SURVIVAL OF SWINE WITH NIFEDIPINE TOXICITY TREATED WITH METHYLENE BLUE

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BACKGROUND
• Calcium channel antagonist-induced shock remains a significant treatment challenge.
• Nifedipine, a dihydropyridine calcium channel antag- gonist, has a proposed mechanism of vasodilatation through increased nitric oxide (NO) production.
• Methylene blue (MB) inhibits NO effects by inhibiting the activity of soluble guanylyl cyclase, thus may be useful to reverse hypotension associated with nifedipine toxicity.
• Methylene blue has not been studied as an antidote for nifedipine toxicity.

HYPOTHESIS
Methylene blue will improve survival following nifedipine intoxication in a swine model.

METHODS
• This IACUC approved study used 29 swine that were sedated with alpha-chloralose, mechanically venti- lated, and instrumented for drug delivery and hemo- dynamic measures.
• Methylene blue dosing had been determined from a dose response experiment prior to this study.
• Epinephrine dosing was determined from previous studies of nifedipine-induced toxicity in swine.

RESULTS
• Nifedipine toxicity was characterized by vasodilatory hypotension, impaired contractility, and tachycardia with terminal bradycardia.
• The mean time to death after reaching toxicity in the control group was 232±67.5 min (Figure 2).
• There was no statistically significant change in survival in animals treated with MB, epinephrine, or epinephrine plus MB (Table 1).

CONCLUSION
• Methylene blue demonstrated no improvement in survival of swine with nifedipine-induced toxicity.
• Further studies with other calcium channel blockers are needed to elucidate the value of MB in treating calcium channel antagonist-induced shock.

DISCUSSION
• We observed no survival treatment effect with MB even in combination with epinephrine.
• Potential limitations of this experiment include:
  – Excessive severity of toxicity
  – Insufficient dose of MB
  – Untreated direct cardiac stress from prolonged compensatory tachycardia
  – NO/soluble guanylyl cyclase may only play a minor role in nifedipine-induced hypotension
  – Alternate sedation methods, alpha-chloralose instead of isoflurane, may have had different effects on hemodynamic measures.

FIGURE 2: Kaplan-Meier Survival curve for each treatment group

TABLE 1: Mean survival time for each treatment group

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Mean Survival Time ± SD (min)</th>
<th>Statistical Significance of Treatment Group Compared to Control*</th>
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</thead>
<tbody>
<tr>
<td>Saline (Control)</td>
<td>232±67.5</td>
<td>p = 0.62</td>
</tr>
<tr>
<td>Methylene Blue</td>
<td>211±90.7</td>
<td>p = 0.99</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>234±115</td>
<td>p = 0.94</td>
</tr>
<tr>
<td>Epinephrine and</td>
<td>229±98.4</td>
<td>p = 0.94</td>
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</tbody>
</table>

*Calculated using unpaired 2-way student’s t-test.