Title: ISOFLURANE BLOCKS RELEASE OF BRAIN INTERSTITIAL FLUID ADENOSINE DURING DELIBERATE HYPOTENSION

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Introduction: Adenosine is thought to play a role in the regulation of cerebral blood flow (CBF). It is elevated during hemorrhagic hypotension,1 seizures,2 and ischemia.3 Isoflurane deliberate hypotension maintains a favorable balance between flow and metabolism (CMRO2) and is associated with fewer signs of cerebral ischemia than halothane.4,5 Because brain adenosine concentration is related to energy balance, we compared brain interstitial fluid adenosine during halothane and isoflurane deliberate hypotension.

Methods: 18 piglets of either sex less than seven days of age were sedated with ketamine 20 mg/kg and xylazine 3 mg/kg im, tracheotomized, and mechanically ventilated in an air/oxygen mixture. Neuromuscular blockade was induced with pancuronium, and anesthesia was induced with isoflurane or halothane. The PaO2 was maintained between 30-40 mmHg, and the PaO2, between 60-100 mmHg. Intraarterial and intravenous catheters were placed in the femoral vessels, and a soft silastic catheter was inserted into the sagittal sinus to measure venous outflow. Brain interstitial fluid adenosine was measured using the brain dialysis technique.2 In brief, brain dialysis catheters were implanted into the frontal cortex under direct vision and perfused at a constant rate with artificial CSF. The dialysate was assayed for adenosine, hypoxanthine, and xanthine by high pressure liquid chromatography. The piglets were divided into two groups and anesthetized with either isoflurane or halothane. Following baseline measurements, the inspired concentration of volatile agent was increased and MAP was reduced to 60 mmHg for 10 minutes. Measurements were repeated at 45 and 30 mmHg. At the conclusion, animals were sacrificed with an overdose of volatile agent or with injection of KCl. Statistical analysis of results was carried out with Duncan multiple range analysis (ANOVA).

Results: Hematocrit, PaO2, PaCO2, and pH were similar among the two groups of piglets. Induced hypotension to MAP 30 mmHg with either isoflurane or halothane resulted in similar reductions of cerebral blood flow (Table 1). Brain interstitial adenosine concentration was significantly higher during halothane hypotension at 30 mmHg (Table 2).

Discussion: Michenfelder et al reported that halothane induced deliberate hypotension resulted in signs of canine cerebral ischemia absent when isoflurane was used. They reported that with halothane, CBF (measured by sagittal sinus outflow techniques) fell 66%, tissue ATP decreased 11%, and lactate increased 181%. In contrast, isoflurane reduced CBF 62% but decreased ATP only 15% while increasing lactate 34%. In piglets, halothane and isoflurane reduced CBF by similar amounts.

Piglet cerebral metabolic response during deliberate hypotension is speculative because we could not measure energy change or brain lactate. We believe that MAP 30 mmHg in the piglet is comparable to 40 mmHg in the dog, even though resting control pressure is 90 mmHg in the piglet6 and 125 mmHg in the dog.5 MAP below 30 mmHg uniformly resulted in piglet death.

Halothane hypotension is associated with a statistically significant increase in brain interstitial adenosine concentration, absent with isoflurane. The rise in brain interstitial adenosine concentration at MAP 30 mmHg is consistent with its role in the regulation of CBF, and supports the suggestion that hypotension induced by halothane is accompanied by ischemic changes which are absent when isoflurane is used. In conclusion, brain interstitial adenosine is elevated during profound halothane, but not by isoflurane, produced by hypotension in the neonatal piglet.

References:

Table 1. Sagittal Sinus Blood Flow (ml/min) During Hypotension

<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>75</th>
<th>60</th>
<th>45</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>5.8±0.9</td>
<td>5.7±1.0</td>
<td>5.2±0.9</td>
<td>3.8±0.9</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>5.2±1.0</td>
<td>5.3±1.7</td>
<td>4.8±1.4</td>
<td>3.8±0.9</td>
</tr>
</tbody>
</table>

Table 2. Dialysate Adenosine Concentration (μM) During Hypotension

<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>75</th>
<th>60</th>
<th>45</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>.12±.17</td>
<td>.08±.056</td>
<td>.11±.154</td>
<td>.76±.686</td>
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<tr>
<td>Isoflurane</td>
<td>.074±.045</td>
<td>.067±.046</td>
<td>.069±.076</td>
<td>.064±.049*</td>
</tr>
</tbody>
</table>

*Indicate significance of p < .005 compared to halothane.