DRUG DISPOSITION AND ANESTHETIC ACTION III

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TITLE: INHIBITION OF SYMPATHETIC NEURAL OUTFLOW CONTRIBUTES TO THE HYPOTENSION DURING PROPOFOL INDUCTION IN HUMANS.

AUTHORS: R.J. Berens, M.D., T.J. Ebert, M.D., Ph.D., J.P. Kampine, M.D., Ph.D.

AFFILIATION: Department of Anesthesiology, The Medical College of Wisconsin and VA Medical Center, Milwaukee, WI 53295

Propofol is a new, rapid-acting, sedative hypnotic agent which can be used for induction (and maintenance) of anesthesia. Although propofol clearly has a beneficial effect on emergence from anesthesia, induction of anesthesia with propofol can produce marked hypotension. The mechanism(s) of this response has been attributed to reductions of cardiac output and/or peripheral resistance. In the present protocol, approved by the human studies committee, efferent sympathetic nerve recordings were evaluated during anesthetic induction with either propofol (2.5 mg/kg) or sodium thiopental (4.5 mg/kg).

Consenting, unmedicated, ASA class I patients scheduled for surgery were monitored with lead II ECG, a radial artery catheter, a forearm plethysmograph, and were given 10 ml/kg of IV saline. Recordings of efferent sympathetic nerve activity directed to skeletal muscle blood vessels (MSNA) were obtained from a 5 μ tipped tungsten needle positioned in the peroneal nerve.

Preinduction HR, MAP, MSNA and forearm vascular resistance (FVR) were similar between groups as were reflex increases in HR and MSNA provoked by a transient hypotensive stimulus (100 μg bolus of nitropride).

Mean percent changes in parameters during a 4 minute period after anesthetic induction and prior to intubation are provided in the table below. In addition, propofol significantly reduced baroreflex mediated tachycardia by 50 ± 14% and decreased baroreflex MSNA by 5% ± 5%. These reductions did not differ from those produced by thiopental. Thus, hypotension during propofol induction is in part mediated by large reductions in sympathetic outflow and peripheral resistance. Hypotension is sustained during propofol secondary to an impaired baroreceptor reflex such that compensatory augmentations in HR and MSNA are severely limited.

<table>
<thead>
<tr>
<th>% Δ during induction</th>
<th>sodium</th>
<th>propofol</th>
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<tbody>
<tr>
<td>HR, b/min</td>
<td>24 ± 5.3</td>
<td>20 ± 8.1</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>-5.5 ± 3.8</td>
<td>-15 ± 5.8*</td>
</tr>
<tr>
<td>FVR, units</td>
<td>-0.1 ± 14</td>
<td>-41 ± 11*</td>
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<tr>
<td>MSNA, freq</td>
<td>-30 ± 12</td>
<td>-85 ± 6*</td>
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Data are mean %Δ SEM. *p < 0.05 compared to thiopental.

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extracellular Ca2+ influx. Halothane 2% and isoflurane 3% induced transient increases in cell fluorescence in both Fura-2 and indo-1 experiments.

Both anesthetics induced a brief increase in cytosolic Ca2+. Each method indicated a similar time course for the Ca2+ increase. However, lower concentrations of halothane evoked the effect. The responses were dependent in part upon Ca2+ entry through the plasmalemma. However, halothane and isoflurane reduce vascular resistance in intact animals and humans. It is possible therefore that the anesthetics have a biphasic effect with initial stimulation of Ca2+ flux followed by inhibition.

Figure 1. Cytosolic Ca2+ measured with aequorin

Figure 2. Cytosolic Ca2+ measured with Fura-2 in five cells before and after halothane 2%