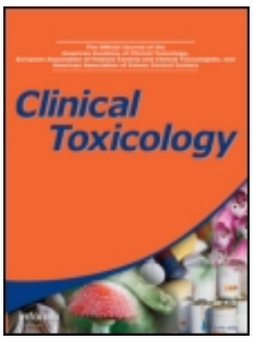

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ARTICLE

Insulin versus vasopressin and epinephrine to treat β-blocker toxicity

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Objective. We compared insulin and glucose (IN/G) to vasopressin plus epinephrine (V/E) in a pig model of β-blocker toxicity. Primary outcome was survival over four hours. *Methods.* Ten pigs received a 0.5 mg/kg bolus of propranolol IV followed by a continuous infusion. At the point of toxicity 20 ml/kg normal saline was rapidly infused and the propranolol drip continued at 0.125 mg/kg/min over four hours of resuscitation. Each pig was randomized to either IN/G or V/E. The V/E group began with epinephrine at 10 mcg/kg/min titrated up by 10 mcg/kg/min every 10 min to 50 mcg/kg/min or until baseline was obtained. Simultaneously, these pigs received vasopressin at 0.0028 units/kg/min, titrated upwards every 10 min to 0.014 units/kg/min or until baseline was obtained. The IN/G group began with a 2 units/kg/hr drip and increased by 2 units every 10 minutes to 10 units/kg/hr, or until baseline hemodynamics were obtained. CO, SVR, systolic blood pressure, HR, MAP, glucose, and potassium were monitored. Glucose was given for values <60 mg/dl. *Results.* The study was terminated early due to marked survival differences after five pigs were entered in each group. All IN/G group pigs survived four hours. All V/E group pigs died within 90 min. CO in the IN/G group increased throughout the four hours, rising above pre-propranolol levels, while MAP, SBP, and SVR all trended slightly downward. CO in the V/E group dropped until death, while MAP, SBP, and SVR rose precipitously until 30–60 minutes when these dropped abruptly until death. Glucose was required in the IN/G group. *Conclusion.* In this swine model, IN/G is superior to V/E to treat β-blocker toxicity. IN/G has marked inotropic properties while the vasopressor effects of V/E depress CO and contribute to death. Increasing SVR in this condition is detrimental to survival.

Keywords β-blockers; Overdose; Poisoning; Insulin; Vasopressin; Epinephrine; Cardiovascular toxicity

Introduction

In the United States, toxicity induced by β-blocker ingestion causes significant morbidity and mortality. In 2004, the American Association of Poison Control Centers reported 17,057 exposures to β-blocker toxicity, including 2,467 cases classified as moderate or major toxicities and 25 deaths due to intentional or accidental ingestion (1). Reversal of the bradycardia and hypotension are the primary goals in treatment of this toxicity. Various modalities have been used as therapy including volume expansion, atropine, cardiac pacing, vasopressors, and inotropes. The effectiveness of the catecholamine vasopressors is often limited, as they act upon many of the same cell membrane receptors that are blocked. Traditionally, glucagon has been considered a first line cardiovascular agent in β-blocker toxicity due to its ability to increase intracellular cyclic AMP via a non-catecholamine receptor on the cell wall (2,3). The ability of glucagon to reverse β-blocker toxicity is variable, however, and glucagon has failed as a single agent in several case reports (4–6).

Recently we found that vasopressin was superior to glucagon in improving mean arterial pressure and systolic blood pressure when used as a first line therapy early in the course of resuscitation in propranolol toxicity using a pig model. This may be due to the superiority of vasopressin in increasing systemic vascular resistance compared to glucagon. These physiologic advantages, however, did not translate into survival advantages, as we found no survival differences between the vasopressin and glucagon resuscitated groups (7). Vasopressin is a peptide hormone that is synthesized in the hypothalamus and stored in the posterior pituitary gland. It is released in response to increased plasma osmolarity, or due to a baroreflex from the aortic body sensing decreases in blood pressure or volume (8). Its renal actions are mediated via the V2 receptors, which are coupled to the generation of cyclic AMP by adenyl cyclase resulting in the resorption of water. In the vasculature, vasopressin acts upon V1 receptors

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on smooth muscle, which are coupled to a phospholipase C mediated increase in intracellular Ca++ via the phosphoinosotide cascade. Vasopressin has also been shown to be an effective vasopressor in septic and other forms of vasodilatory shock (9,10). There is debate about whether the combination therapy of vasopressin and epinephrine may be more effective than epinephrine alone in cardiopulmonary resuscitation (11). There is evidence in animal models that the combination of vasopressin and epinephrine improves survival in cardiac arrest. (12,13). This was also shown in a human clinical trial of refractory cardiac arrest (11). Vasopressin and a catecholamine may have complex interactions, although these are not yet well defined. Vasopressin acting on vascular smooth muscle receptors may potentiate α-agonists and block ATP-sensitive potassium channels to help restore vascular tone (14).

Insulin has also been found to be effective in β–blocker toxicity in several animal and human case reports. Kerns et al. found insulin improved survival compared to either glucagon or epinephrine in a canine model of β-blocker overdose (15). The mechanism of this effect is unclear. Insulin is an inotropic agent and promotes aerobic metabolism in the myocardium (16,17). Insulin protects against apoptosis and ischemia/reperfusion injury during the shock state. Other possibilities include enhancement of glucose transport in the myocardium during the toxic state, the improvement of intracellular calcium homeostasis by enhancing calcium channels, and stimulation of catecholamine release (17,18).

In 1997, Kerns demonstrated that insulin did improve survival when compared to glucagon or epinephrine in a canine β-blocker toxicity model. In our recent study, we demonstrated that vasopressin as a single agent improved hemodynamics compared to glucagon in a similar swine model, though this did not result in improved survival. Theoretically, and due to the above mentioned evidence, we felt that the addition of epinephrine to vasopressin may be beneficial in this clinical setting. In this study we compare vasopressin plus epinephrine to insulin and glucose in a model of β-blocker toxicity. Our hypothesis is that a combination of insulin and glucose will be superior to a combination of vasopressin and epinephrine.

Methods

Our Institutional Animal Care and Use Committee approved this research. Healthy 12-week-old pigs weighing approximately 27–35 Kg were acclimated for a minimum of five days prior to the study. Each pig was temporarily sedated with Telazol (Fort Dodge Animal Health, Southampton, U.K.) intramuscularly to facilitate the establishment of an ear vein. Thiopental sodium (2.5%) was administered to effect while a tracheotomy was performed. Anesthesia was then maintained throughout the protocol using a combination of 30% nitrous oxide and isoflurane and titrated by monitoring of reflexes in order to minimize cardiovascular depressant effects. Each pig was mechanically ventilated at a rate of 10 breaths per minute and FiO_2 was maintained at 30%. An incision was then made to expose the internal jugular vein and a Swan-Ganz catheter was placed into the pulmonary artery. A femoral cut down was performed to allow placement of femoral arterial and vein catheters. ECG electrodes were attached for continuous monitoring. Body temperature was maintained at 37–38 degrees, utilizing a heating blanket as needed. Continuous cardiac output (CO) was measured by the thermodilution technique. Continuous ECG, O_2 saturation, heart rate (HR), systolic BP (SBP), mean arterial BP (MAP), central venous pressure (CVP), systemic vascular resistance (SVR)-calculated, arterial pH, and SVO_2 monitoring were performed and recorded every 10 minutes.

At the beginning of the experimental protocol, baseline hemodynamic and metabolic determinations were documented. Each pig received an initial bolus of propranolol at a dose of 0.5 mg/kg. An infusion of propranolol was then initiated at 0.25 mg/kg/min and continued until the point of toxicity. A point of toxicity was defined as the time when the product of the HR and MAP decreased to a value that was 75% of the baseline product. This definition was based on a previously published protocol by Kerns et al. (15). When the point of toxicity was obtained, a fluid resuscitation bolus of 20 ml/kg of 0.9% saline was administered over the next 10 minutes. At this time the propranolol infusion rate was decreased 50% to 0.125 mg/kg/min to simulate continued absorption. This reduction in the continuous dose was chosen due to concerns from our previous model that the continuation at 0.25 mg/kg/min produced a model that was too toxic to find subtle differences in treatment arms.

Each pig was randomly assigned to either the insulin and glucose (IN/G) group or to the epinephrine and vasopressin (V/E) group. After the fluid resuscitation, the V/E group received an initial dose of .0028 units/kg/min of vasopressin and 10 mcg/kg/min of epinephrine. The vasopressin (American Pharmaceutical Partners, Schaumburg, IL) infusion was increased by .0028 units/kg/min every 10 minutes until the HR × MAP was equal to their baseline value or up to a maximum value of 0.014 units/kg/min. The vasopressin infusion was based on the human equivalency infusion of a titration between 11.8 and 58.8 units per hour (70 kg person), and the identical rate as our previous model. The vasopressin solution was made by diluting 1 ml of 0.2 u/ml vasopressin in 50 cc of normal saline. The epinephrine infusion was increased by an additional 10 mcg/kg/min until the HR × MAP was equal to their baseline value or up to a maximum of 50 mcg/kg/min. Insulin infusions were started at 2 units/kg/hr and increased every 10 minutes by an additional 2 units/kg/hr until the HR × MAP was equal to their baseline value or up to a maximum of 10 units/kg/hr. A glucose level was performed on both groups at baseline, at the point of toxicity, and every 10 minutes after the point of toxicity until the end of the protocol or death. A glucose less than 60mg/dl was treated with 25 grams of intravenous dextrose. A glucose less than 40mg/dl was treated with 50 grams of intravenous dextrose. Potassium levels were determined at baseline, the point of toxicity, and at 60 minute intervals until the end of the study or death. Total resuscitation time was until death or when four hours elapsed.

At this point any living pigs were euthanized with a concentrated sodium pentobarbital solution.

Our primary outcome measure was survival. A 50% difference in survival rates would be considered significant and would lead us to believe that IN/G is superior to V/E in treating β-blocker toxicity. We anticipated that approximately 50% of the animals receiving V/E would survive four hours of resuscitation, and all pigs receiving the IN/G treatment would survive. Under these assumptions, a log-rank test for equality of survival curves with an $\alpha = 0.05$ two-sided significance level will have approximately 82% power to detect a 50% difference (i.e., 100% vs. 50% survival). Based on this, we anticipated studying 10 pigs in each group.

Data analysis was conducted using SAS V8.1 statistical analysis software. A Kaplan-Meier survival curve with a log-rank test was used to analyze differences in survival between the two treatment groups. A Fisher's exact test was used to compare the proportion of animals surviving at the end of the study. Hemodynamic and metabolic data was expressed encompassed by 95% confidence regions. Repeated measures analyses using SAS PROC MIXED was used to analyze physiologic data. The type 1 error rate was set at the 5% level.

Results

The mean pig weight was 30.1 kg in the V/E group and 32.6 in the IN/G group. Baseline measurements did not show differences between the groups prior to infusion of propranolol in respect to MAP, CO, SBP, HR, CVP, SVR or pH (see Table 1). All animals reached time to toxicity within 60 minutes, and there was no difference between the groups ($p = 0.91$). All animals in the V/E group were titrated to the maximum drip rates for both drugs. All but one animal in the IN/G group were titrated to the maximum insulin drip rate (one pig returned to baseline after titration to 6 units/kg/hour).

For the primary outcome measure of survival, after five pigs were entered in each group, a planned midway interim analysis was conducted. At this point in the study there was 100% survival to four hours in the IN/G group, and 0% survival in the V/E group, with all pigs dying within 1.6 hours from the beginning of resuscitation (time 0). Results from this analysis indicated a significant difference in survival ($p < 0.001$) (20). In order to allow for conservation of animal resources we elected to terminate the study. The survival curve is shown in Figure 1.

Analysis of the secondary endpoints found significant differences throughout the resuscitation period especially in respect to CO, HR, MAP, SVR, and CVP. These data are represented in Figure 2, with the confidence bands included. In general, the IN/G group is characterized by a maintenance of MAP over time, an increase in HR, a decrease in SVR, and a dramatic increase in CO. The V/E group is characterized by a marked increase in MAP until 30 minutes into the resuscitation followed by a significant decrease until death. SVR demonstrated a similar shaped curve, peaking at 30 minutes, then falling until death. The CO and HR fell continuously over time from the onset of resuscitation. Figure 3 demonstrates the relationship between CO and SVR in the two groups. There is an inverse relationship between these parameters. The CVP trended upwards in the V/E group, while falling in the IN/G group (Fig. 2).

Glucose was required only in the IN/G group, with requirements as shown in Figure 4. Potassium levels dropped mildly lower in the IN/G group as expected, with no level recorded less than 2.7 in any animal and these results are graphed in Figure 5. We did not observe any ectopic or ventricular arrhythmias, and we did not observe QRS widening during propranolol toxicity.

Discussion

In this model of severe β-blocker toxicity, we found insulin to be a clearly superior resuscitative agent than the combination of vasopressin and epinephrine. Insulin was superior not only in a survival benefit, but also showed markedly different profiles

Table 1. Mean baseline values

	IN/G	V/E	P value
CO (L/min)	4.64	4.4	0.69
HR	101.6	105.4	0.48
MAP (mmHg)	83	78	0.45
SVR	0.64	0.58	0.47

CO: cardiac output; HR: heart rate; MAP: mean arterial pressure. SVR: systemic vascular resistance.

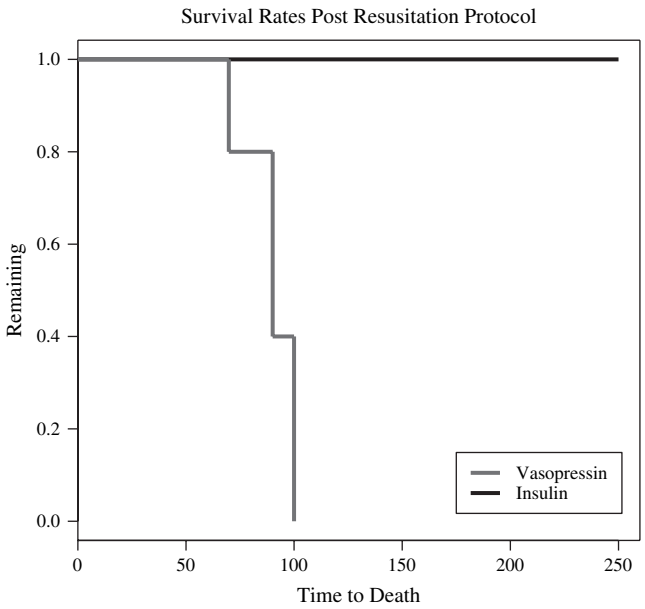

Fig. 1. Kaplan-Meier survival curve.

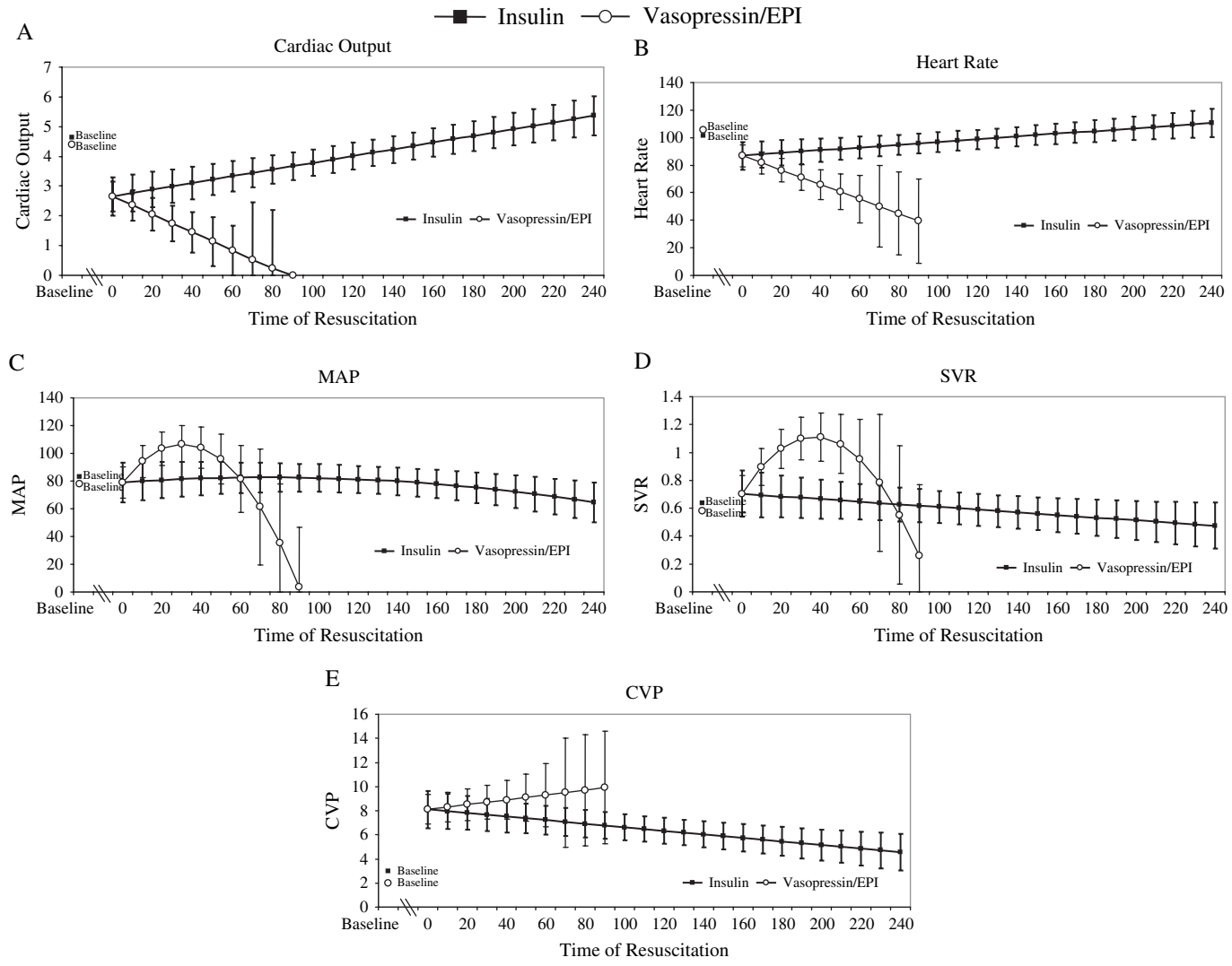

Fig. 2. Mean hemodynamic measurements with 95% confidence intervals.

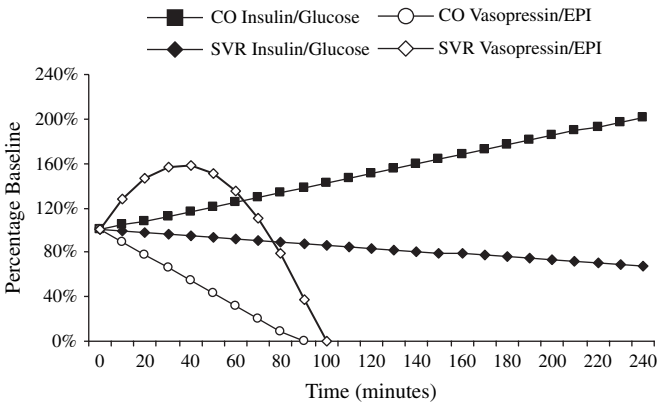

Fig. 3. Relationship of cardiac output and SVR.

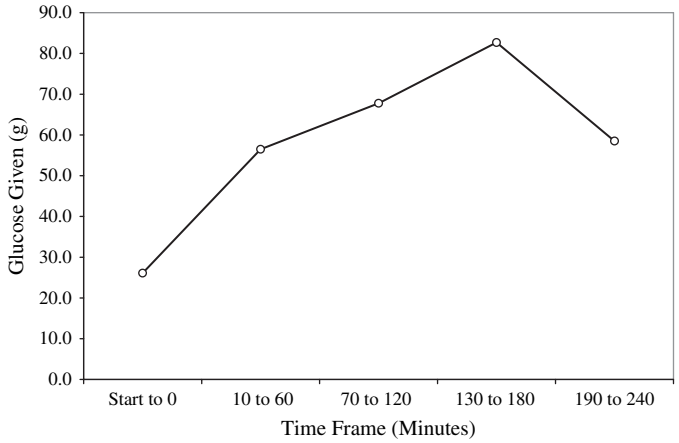

Fig. 4. Glucose requirements per hour in the insulin-glucose group.

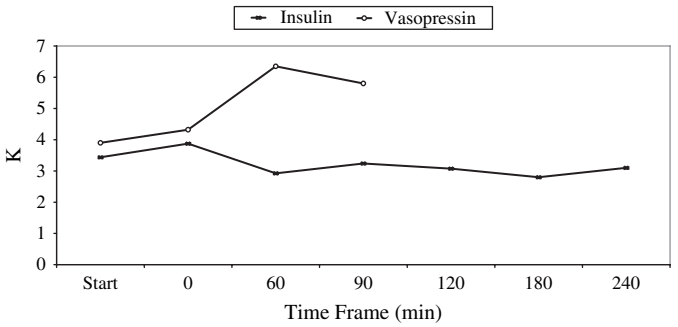

Fig. 5. Comparison of mean potassium levels during resuscitation.

of cardiovascular function. Glucagon, another inotropic agent, has been accepted as a standard agent to be used in β-blocker overdose. Although we did not test the effect of glucagon in this study, it has been tested directly against insulin by Kerns in his dog model, and was inferior to insulin in terms of mortality and cardiovascular parameters (15). We also found vasopressin to be equal to glucagon in terms of survivability (7). We did not include a placebo (saline) control group as Kerns demonstrated 100% mortality by 150 minutes in this arm in his study, and we did not feel it was ethical to repeat this (15). We also used the equivalent doses of insulin on a unit/kg/hour basis that he used in his dogs when he found 100% survival in his insulin group.

Examining the curves over time of the measured cardiovascular parameters in this study clearly depicts each drug's effect on hemodynamics and thus offers clues to the physiological mechanisms of their effect. Insulin was found to be an inotropic agent and this mechanism is demonstrated by observing the relationship of the CO and HR. In the IN/G group the CO increased during the resuscitation period, to the point of being higher than the baseline CO in the animals prior to any infusion of propranolol. This occurred with only a modest increase in HR. Thus, stroke volume, although not directly measured, likely increased significantly.Stroke volume is mostly dependent on preload and contractility (with a small, inverse contribution from afterload). We observed the preload to decrease in the IN/G group and the SVR to decrease over time, leaving the increased inotropic state likely to account for the increase in CO. The decreasing SVR may be artifactual due to the fact that this is a calculated value, which includes the CVP in the numerator. Insulin does have, however, a vasodilating effect in vascular smooth muscle. We could postulate that increasing preload by giving more fluids in the IN/G group would increase the CO even further.

In the V/E group, the CO continued to decrease in a linear fashion from the point of beginning of resuscitation until death. The CVP levels rose during this time, which should enhance CO, however this was accompanied by a sharp rise in SBP and SVR in the initial stages of resuscitation while the HR decreased steadily. This suggests that there was an inverse relationship in this group between SVR and CO. The depressed β-blocked heart was unable to overcome the increasing vasoconstriction of the combined vasopressors, further reducing CO. Our model did not show any evidence of an inotropic effect using vasopressors. The SVR and SBP likely rose until the point of impending death, at which point SVR and SBP dropped precipitously. It is also clear that the very large doses of epinephrine used were unable to overcome the depressed chronotropic state in this severe β-blocked model.

In the clinical setting, the effects of using potent vasopressors would be typically monitored using the HR and blood pressure. Our model demonstrated a marked increase in SVR with a concomitant decrease in CO during the administration of vasopressor agents. These clinically significant hemodynamic changes would not be appreciated through HR and BP monitoring alone, and may be masked by the appearance of an improving hemodynamic situation, until the SVR is too great to be overcome by the depressed contractility of the heart, at which point death might be imminent. In the insulin arm, all cardiovascular parameters improved (except CVP), including SV02, suggesting an improvement in tissue perfusion and oxygenation as well.

We did not supplement the insulin group with additional potassium, and the potassium dropped to moderate levels of hypokalemia (lowest level was 2.7 mmol/L). However, we did not observe any deleterious effects due to this drop. The V/E group demonstrated a mild hyperkalemia until late in the course of resuscitation when this became more severe; this may represent a leak from ischemic tissue or due to acidosis as a preterminal event. β-blockers suppress adrenergic mediated uptake of potassium by peripheral tissues, and this may have exacerbated the hyperkalemia.

Clinical relavence

This study adds significant animal model evidence to support the use of insulin in this toxicity in high doses up to 10 units/kg/hour. This ceiling dose was arbitrarily chosen and based on previous studies (15). The efficacy of insulin was evident not only in terms of survivability but also in terms of cardiovascular performance, comparing a vasopressor versus an inotropic approach. We did not observe a plateau of cardiovascular function at the 10 units/kg/hour level; the maximum effective dose of insulin may even be higher. Could a combined approach of both inotropes and vasopressors be even more successful? We did not test this, although it is possible that the use of vasopressors may require even higher doses of inotropic agents to overcome the increase in the SVR to augment cardiac output in this setting of profound myocardial depression.

Limitations

Data derived from this animal model may have limited applicability in humans. Prospective human clinical trials in toxicology are difficult to perform, and much of what we

believe is therapeutically effective is based on animal models and case reports.

Most animal cardiovascular models will have some myocardial depressant properties inherent in them due to the anesthesia chosen. We believe that the combination of nitrous oxide and low dose isoflurane, however, minimized these effects.

We did not measure coronary artery blood flow. It is possible that the combination of vasopressin and epinephrine caused cardiac ischemia that contributed to the depressed cardiac output. We did not, however, observe any ST segment deviations in the V/E group, and this combination in a pig cardiac arrest model markedly increased coronary blood flow compared to either agent alone (20).

Conclusion

In this animal model of severe β-blocker-induced cardiovascular toxicity, we found the combination of insulin in doses up to 10 units/kg/hour and glucose to demonstrate a clear and definitive superiority over the combination of vasopressin and epinephrine. The cardiovascular physiology we measured also demonstrates the advantages of an inotropic approach over a vasopressor approach in this toxicity where there is profound myocardial depression.

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