SURVIVAL OF SWINE WITH NIFEDIPINE TOXICITY TREATED WITH METHYLENE BLUE

Murphy CM[1] | Williams C[1] | Quinn M[1] | Nicholson B[1] | Shoe T[1] | Dulaney AR[1,2] | Beuhler MC[1,2] | Kerns WP[1]

[1]Carolinas Medical Center, Charlotte, NC | [2]Carolinas Poison Center, Charlotte, NC

Carolinas HealthCare System

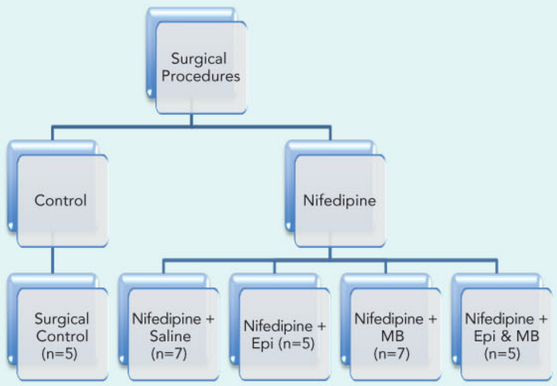
BACKGROUND

- Calcium channel antagonist-induced shock remains a significant treatment challenge.
- Nifedipine, a dihydropyridine calcium channel antagonist, 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

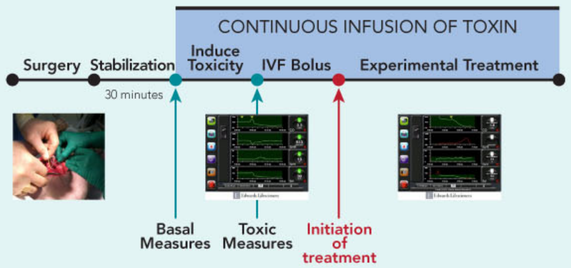
Methylene blue will improve survival following nifedipine intoxication in a swine model.

FIGURE 1: Breakdown of experimental treatment groups



METHODS

- This IACUC approved study used 29 swine that were sedated with alpha-chloralose, mechanically ventilated, and instrumented for drug delivery and hemodynamic 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.



- After stabilization and basal measures, nifedipine (0.01875 mg/kg/min) was infused until toxicity, defined as a reduction in product of cardiac output and mean arterial pressure of 20%, was reached.
- Animals received a bolus of 20 mL/kg 0.9% normal saline once toxicity occurred immediately followed by equal volume amounts of either normal saline as a sham treatment, MB (1 mg/kg as a bolus and subsequent infusion), epinephrine (0.1 mcg/kg/min), or MB and epinephrine (see Figure 1).
- All treatments were continued for 5 hours after the initiation of toxicity or until death occurred.
- Hemodynamics were monitored throughout the study.
- Surviving animals were euthanized.
- Survival data was analyzed using the student's t-test.

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).

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

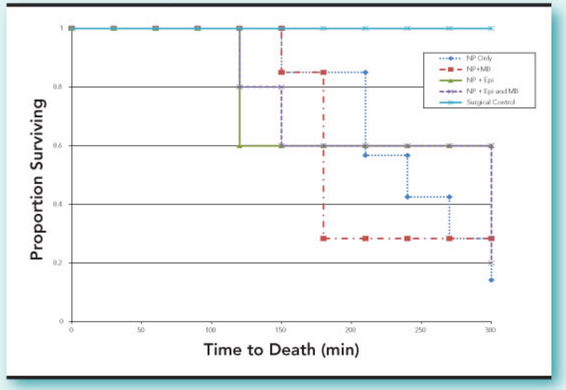


TABLE 1: Mean survival time for each treatment group

Treatment Groups	Mean Survival Time ± SD (min)	Statistical Significance of Treatment Group Compared to Control*
Saline (Control)	232±67.5	
Methylene Blue	211±90.7	p = 0.62
Epinephrine	234±115	p = 0.99
Epinephrine and Methylene Blue	229±96.4	p = 0.94

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

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.

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.