidine group required 17% less thiopental to induce anesthesia, and patients in the high-dose dexmedetomidine group needed approximately 30% less than did those in the control group (P = 0.013 and P = 0.0001, respectively, in pairwise comparisons; table 1). There were no significant differences in plasma thiopental and alfentanil concentrations between the groups at the time of skin incision (table 2). The mean plasma dexmedetomidine concentration was 0.10 (0.013) ng/ml in the low-dose group and 0.31 (0.048) ng/ml in the high-dose group immediately before induction of anesthesia and 0.37 (0.021) ng/ml and 0.69 (0.041) ng/ml, respectively, at the time of skin incision (table 2).

Discussion

Dexmedetomidine has been shown to reduce perioperative dose requirements for thiopental,12 fentanyl,13 and isoflurane.5 Most of these studies, however, have used hemodynamic criteria to assess anesthetic depth, which may be inappropriate when compounds with direct cardiovascular effects are used as part of the anesthetic regimen.5 The MAC for volatile anesthetics represents one point on the dose-response curve of the anesthetic, and it allows quantitative analysis of the effect, if any, of pharmacologic and physiologic factors.5 The present study was designed to define the interaction of isoflurane and intravenous infusion of dexmedetomidine by using the MAC of isoflurane as the measure of anesthetic potency with both agents at a steady concentration and equilibrated with the effect site.

Dexmedetomidine has been shown to decrease the MAC of halothane to the extent that it may act as an anesthetic by itself at high doses in animal studies.14 The site of the anesthetic action of dexmedetomidine and other specific α2-adrenergic agonists resides in the locus ceruleus in the brain stem.15 More specifically, the mechanism of the hypnotic action of α2-adrenergic agonists has been attributed to inhibition of adenylate cyclase,16 with consequent changes in transmembrane ion conductance and hyperpolarization of excitatory neural cells.17

In this study, the MAC of isoflurane calculated by the method described by Dixon and Mood7 was 47% smaller in the presence of an average plasma concentration of 0.69 ng/ml of dexmedetomidine (the high-dose group) and 35% smaller with 0.37 ng/ml of dexmedetomidine (the low-dose group) than was the MAC in the control group. The MAC values determined by logistic regression model were essentially the same as these determined by the method of Dixon and Mood (table 2). Although the logistic regression model has been used commonly to determine the MAC of volatile anesthetics

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Table 2. The MAC of Isoflurane as Determined by the Dixon’ Method and by Logistic Regression, and Plasma Dexmedetomidine, Plasma Alfentanil, and Plasma Thiopental Concentrations at the Time of Determination of the MAC (Skin Incision)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low-dose Dexmedetomidine</th>
<th>High-dose Dexmedetomidine</th>
<th>Level of Significance (test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC by Dixon method</td>
<td>0.85 (0.39)</td>
<td>0.55 (0.33)</td>
<td>0.45 (0.05)</td>
<td>—</td>
</tr>
<tr>
<td>[% end-tidal; median (SD)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% confidence intervals for MAC by Dixon method</td>
<td>0.54, 1.16</td>
<td>0.31, 0.79</td>
<td>0.41, 0.49</td>
<td>—</td>
</tr>
<tr>
<td>MAC by logistic regression</td>
<td>0.81</td>
<td>0.51</td>
<td>0.45</td>
<td>0.06 (logistic regression)</td>
</tr>
<tr>
<td>(mean [SEM])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine [μg·ml⁻¹; mean [SEM]]</td>
<td>—</td>
<td>0.37 (0.021)</td>
<td>0.69 (0.041)</td>
<td>&lt;0.001 (ANOVA)</td>
</tr>
<tr>
<td>Alfentanil [μg·ml⁻¹; mean [SEM]]</td>
<td>39.2 (2.88)</td>
<td>42.9 (2.75)</td>
<td>46.9 (4.13)</td>
<td>0.28 (ANOVA)</td>
</tr>
<tr>
<td>Thiopental [μg·ml⁻¹; mean [SEM]]</td>
<td>4.3 (0.65)</td>
<td>3.4 (0.11)</td>
<td>2.8 (0.40)</td>
<td>0.10 (ANOVA)</td>
</tr>
</tbody>
</table>

in previous similar studies, the model may be inaccurate in these circumstances. Because the end-tidal concentration of the anesthetic assigned to each patient was related to how the previous patient responded, the outcome measurements for all patients are not independent, as assumed by a logistic regression model. Nevertheless, the model allows pairwise comparisons between the treatment groups and we present the results for their value compared with previous studies.

The MAC of isoflurane in the control group was 0.85% end-tidal as assessed by the method of Dixon and Mood (0.81% by the logistic regression model), which is less than that (1.2% end-tidal) reported previously. Although MAC determinations are usually done using inhalational induction, we chose to use intravenous induction for the present study, as has been done previously. We did this to avoid potential difficulties in inhalational induction with isoflurane and to follow the clinical practice of our institution, where inhalational induction would be unacceptable to most adult patients. Consequently, there were small but significant residual concentrations of thiopental (from 2.8 μg/ml in the high-dose dexmedetomidine group to 4.3 μg/ml in the control group) and alfentanil (from 39.2 ng/ml in the control group to 46.9 ng/ml in the high-dose dexmedetomidine group) present at the time of skin incision. In previous reports, this concentration range of thiopental did not significantly affect the MAC of isoflurane. The seemingly low doses of alfentanil that we used produced plasma levels that have been reported to reduce the MAC of isoflurane by as much as 50% under steady-state conditions. Although the alfentanil concentrations in our patients were a result of a bolus injection and do not reflect steady-state plasma or effect site concentrations, it is reasonable to assume that the lower-than-expected MAC in the control group was due to the effect of alfentanil or the combined effect of alfentanil and thiopental. In addition, opioids and α2-adrenergic agonists have been shown to have significant analgesic interaction at the spinal cord level, which may add to the MAC decreasing effect of dexmedetomidine observed in our study. Because there were no significant differences in the alfentanil or thiopental concentrations across the treatments at the time of skin incision, the MAC should have been equally affected by these agents in all groups, although the effects of possible spinal synergism of alfentanil and dexmedetomidine cannot be ruled out in the two dexmedetomidine groups.

There is some evidence that dexmedetomidine also may alter the distribution pharmacokinetics of intravenous agents, possibly because of decreased cardiac output after dexmedetomidine. The present study design with only one sample collection point for alfentanil and thiopental does not allow assessment of the effect, if any, of dexmedetomidine on the pharmacokinetics of these agents.

Our aim was to ensure a steady-state brain (theoretical effect compartment) concentration of dexmedetomidine and partial pressure of isoflurane at the time of skin incision. Maintenance of end-tidal isoflurane concentrations for 15 min before skin incision should have ensured equilibration of blood and brain partial pressures of isoflurane. The dexmedetomidine infusion achieved the target concentration reasonably well but resulted in a slightly increasing concentration through-
out the equilibration phase. The pharmacokinetic parameters for dexmedetomidine that we used to calculate the infusion rates were determined from a group of young healthy male volunteers and may have been slightly inaccurate for the older patients in our study.

In conclusion, our results suggest that clinically relevant doses of dexmedetomidine induce a dose-dependent and significant reduction of isoflurane MAC in persons having surgery. These results should be interpreted with caution until they are confirmed in a study in which no other agents are used that could interact with dexmedetomidine.

References