Effect of Thiopental Induction on Sympathetic Activity

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Several recent studies with different anesthetic agents have reported increases in plasma norepinephrine concentration during induction. To determine if induction with intravenous injection of thiopental also is associated with initial sympathetic activation, 24 ASA class I patients were assigned randomly to receive one of the following anesthetics: Group I, thiopental 3 mg/kg, iv, followed by inhalation of 100% oxygen and a continuous intravenous infusion of thiopental 0.2–0.3 mg·kg\(^{-1}\)·min\(^{-1}\); Group II, thiopental 3 mg/kg followed by inhalation of halothane (1.5% end-tidal concentration) in oxygen; and Group III, thiopental 3 mg/kg followed by inhalation of 70% nitrous oxide in oxygen. After thiopental injection, ventilation was controlled to maintain P\(_{\text{CO}}\)\(_2\) near control levels. In Group I, plasma norepinephrine concentration decreased with continued administration of thiopental. This decrease became statistically significant (P < 0.05) 10 min after injection. Plasma epinephrine concentration did not change. For Groups II and III, both plasma norepinephrine and epinephrine concentration did not change. For Groups II and III, the stability of the catecholamine concentrations during induction may have been caused by the circumvention of the second stage of anesthesia, equal depression of both inhibitory and excitatory synapses, or the combined effects of the agents. Regardless of the cause, the use of a modest induction dose of thiopental appears to allow the induction of anesthesia without sympathetic activation. When it is important to prevent sympathetic activation, administering a modest dose of thiopental before the inhalation of halothane or nitrous oxide may be preferable to inducing anesthesia with inhalation agents or narcotics alone. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: thiopental. Anesthetics, volatile: halothane. Sympathetic nervous system: catecholamines; norepinephrine.)

The plasma concentration of norepinephrine increases during induction of halothane, nitrous oxide, or morphine anesthesia.\(^{1,2}\) This increase is not due to placement of a face mask.\(^1\) At least three other explanations are possible. The sympathetic nervous system activity may reflect patient excitement during the second stage of anesthesia. Second, anesthesia initially may cause a greater depression of inhibitory than excitatory synapses. Third, halothane, nitrous oxide, or morphine may act directly on the nerve ending to increase norepinephrine release initially. Whether induction with thiopental before administering other agents affects this initial sympathetic activation has not been studied. Induction with thiopental might prevent such an increase by circumventing the second stage of anesthesia, by depressing excitatory as much (or more) than inhibitory synapses, or by directly inhibiting the release of norepinephrine at the nerve endings. The present report indicates that thiopental induction eliminates the increase in plasma norepinephrine associated with induction of anesthesia.

Methods

The Committee on Human Research approved the study protocol, and each patient gave informed consent. Twenty-four ASA class I patients (19–55 years of age) were given thiopental, 3 mg/kg, iv, followed by one of three regimens: inhalation of 100% oxygen and a continuous intravenous infusion of thiopental, 0.2–0.3 mg·kg\(^{-1}\)·min\(^{-1}\) for the duration of the study (Group I); inhalation of halothane (given in increasing concentrations until an end-tidal concentration of 1.5% was obtained, as determined by mass spectroscopy) in oxygen (Group II); or inhalation of 70% nitrous oxide in oxygen (Group III). After injection of thiopental, ventilation was controlled to maintain P\(_{\text{CO}}\)\(_2\) near control levels (as determined by mass spectroscopy).

An intravenous catheter was inserted into an ante-cubital fossa vein at least 15 min before control sampling. Venous blood samples were obtained 5 and 2 min before injection of thiopental (the control samples), and 2, 4, 6, 8, 10, 12, and 16 min after injection. All samples were analyzed for gas content (oxygen and carbon dioxide) and plasma catecholamines, the latter by using a modification of the Peuler–Johnson radioenzymatic assay.\(^3\) In this laboratory, the assay has a sensitivity of 6–10 pg of norepinephrine and 6–12 pg of epinephrine. Coefficients of variation have been 7% and 11%, respectively, over the last 20 assays. In seven of the patients given nitrous oxide (Group III), an additional bolus of thiopental (1 mg/kg) was necessary to prevent awakening; two of these patients required more than one bolus. A patient was eliminated from study if any value for venous P\(_{\text{CO}}\)\(_2\) was not within 6 mmHg of control values (three patients) or if any value for venous pH was not between 7.33 and 7.43 (two patients).

Heart rate and systolic and diastolic pressures were measured, and rate–pressure product, mean arterial pressure, and pulse pressure were calculated at each sampling time. Data for hemodynamic variables and plasma catecholamine concentrations were analyzed sta-
Table 1. Mean (±SEM) Plasma Concentrations (pg/ml) of Norepinephrine (NE) and Epinephrine (E) during Induction of Anesthesia with Thiopental

<table>
<thead>
<tr>
<th>Time after Injection of Thiopental (min)</th>
<th>Group I (Thiopental)</th>
<th>Group II (Thiopental and Halothane)</th>
<th>Group III (Thiopental and N₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE</td>
<td>E</td>
<td>NE</td>
<td>E</td>
</tr>
<tr>
<td>0</td>
<td>147 ± 32</td>
<td>43 ± 21</td>
<td>243 ± 45</td>
</tr>
<tr>
<td>2</td>
<td>155 ± 33</td>
<td>20 ± 7</td>
<td>201 ± 42</td>
</tr>
<tr>
<td>4</td>
<td>124 ± 26</td>
<td>20 ± 7</td>
<td>178 ± 30</td>
</tr>
<tr>
<td>6</td>
<td>124 ± 26</td>
<td>24 ± 14</td>
<td>167 ± 38</td>
</tr>
<tr>
<td>8</td>
<td>95 ± 23</td>
<td>24 ± 14</td>
<td>163 ± 29</td>
</tr>
<tr>
<td>10</td>
<td>75 ± 23</td>
<td>22 ± 11</td>
<td>187 ± 31</td>
</tr>
<tr>
<td>12</td>
<td>96 ± 23</td>
<td>19 ± 11</td>
<td>207 ± 38</td>
</tr>
<tr>
<td>16</td>
<td>84 ± 23</td>
<td>22 ± 23</td>
<td>211 ± 36</td>
</tr>
</tbody>
</table>

* P < 0.05.

statistically in each group and between groups using repeated-measures analysis of variance followed by the Newman–Keuls test. Comparison of changes in each cardiovascular variable with changes in plasma catecholamine concentrations were analyzed by least-mean-square regression. Results were considered statistically significant if P < 0.05 for differences from both control periods or if P < 0.05 for differences between groups.

Results

The concentration of norepinephrine in plasma progressively decreased in patients receiving the infusion of thiopental (Group I). The decrease became statistically significant (P < 0.05) 10 and 16 min after injection (table 1). The plasma concentration of epinephrine did not change. Plasma concentrations of neither catecholamine changed in patients receiving thiopental followed by halothane or nitrous oxide (table 1). Plasma levels of catecholamines for Group I almost became, but did not become, significantly less than levels for the other two groups at any time. Changes in P CO₂ (all of which were small, as set by study limits) did not correlate with changes in plasma norepinephrine or epinephrine levels.

The combination of thiopental and halothane (Group II) decreased pulse pressure, mean arterial pressure, and rate–pressure product (table 2), while the combination of thiopental and nitrous oxide (Group III) decreased only pulse pressure at isolated sampling times. The bolus of thiopental and the subsequent intravenous infusion (Group I) did not affect these hemodynamic variables. Changes in cardiovascular variables did not correlate with changes in plasma norepinephrine or epinephrine levels.

Discussion

The present results differ from those of recent studies, which suggested that induction of anesthesia was associated with sympathetic activation, whether accomplished by administration of halothane, nitrous oxide, or morphine. Administration of thiopental before other agents appears to stabilize both the absolute plasma concentration of catecholamines (table 1) and the percentage of change from control.

For comparison, data from the present study are shown with results from our previous study on induction of anesthesia with halothane (fig. 1). While the data

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**Fig. 1.** Mean percentage change in plasma norepinephrine concentration from control (mean) after initiation of anesthetic. Asterisk indicates that values differed significantly (P < 0.05) from both control periods for that group (intragroup comparison), as determined by repeated measures analysis of variance (see "Methods"). Data for the halothane/nitrous oxide group are from Joyce et al. (with permission of the author) and are added only for comparison (see "Discussion").
from induction with inhalation agents alone represents a historic control (the patients were not assigned randomly to one study or the other), the two studies encompassed the same patient population at the same institution. The two studies were conducted somewhat concurrently, the final half of the earlier investigation overlapping the first part of the present study by 2 months. The patients were similar in basal catecholamine levels, blood pressures, and other physiologic variables. Thus, we believe that comparison of these studies is useful, although limited by the historic reservations. Within these limitations, it appears that injection of thiopental before the administration of other agents blocks the initial sympathetic activation caused by inhalation of halothane or nitrous oxide.

Circumvention of the second stage of anesthesia may have caused the stability of the catecholamine concentrations during induction with thiopental for Groups II and III. This conclusion does not rule out the possibility that the increase in plasma catecholamines during induction with halothane or nitrous oxide might be secondary to an initially greater depression of inhibitory than excitatory synapses, because the second stage of anesthesia may result from depression of inhibitory synapses. The injection of thiopental before administration of halothane or nitrous oxide may depress both inhibitory and excitatory synapses equally. Alternatively, the stability of the catecholamine concentrations may have been caused by counterbalancing effects of the agents. Perhaps the tonic activity of the sympathetic nervous system is decreased by thiopental and increased initially by halothane and nitrous oxide.

The decrease in plasma norepinephrine concentration with thiopental alone implies that thiopental decreases tonic sympathetic nervous system activity. Previous studies support this conclusion. Skovsted et al. demonstrated that both thiopental and methohexitol inhibited cervical sympathetic preganglionic activity and decreased barostatic responses in cats. In humans, Wallin and König demonstrated a decreased sympathetic activity of cutaneous nerves during induction with thiopental.

The relative stability of plasma catecholamine concentrations in Group II patients, despite decreases in systolic blood pressure, rate-pressure product, mean arterial pressure, and pulse pressure, is in agreement with results of previous studies. In these studies, both thiopental and halothane blocked baroreceptor reflexes that otherwise would have elicited an increase in sympathetic activity as systemic blood pressure decreased.

The concentration of norepinephrine in the plasma represents only the small fraction of norepinephrine released at the nerve ending that remains after reuptake
and metabolism. Small increases in such concentrations may reflect small or large increases in norepinephrine release. The change in the concentration of norepinephrine in the plasma that results from a given change in sympathetic nerve activity depends on local factors at the specific sympathetic nerves affected. The density, distribution, and width of the neuroeffector junction between nerves cause differences in the plasma level for a given change in release of norepinephrine from the neuron. At narrow junctions reuptake predominates; whereas, at wider junctions more norepinephrine diffuses into the surrounding tissue or circulation. Thus, changes in sympathetic activity of nerves innervating arteries and veins (wide junctions) produce proportionately greater changes in plasma norepinephrine levels than do changes in release of norepinephrine from the vas deferens (narrow junctions).9

Regardless of the explanation of our results, the use of a small dose of thiopental appears to prevent the net increase in sympathetic activity associated with induction of anesthesia. In certain patients (e.g., those with angina or those who have undergone spinal cord transsection) it may be important to diminish or prevent sympathetic activation. If so, the administration of a small dose of thiopental before halothane or nitrous oxide is given may be preferable to induction with those agents alone.

References