7. Efficacy of Hydroxocobalamin as Treatment for Nifedipine-Induced Shock

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**Background:** Calcium channel antagonist-induced shock remains a significant treatment challenge. Nifedipine, a dihydropyridine calcium channel antagonist, is thought to induce vasodilatation by increasing nitric oxide (NO) production. Hydroxocobalamin (HX), a hypothesized NO scavenger, may reverse hypotension associated with nifedipine toxicity.

**Hypothesis:** Hydroxocobalamin will improve survival and hemodynamics in a swine model of nifedipine toxicity.

**Methods:** This IACUC approved prospective animal study used Yorkshire swine sedated with alpha-chloralose, mechanically ventilated, and instrumented for drug delivery and hemodynamic measures. After stabilization and basal measures, nifedipine (0.0266 mg/kg/min) was infused until toxicity, defined as a reduction in mean arterial pressure (MAP) of 20%, was reached. Animals received a bolus of 20 mL/kg 0.9% saline once toxicity occurred immediately followed by 60 mL of either saline as a sham treatment (n=9) or HX (150 mg/kg; n=9). The nifedipine infusion continued for 4 hours after initiation or until death. Hemodynamics were monitored throughout the study. Surviving animals were euthanized. Survival data was analyzed using a log rank test and linear mixed models were used to compare the change in MAP from the nadir across time between groups.

**Results:** Nifedipine toxicity was characterized by vasodilatory hypotension and tachycardia with terminal bradycardia. Median time to death after reaching toxicity was 209 min (IQR: 177/240) in the HX group and 212 min (IQR: 201/240) for animals receiving the sham treatment. There was no significant change (NS) in mortality between groups. However, there was a significant improvement in the change in MAP from nadir over time (p=0.0021).

**Discussion:** While MAP improved significantly, we observed no decrease in mortality for swine treated with HX. Potential limitations of this experiment include: excessive severity of toxicity, insufficient dose of HX, the potential need for repeated dosing or continuous infusion of HX, untreated direct cardiac stress from prolonged compensatory tachycardia, and that NO production may play a minor role in nifedipine-induced hypotension. Further studies are needed to evaluate alternative dosing strategies of HX in treating calcium channel antagonist-induced shock and compare it to existing treatments.

**Conclusion:** Hydroxocobalamin demonstrated no improvement in survival of swine with nifedipine-induced toxicity, but did improve MAP.

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