Verapamil Decreases MAC for Halothane in Dogs

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Verapamil hydrochloride is a calcium entry blocking drug that is being prescribed with increasing frequency for cardiovascular disorders in the perioperative setting. Verapamil's calcium channel blocking effect is not selective, because it also exerts activity on the sodium channel. Because of the well-described effects of sodium channel blockers on anesthetic requirements, the authors studied the MAC for halothane in dogs before and after a therapeutic dose of verapamil 0.5 mg·kg⁻¹. There was a 25% reduction in halothane MAC from 0.97–0.72% (P < 0.01) when a therapeutic plasma level of verapamil (64 ng·mL⁻¹) was present. Anesthetic requirements for halothane are reduced by di-verapamil possibly on the basis of its local anesthetic-like sodium channel blocking properties. Adjustments in anesthetic dosage may be necessary in patients receiving verapamil. (Key words: Anesthetics, volatile: halothane. Ions: calcium. Pharmacology: verapamil. Potency, anesthetic: MAC)

Calcium entry blocking agents are being prescribed for an increasing number of patients for the treatment of supraventricular tachyarrhythmias and ischemic heart disease. These drugs also are used for a host of other indications such as hypertension and obstructive cardiomyopathy.

Because calcium may mediate the pharmacologic and toxicologic actions of numerous drugs and chemicals, the possibility of drug–drug interactions can be expected. This is especially true in the anesthetic paradigm in which patients already on these drugs will present for surgery or will be administered calcium entry blocking agents intraoperatively, raising the specter of possible interactions with anesthetic and adjuvant agents. The myocardial depressant effects of volatile anesthetic agents are exacerbated by verapamil, and this agent also potentiates the neuromuscular blockade caused by both depolarizing and nondepolarizing agents. Verapamil exhibits profound local anesthetic activity that exceeds that of procaine on a molar basis.

Because of the well-described decrease of volatile anesthetic requirements by systemically administered local anesthetics, we have examined the effects of acutely administered verapamil on the minimum alveolar concentration (MAC) for halothane in dogs.

Methods

Anesthesia was induced by mask inhalation of halothane in oxygen in six female mongrel dogs (15–30 kg). Tracheal intubation was accomplished without the use of muscle relaxants, and ventilation was controlled to avoid respiratory acidosis and maintained at an end-tidal CO₂ of 4.0% as determined by an infrared gas analyzer (Beckman® LB-2). Catheters were inserted percutaneously for intraarterial blood sampling and pressure monitoring and for intravenous fluid and drug administration. Halothane concentration was determined by means of a second infrared gas analyzer and recorded continuously together with the CO₂ concentration, heart rate and rhythm from lead II of the EKG, and arterial pressure on a direct writing four-channel oscillographic recorder (Beckman® R-511A). Temperature was recorded continuously with a rectal probe and maintained at 37°C with a heating pad.

The minimum alveolar concentration of halothane (MAC) necessary to prevent purposeful movement in response to the application of a tail-clamp was determined according to the method of Eger et al. Anesthetic concentration was changed by no more than 5% between each stimulus to facilitate a more precise determination of MAC within very narrow brackets. Verapamil hydrochloride 0.5 mg·kg⁻¹ was infused over 10 min to achieve a pharmacologic effect as evidenced by a prolongation of the PR interval on the EKG to approximately 160 ms. After a further 10-min equilibration phase, blood was sampled and the MAC again was determined as described above. The blood samples were analyzed for verapamil by a high-performance liquid chromatography procedure. Because verapamil may interfere with neuromuscular transmission, and therefore the defined endpoint of purposeful movement, a neuromuscular nerve block monitor (Ministim® Professional Instruments Company) was used to confirm that clinically significant neuromuscular blockade was absent. The results were analyzed by the two-tailed t test for paired data.

Results

As shown in table 1, the MAC for halothane in the dog decreased from 0.97 ± 0.08% (±SD) to 0.72
± 0.04% after verapamil (P < 0.01). The acid base status as determined by arterial blood gases was maintained between pH 7.38–7.42 and the mean PaO₂ was 464 ± 32 mmHg. The mean arterial blood pressure (MAP) significantly decreased during the verapamil infusion from 82 ± 18 mmHg to 65 ± 14 mmHg (P < 0.05) but had returned to near pretreatment values of 79 ± 16 mmHg at the time the MAC was determined (P > 0.05). The mean plasma verapamil level (±SD) at the time the MAC was repeated was 64 ± 20 ng·mL⁻¹, which effected a 40% increase in the PR interval from a mean of 114 ± 16 ms before the verapamil to 159 ± 15 ms after the verapamil infusion. The mean period of time between the pre- and post-MAC determinations was 169 ± 34 min.

Discussion

The verapamil infusion resulted in blood levels at the lower end of the therapeutic range and there was no electrocardiographic evidence of toxicity, i.e., Wenckebach phenomenon. The magnitude of increase in the PR interval noted on the electrocardiogram after verapamil infusion was consistent with previous reports and is indicative of a clinical effect. The halothane MAC for the dog, which should be stable for up to 8 h, was reduced by 25% following verapamil infusion.

Verapamil hydrochloride (Isoptin®) is supplied as a racemic mixture of both the dextro- and levorotatory stereo-isomers, which exert different effects. The D-isomer increases the threshold intensity of electrical stimuli needed to elicit conducted action potentials in a frequency-dependent manner. It is highly suggestive that the mechanism for this effect results from a specific inhibition of the fast Na⁺-inward channel. The L-isomer does not possess this Na⁺ channel blocking effect but is the active isomer in Ca²⁺ channel blockade.

Thus it would appear the the D-isomer confers the local anesthetic effect present in DL verapamil, while the L-isomer possesses the pharmacologically desirable effects on nodal conduction. That local anesthetics block Na⁺ channels is well known and the pivotal role that this channel plays in the anesthetic state now is unfolding. It is possible that the effect of DL verapamil in decreasing MAC is on the basis of Na⁺ fast channel blockade.

Alternatively, MAC may be affected by the indirect action of verapamil by lowering the blood pressure, which may decrease anesthetic requirements. In that study, if persistent arterial hypotension (MAP = 40–50 mmHg) was reversed even after 3 h, the MAC returned to control values. However, after 1 h of profound hypotension (MAP = 20–30 mmHg) the MAC did not normalize, despite adequate recovery of the blood pressure. In our experiments, the MAP did not drop below 40 mmHg (table 1), and by the time the MAC was repeated (169 ± 34 min) the blood pressure had long since returned to control values. Therefore, the modest and short-lived hypotension induced by the verapamil infusion is not a tenable explanation for the alteration in MAC.

There are now many reports of potentiation of neuromuscular blockers by verapamil, but none in which verapamil when given alone in therapeutic doses effected a clinically significant neuromuscular blockade. We could not demonstrate any decrement in the response to the nerve block monitor. Therefore, we discount the possibility that the decrease in MAC noted after verapamil infusion was related to muscle paralysis.

Inhibition of the slow inward calcium current is an effect shared by all calcium entry blockers, yet most of these agents possess other properties that not only contribute to their mechanism of action but also to the

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**Table 1. Effects of Verapamil on MAC, Hemodynamics and Acid Base Balance during Halothane Anesthesia**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Pre-§</th>
<th>Post-§</th>
<th>Time* min</th>
<th>Verapamil† ng/mL</th>
<th>Mean Arterial Pressure mmHg</th>
<th>Arterial Blood Gases‡ mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-†</td>
<td>Intra-†</td>
<td>Post-†</td>
<td>Pre-†</td>
<td>Intra-†</td>
<td>Post-†</td>
</tr>
<tr>
<td>1</td>
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<td>0.67</td>
<td>161</td>
<td>56</td>
<td>74</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>1.10</td>
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<tr>
<td>3</td>
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<td>66</td>
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<tr>
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<td>0.78</td>
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<td>63</td>
</tr>
<tr>
<td>5</td>
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<td>227</td>
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</tr>
<tr>
<td>6</td>
<td>0.86</td>
<td>0.70</td>
<td>185</td>
<td>104</td>
<td>84</td>
<td>82</td>
</tr>
</tbody>
</table>

Mean 0.97 0.72††‡‡ 169 64 82 65** 79 7.41 464 38
SD 0.08 0.04 34 20 18 14 16 0.02 32 3

* Elapsed time between the two MAC determinations.
† Plasma verapamil concentration at postverapamil MAC.
‡ Arterial blood gases at post-verapamil MAC.
§ Before and after verapamil infusion.

** P < 0.05 compared with preverapamil MAP.
†† P < 0.01 compared with preverapamil MAC.
genesis of side effects. Verapamil has local anesthetic-like properties, which is a possible mechanism whereby the MAC for halothane in dogs is decreased. Confirmation of this hypothesis requires that these experiments be repeated with the individual optical isomers, which are very difficult to isolate in the pure state.

Based on our findings, it would seem prudent to decrease the concentrations of halothane used in the presence of verapamil both because less anesthetic is required and because the additive adverse effects on hemodynamic alterations can be minimized.

References