A Swine Model of Severe Propranolol Toxicity Permitting Direct Measurement of Brain Tissue Oxygenation

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Abstract

Introduction High-dose insulin (HDI) therapy has been used successfully for beta-blocker toxicity, but needs further study when hypotension persists despite HDI. The objective was to develop a model of propranolol toxicity with persistent hypotension despite HDI and to develop means to measure cerebral oxygen tension (PbrO₂).

Methods Eight anesthetized Yorkshire pigs were instrumented with a tracheostomy, Swan–Ganz catheter, arterial catheter, and intra-cerebral pressure and oxygen monitor. Intravenous propranolol was given until the initial point of toxicity (POT); 25% reduction from baseline mean arterial pressure (MAP) × heart rate (HR). At the initial POT, normal saline (NS) bolus and infusion along with HDI infusion were started. The propranolol infusion was titrated up slowly to induce hypotension. Group 2 pigs received a norepinephrine (NE) infusion after a secondary POT defined as a MAP < 50 mmHg. NE was titrated to maintain subsequent MAPs > 50 mmHg. Cardiac output, HR, MAP, PbrO₂, and intracranial pressure were then recorded every 5 min until death or 4 h. Systemic vascular resistance, potassium, and glucose were also measured. Surviving pigs were euthanized.

Results Two pigs received unique doses for protocol development. One pig developed a tachyarrhythmia prior to protocol, one failed to reach secondary POT, leaving 2 pigs in each group reaching secondary POT. The range of PbrO₂ recordings for group 1 was 12.7–48.5 mmHg and 9.2–26.2 mmHg for group 2.

Conclusion We report a pilot study swine model of propranolol toxicity with hypotension despite HDI, in which physiologic measures including PbrO₂ are achieved. Our toxicity model can be used in the future, and the hemodynamic and brain monitoring model may prove important for subsequent research in various contexts.

Keywords Overdose · High-dose insulin · Pig · Licox · Brain

Introduction

Beta-blocker-induced toxicity causes significant morbidity and mortality in the USA despite recent advances in management [1]. The toxicity resulting from such ingestion is manifested as severe hypotension and bradycardia, which may lead to organ hypoperfusion, hemodynamic collapse, and eventual death. No therapy has proven universally effective. Experience with

high-dose insulin demonstrates that humans respond to high-dose insulin (HDI) when other agents have failed [2]. Insulin, an inotropic agent, restores tissue perfusion via increase in cardiac output. Cases of severe poisoning may cause hypotension despite maximal HDI therapy. Vasopressors increase mean arterial pressure (MAP) but also increase afterload. Some animal models show increased mortality with vasopressor use in poison-induced cardiogenic shock (PICS) [3]. Vasopressor use may be justified when the MAP is below the lower limit of cerebral blood flow autoregulation, but the impact of vasopressors on cerebral perfusion in PICS remains unclear. Studying brain perfusion during severe poison-induced cardiac toxicity and subsequent treatment could shed light on this subject, but there is not a repeatable model allowing for this sort of study. The objective of this study was to develop a swine model of propranolol toxicity that allowed for the repeated measurement of brain tissue

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oxygenation (PbtO₂) in addition to hemodynamic monitoring in the context of poison-induced cardiogenic shock.

Methods

Our study was approved and monitored independently by our institutional review board and animal care and use committee; funded was obtained through a research grant internal to our institution. The purpose of this pilot study was to develop a model for feasibility and to allow for post hoc analysis in order to power future studies. Therefore, the study length and the number of subjects were based on the researchers' experience with similar toxicity models rather than a priori statistical powering. Interventions were not randomized and the study was not blinded. This allowed researchers to adjust the protocol in real time to achieve the final protocol and a viable model (Fig. 1).

Eight anesthetized adult Yorkshire pigs were instrumented with a tracheostomy, Swan–Ganz catheter, arterial catheter, and intra-cerebral pressure and oxygen monitor (Licox® and Camino®, Integra LifeSciences). After induction of anesthesia via inhaled nitrous oxide and isoflurane, peripheral intravenous (IV) access was established and a tracheostomy was placed with a standard technique. Next, after identification of surface landmarks, the scalp was reflected to expose the calvaria for placement of the bolt for the intra-cerebral monitors. The bolt was placed approximately 1 cm caudal to the frontal–parietal cranial suture and 1 cm left lateral to the sagittal cranial suture and the monitors inserted [4]. Once secured and calibrated, the brain tissue oxygenation (PbtO₂) was

monitored until stable readings were obtained [5]. While allowing for stabilization of PbtO₂ readings, a Swan–Ganz catheter and arterial catheter were placed via a standard technique. Once PbtO₂ was stable and all instruments in place, baseline measurements of hemodynamics and laboratory markers were taken, including heart rate, MAP, and PbtO₂.

After instrumentation, toxicity was induced with IV propranolol. Of note, propranolol dosing initially followed previously published models from this group, but adjustments were required to achieve greater toxicity [6, 7]. Thusly, the first two pigs in our study had unique doses of propranolol titrated in order to derive the dosing protocol for the remaining six animals, four of which ultimately completed the protocol. In the animals that followed, a 0.5 mg/kg bolus of propranolol was given, then a 0.25 mg/kg/min infusion (gtt) until the initial point of toxicity (POT), defined as 25% reduction from baseline MAP × heart rate (HR). The initial POT marked the start of the resuscitation protocol. At the initial POT, a 20 ml/kg normal saline (NS) bolus was given along with a 1 ml/kg/h NS gtt and a 10 units/kg/h insulin gtt. The 20 ml/kg bolus was pushed by hand rapidly to prevent hemodynamic collapse. Pigs were divided into two groups in unblinded, nonrandom fashion to allow for guided protocol development. Group 1 pigs received IV fluids and HDI for resuscitation after the initial POT. The propranolol infusion was then set at 0.125 mg/kg/min for 60 minutes (min), then 0.1875 mg/kg/min for 30 min, and finally to 0.2188 mg/kg/min for the rest of the protocol. This empirically derived titrated dosing was utilized in lieu of the constant infusion from previous models to achieve progressive toxicity and hypotension despite HDI. A

Fig. 1 The final protocol and the viable model achieved

secondary POT was defined as a MAP < 50 mmHg after the resuscitation with HDI and IV fluids. After the secondary POT, pigs in group 1 received ongoing HDI only and group 2 pigs received a norepinephrine (NE) gtt in addition to HDI. The NE gtt was titrated from 0.1 to 0.3 mcg/kg/min to maintain subsequent MAPs > 50 mmHg. Cardiac output, HR, MAP, PbtO₂, and intracranial pressure were recorded every 5 min from the initial POT (Table 1). Systemic vascular resistance, potassium, and glucose were also measured. Pigs surviving 4 h beyond secondary POT were euthanized.

PbtO₂ and MAP measures were analyzed from the four pigs that completed the protocol. PbtO₂ measurements for each group were plotted over time and a trend line for each group was fit to the scatter plot via simple linear regression. Pooled MAP readings across groups were divided into MAP > 50 mmHg and MAP < 50 mmHg and correlated with PbtO₂.

Results

Figure 2 demonstrates the fate of the 8 subjects. Two pigs received unique dosing in order to derive the protocol and were excluded from analysis. One pig suffered an arrhythmia during instrumentation and died prior to beginning the protocol and was excluded from analysis. One pig failed to reach the secondary POT and was excluded from analysis. The remaining four pigs completed the protocol and were ultimately utilized for data analysis. Two pigs (subjects C and G, Figs. 2 and 3) completed the entire protocol in group 1 with HDI. Two pigs (subjects D and E, Figs. 2 and 3) completed the protocol in group 2 with HDI and norepinephrine after MAP was < 50 mmHg. The trend line of PbtO₂ over time for group 1 is represented by $\text{PbtO}_2 = 25.5 \text{ mmHg} - 2.2 \text{ mmHg/h}$. For group 2, the trend line of PbtO₂ over time is represented by $\text{PbtO}_2 = 24.4 \text{ mmHg} - 0.51 \text{ mmHg/h}$ (Fig. 3). The difference in slopes was estimated to be 1.69 mmHg/h. These were estimated by a linear mixed effects model, which found the interaction between treatment group and time to be statistically significant ($p = 0.0005$). PbtO₂ correlated with pooled MAP readings across subjects when MAPs were less than 50 mmHg across subjects ($r = 0.625$, 0.502–0.723). When pooled MAP

recordings were greater than 50 mmHg, MAP correlated poorly with PbtO₂ ($r = 0.050$, –0.133 to 0.229) (Fig. 4).

Discussion

Data in our pilot study provide meaningful insights into hypotension from propranolol toxicity despite maximal HDI therapy. The correlation of PbtO₂ and MAP when MAP is less than 50 mmHg suggests a failure of cerebral blood flow autoregulation and resulting flow-dependent cerebral perfusion. PbtO₂ did not correlate with MAP when MAP is greater than 50 mmHg consistent with flow-independent cerebral perfusion and intact cerebral blood flow autoregulation. These findings are consistent with our understanding of the physiology in both humans and swine at the lower limit of autoregulation of cerebral blood flow and strengthen the applicability of our model of cerebral perfusion in PICS [8, 9]. In head-injured humans, PbtO₂ values of less than 15 mmHg are associated with poor outcomes, while greater than 25 mmHg is normal [10]. Others have used swine models to study brain tissue oxygenation and perfusion in other contexts and with other monitoring techniques [4, 8, 11–14]. Our swine model provides multiple data points of PbtO₂ responsive to treatment and crossing these clinically relevant thresholds in the unique setting of progressive PICS (Fig. 2). In this limited data, there is a notable difference in the change in PbtO₂ over time; group 1 subjects treated with HDI have a decline of 2.2 mmHg/h while group 2 subjects treated with HDI and titrated norepinephrine have a PbtO₂ decline of only 0.51 mmHg/h despite worsening PICS (Fig. 2). These data can be used to power future studies. At this preliminary state, the difference in PbtO₂ over time between groups only suggests that PbtO₂ is a reasonable endpoint for studying the effect of vasopressors on cerebral perfusion in the setting of PICS. Moreover, we believe this model could also be utilized and adapted to study cerebral perfusion in shock states outside of PICS.

Limitations

This is a pilot study for toxicity model development and for the development of repeatable monitoring including hemodynamic

Table 1 Recorded cardiac output, HR, MAP, PbtO₂, and intracranial pressure

Subject ID	Weight (kg)	Cardiac output (l/min)	Heart rate	Mean arterial resistance	Systemic vascular resistance	Intracranial pressure (cm water)	Cerebral oxygen (PbtO ₂ mmHg)	Intervention
C	39.5	3.5 (2.4–4.9)	75 (69–88)	59 (33–66)	1143	16 (15–23)	36.8 (4.7–36.8)	HDI
G	42.2	4.5 (2.8–5.2)	97 (65–100)	61 (40–62)	1013	15 (15–20)	28.5 (12.3–41.7)	HDI
D	37.5	3.2 (2.0–3.2)	77 (59–90)	68 (30–68)	1500	17 (17–23)	23.5 (6.8–28.3)	HDI + NE
E	41.2	3.5 (1.7–4.2)	96 (50–96)	67 (35–67)	1322	15 (14–21)	20.1 (18–26.6)	HDI + NE

HDI high-dose insulin, NE norepinephrine

Fig. 2 The fate of the 8 subjects

parameters and brain oxygenation. The small number of subjects makes this useful in achieving the model but not in

drawing treatment conclusions. The study was not blinded and 4 of the 8 initial animals were excluded from the analysis

Fig. 3 Cerebral O₂ pressure (PbTO₂) vs time from secondary toxicity

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