Early use of high-dose insulin euglycaemic therapy for verapamil toxicity

Christopher P Nickson and Mark Little

A 49-year-old man presented with verapamil toxicity complicated by hypotension and a junctional rhythm, in the context of deliberate self-poisoning with multiple drugs. The patient's hypotension normalised following the early use of high-dose insulin euglycaemic therapy (HIET), without the need for additional vasopressors; it recurred when HIET was prematurely stopped, and again stabilised when HIET was recommenced. Consideration should be given to the early use of HIET in treating severe calcium channel blocker toxicity, rather than as a last resort after other therapies have failed. **(MJA 2009; 191: 350-352)**

Clinical record

A 49-year-old man presented to a peripheral hospital emergency department 1–1.5 h after deliberately ingesting multiple medications: verapamil (unknown amount), controlled-release morphine sulfate (20 × 30 mg), diazepam (50 × 5 mg) and tramadol (15 × 200 mg). He was a smoker with a history of depression, ethanol misuse, chronic back pain, hypertension and a previous instance of deliberate self-poisoning with multiple drugs.

At initial assessment, the patient's vital signs were: temperature, 36.8° C; pulse, 84 beats/min; respiratory rate, 19 breaths/min; blood pressure (BP), 115/80 mmHg; oxygen saturation, 95% on room air; and Glasgow Coma Scale score, 14/15. He was drowsy, disorientated to time, and had 2 mm pupils that were equal and reactive. He had ataxia, dysarthria and was generally weak. His breath ethanol concentration was 0.172 mg%.

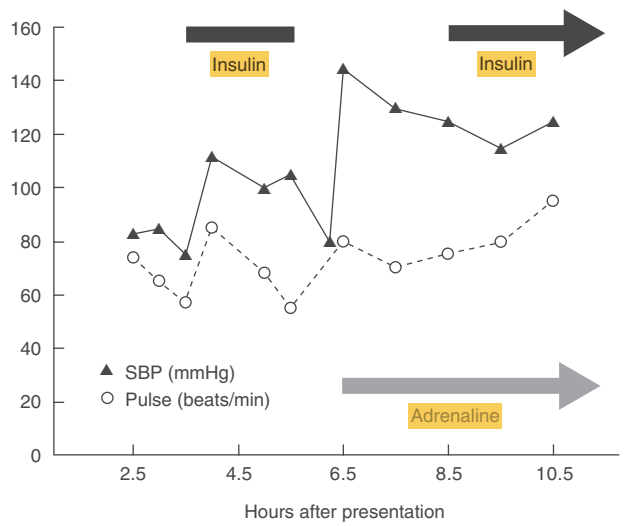
Thirty minutes later, the patient was hypotensive (BP, 85/45 mmHg; pulse, 72 beats/min). He was treated with oxygen, 2 L intravenous (IV) 0.9% saline, a naloxone IV infusion (400 μg/h), and 10 mL IV 10% calcium gluconate. He was transferred to a tertiary referral centre and, on arrival (at 2.25 h after initial presentation), his BP was 85/45 mmHg, pulse was 64 beats/min, and an electrocardiogram (ECG) showed a junctional rhythm. Rapid sequence intubation (with propofol 40 mg + 20 mg IV and suxamethonium 100 mg IV) was performed for airway protection and ongoing management of haemodynamic instability, while metaraminol IV boluses (total, 0.7 mg) were administered. Activated charcoal (50 g) was given, and sedation was maintained with a propofol infusion.

The patient remained hypotensive (BP, 75/45 mmHg; pulse, 56 beats/min) after intubation, so high-dose insulin euglycaemic therapy (HIET) was commenced at 3.5 hours after presentation. He was given dextrose (50 mL 50% glucose) and a 30 IU short-acting insulin IV bolus (~ 0.5 IU/kg), followed by a further bolus of 50 mL 50% glucose and a short-acting insulin IV infusion (30 IU/h) (Box 1). His BP improved to 110/70 mmHg at 4 hours, with a pulse of 82 beats/min and sinus rhythm on ECG, and he remained stable during transfer to the intensive care unit (ICU).

The insulin infusion was abruptly stopped 5.5 hours after presentation, on arrival in the ICU. The patient's hypotension subsequently recurred (systolic BP, 70 mmHg; pulse, 75 beats/min), prompting administration of 500 mL IV Gelofusine (a colloidal plasma volume substitute; B. Braun, Sydney, NSW) and commencement of an adrenaline IV infusion (20 μg/min). The insulin infusion (30 IU/h) was restarted at 8.5 hours, and his BP again stabilised (Box 1). The propofol IV infusion was gradually increased from 50 mg/h to 150 mg/h between 5.5 hours and 11.5 hours after presentation, and a noradrenaline IV infusion was commenced at 9.5 hours to maintain normotension. At 15.5 hours, pulmonary artery catheter measurements showed a high cardiac index (5.1 L/min/m^2; reference range [RR], 2.5–4.0 L/min/m^2) and a low systemic vascular resistance index (1047 dynes·s/cm^5/m^2; RR, 1900–2400 dynes·s/cm^5/m^2); the patient's pulse was 85 beats/min and BP was 140/60 mmHg.

HIET was continued and the patient remained haemodynamically stable. Adrenaline and noradrenaline were weaned off (at 17.5 hours and 23.5 hours, respectively), despite the propofol infusion rate being increased to 500 mg/h at 18.5 hours. Once

1 Early changes in the patient's systolic blood pressure (SBP) and heart rate, relative to treatment with high-dose insulin and adrenaline infusions



Following administration of a 0.5 IU/kg short-acting insulin bolus 3.5 hours after presentation, a short-acting insulin intravenous infusion (0.5 IU/kg/h) was commenced (black line), and the patient's blood pressure improved. The infusion was abruptly discontinued 2 hours later and the patient again became hypotensive. This resolved following commencement of an adrenaline infusion (20 μg/min) (grey arrow), and the insulin infusion (0.5 IU/kg/h) was restarted 8.5 hours after presentation (black arrow).

sedation was withdrawn, the patient was extubated at 26.5 hours. Insulin was weaned over 5 h and discontinued at 30.5 hours; dextrose was stopped 1 h later. The patient was transferred to the observation ward and discharged well later that day, after psychiatric clearance.

During treatment with HIET, the patient's blood glucose levels were checked hourly and ranged from 6.6 mmol/L to 13.2 mmol/L (RR, 3.5–5.5 mmol/L). He received about 25 g/h of dextrose (mostly as 50% dextrose infusions). Potassium and magnesium levels were also serially monitored; the minimum potassium level was 2.7 mmol/L (RR, 3.5–5.0 mmol/L) at 8.75 hours, and the magnesium level troughed at 0.5 mmol/L (RR, 0.75–1.05 mmol/L) at 15 hours. These were corrected with a total of 200 mmol of potassium chloride and 20 mmol magnesium chloride.

Discussion

HIET is an increasingly accepted therapy for calcium channel blocker (CCB) toxicity, but reports of its use are limited and it remains controversial. Indeed, the scarcity of severe CCB poisoning cases means that a randomised controlled trial of HIET may not be feasible.[1] Treating clinicians who seek advice from clinical toxicologists are often hesitant about the high doses required and the potential for adverse effects. Such hesitancy is potentially harmful, as a hypotensive patient with a CCB overdose who otherwise appears well is at risk of abrupt lethal cardiovascular collapse.[1] HIET is traditionally recommended after other therapies have failed.[2,3] This case report aims to raise awareness of HIET for the treatment of CCB toxicity and supports its early use, rather than as a last resort.[4]

Verapamil binds the alpha-1 subunit of L-type calcium channels, preventing the intracellular influx of calcium.[5] These channels are functionally important in cardiac myocytes, vascular smooth muscle cells, and islet beta cells.[5] Verapamil's cardiac toxicity results from excessive negative inotropy, negative chronotropy and negative dromotropy, characterised by myocardial depression, sinus bradycardia, and atrioventricular node blockade.[4] Vascular smooth muscle tone is impaired, resulting in decreased afterload, systemic hypotension, and coronary vasodilation.[5]

Less well known are the metabolic effects of CCBs such as verapamil. Under the stress of the drug-induced shock state, the cardiac myocytes shift from using free fatty acids, their favoured "resting state" energy substrate, to carbohydrates.[3,4] CCB toxicity also impairs the uptake of glucose and free fatty acids by cardiac myocytes[3,4] and inhibits calcium-dependent mitochondrial activity required for glucose catabolism.[3,4] Furthermore, insulin release is dependent on calcium influx into islet beta cells through L-type calcium channels.[3,4] Thus, CCB toxicity can cause hypoinsulinaemia,[3,4] which, in conjunction with CCB-induced insulin resistance, may lead to hyperglycaemia and a ketoacidotic state.[6]

Atropine, calcium boluses and infusions, glucagon, inotropes, vasopressors, and cardiac pacing have all been advocated for managing CCB toxicity, despite questionable efficacy.[3,4,7-9] For instance, the evidence for glucagon is limited to small, non-blinded animal studies where no survival benefit or improvement in mean arterial pressure was shown, although heart rate improved in some cases.[7] Rarely, heroic measures such as extracorporeal circulatory support and intra-aortic balloon counterpulsation have been successfully employed.[5,10]

HIET was first used to treat verapamil toxicity in humans in 1993, with a favourable outcome.[6] Since then, in addition to animal studies, there have been nearly 70 cases reporting the beneficial use of HIET in humans, with an overall survival rate of 85%.[8] However, to our knowledge, use of HIET in humans before the administration of glucagon or vasopressors has only been reported once.[6] There have been some reports of HIET failure in treating CCB toxicity, although the dosing of insulin was low or uncertain, or it was used late.[6,8] Early use of HIET may be more effective than HIET rescue therapy, as CCB-induced insulin resistance is greatest in the first 24 hours[2] and the maximal haemodynamic benefit of HIET may not occur immediately.[6]

HIET may allow the heart to overcome metabolic starvation in CCB toxicity, which compounds the direct CCB impairment of myocardial contractility.[3,4] Insulin increases glucose and lactate uptake by myocardial cells and improves function without increased oxygen demand.[11,12] It also induces pyruvate dehydrogenase, hastening myocardial lactate oxidation, and helps clear the cytosol of glycolytic byproducts that impair calcium handling and cause diastolic dysfunction.[3] Insulin promotes excitation–contraction coupling and contractility because enhanced glycolysis promotes increased sarcoplasmic reticulum-associated calcium ATPase activity and increased cytoplasmic calcium concentrations, and promotes calcium entrance into mitochondria and sarcolemma.[3]

HIET may be best used adjunctively with other measures such as catecholamines, for two reasons. First, insulin-mediated inotropy is not catecholamine-mediated, and is not affected by β blockers.[3] Second, although insulin appears to improve myocardial contractility, it has no chronotropic effect and may cause vasodilation.[3,8]

HIET is safe, and adverse events are predictable, uncommon, and easily managed.[2,8] The maximum safe dose of insulin is unknown, but loading doses of 0.5–1.0 IU/kg followed by infusions of 0.1–2.5 IU/kg/h are typically used.[8] Interestingly, neither the inadvertent administration of a 1000 IU insulin loading dose for verapamil toxicity[13] nor treatment of toxic cardiogenic shock for 2 days with a 6 IU/kg/h insulin infusion had any adverse effects.[14] Adverse effects of HIET include hypoglycaemia, hypokalaemia, hypomagnesaemia, and hypophosphataemia.[2,6,8] Although these are rarely clinically significant, they necessitate careful monitoring. Hypoglycaemia (blood glucose < 3.3 mmol/L) occurred in 16% of 55 published cases,[8] and no cases of hypoglycaemia within 24 hours of CCB overdose were noted in Greene and colleagues' series of seven cases.[2] Greene et al also reported a mean dextrose requirement of 0.05 g/kg/h (range, 0–0.17 g/kg/h), although the mean blood glucose level exceeded the euglycaemic range.[2] Some cases of severe CCB toxicity in patients presenting with hyperglycaemia do not require any additional glucose administration despite high-dose insulin therapy,[15] and hypoglycaemia may be more likely in milder cases without marked hypotension.[8] In addition, hypokalaemia (potassium < 3.5 mmol/L) was noted in only two patients in Greene et al's small series, with a minimum potassium level of 2.8 mmol/L.[2] Excessive correction of hypokalaemia should be avoided, because it reflects the intracellular shift of potassium from the extracellular compartment due to the action of insulin, rather than a potassium-depleted state.[4] Interestingly, hypokalaemia in HIET may augment myocardial contractility by enhancing calcium entry during systole, and increased intracellular potassium may have a membrane-stabilising effect in excitable cells.[4,6]

2 Recommended high-dose insulin euglycaemic therapy protocol,[3,4,9] based on the clinical experience of the Western Australian Toxicology Service, published case reports, reviews and animal studies

Commence therapy with:

- Glucose 25 g (50 mL of 50% solution) IV bolus, unless marked hyperglycaemia (blood glucose > 22 mmol/L) is present
- Short-acting insulin 1 IU/kg bolus to maximally saturate insulin receptors

Continue therapy with:

- Short-acting insulin infusion starting at 0.5 IU/kg/h and titrated every 30 min to a maximum of 5 IU/kg/h*
- Dextrose 25 g/h IV infusion titrated to maintain euglycaemia (blood glucose, 5.5–14 mmol/L); central venous access may be required to allow use of concentrated solutions (eg, 50% dextrose) and limit excess volume administration

Monitor:

- Glucose — every 20 min for first hour, then every 1 h
- Potassium — replace only if < 2.5 mmol/L and there is a source of potassium loss

Therapeutic end points:

- Improvement in myocardial ejection fraction (> 50%); increased BP (systolic BP > 90 mmHg in adults)
- Adequate heart rate (> 60 beats/min)
- Resolution of acidaemia; euglycaemia; adequate urine output (1–2 mL/kg/h)
- Reversal of cardiac conduction abnormalities (QRS interval < 120 ms)
- Improved mentation

Therapy is weaned after the withdrawal of other vasopressors, as cardiotoxicity resolves. Dextrose may be required after cessation of insulin.

IV = intravenous. BP = blood pressure. * The maximum safe and effective rate of infusion is unknown but may be even higher than 5 IU/kg/h. In animal studies, insulin infusions as high as 10 IU/kg/h have been safely used.[11] ◆

In conclusion, we advocate consideration of the early use of HIET (as detailed in Box 2) for the prevention and treatment of life-threatening complications from potentially lethal CCB overdoses. HIET is safe, inexpensive and freely available, and suitable for use even in remote settings before transfer to a referral centre.

Competing interests

None identified.

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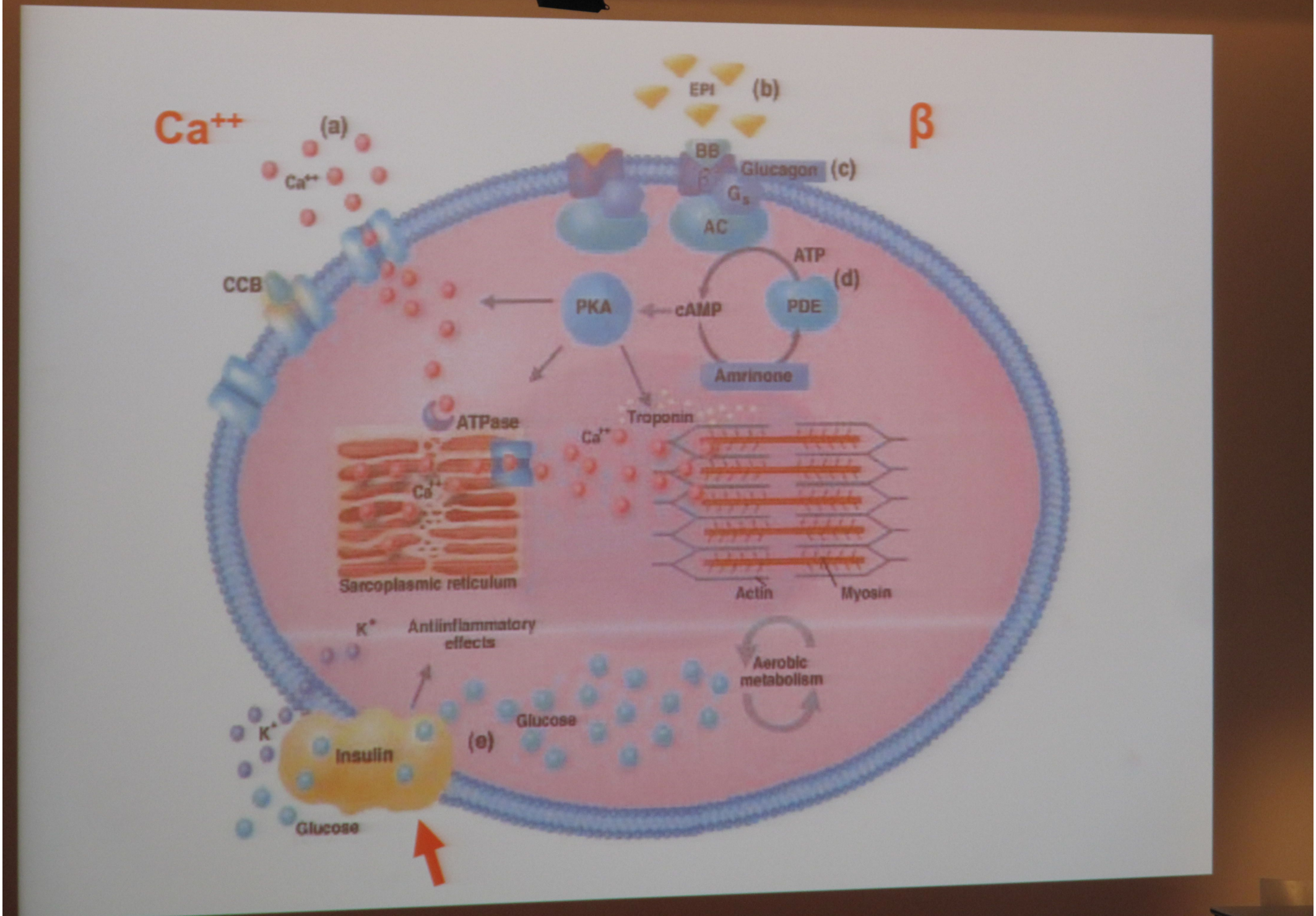
Hi dose Insulin Protocol – Mayo Clinic

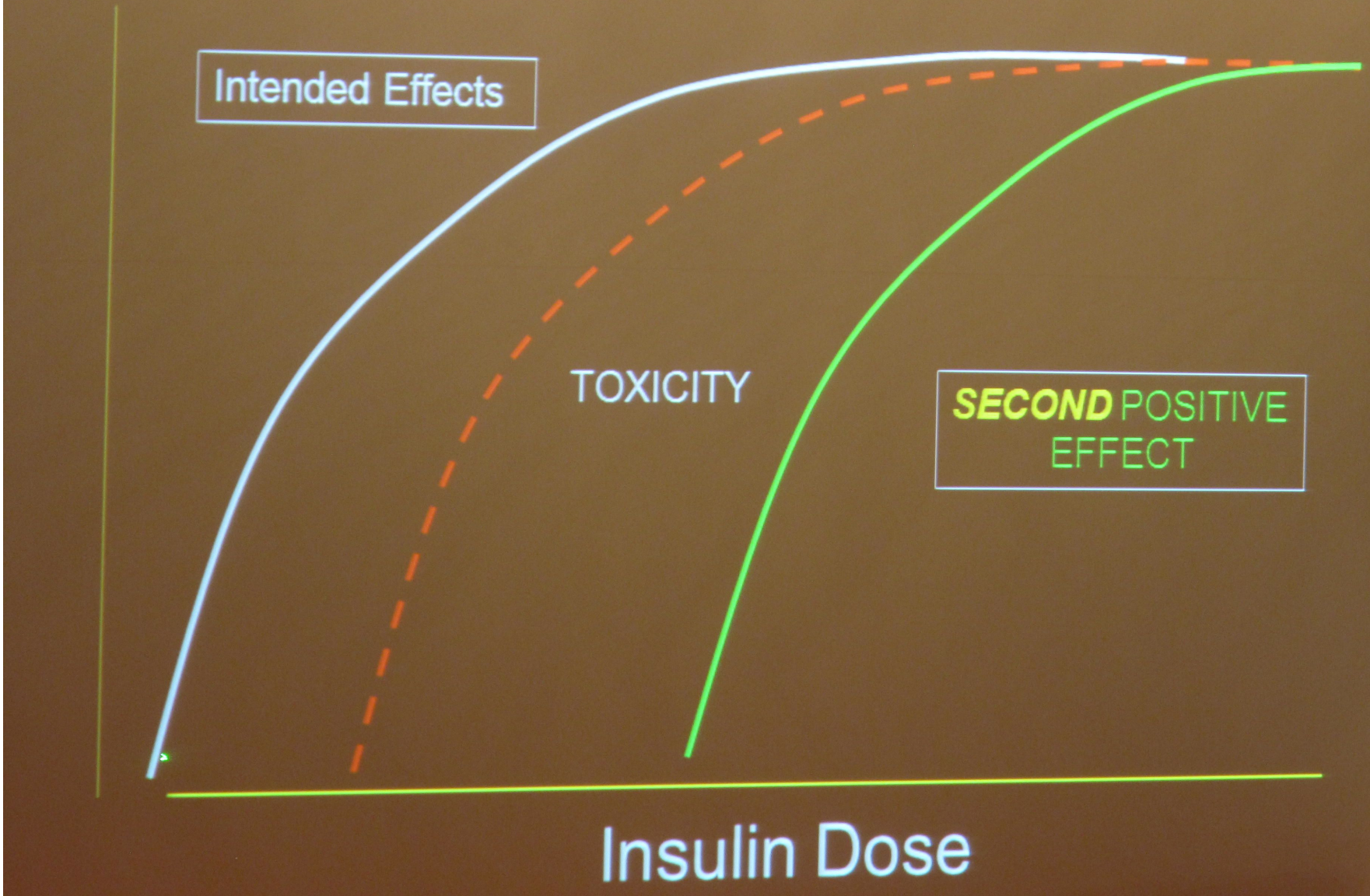
Insulin Orders:	
Insulin regular (Novolin R) 100 units.ml. 1 unit/kg IV push then start high dose infusion	IV Once Starting today
Insulin regular 10 units/ml (high dose) infusion 1-10 units/kg/hour IV Titrate to MAP greater than 65	1-10 Units/kg/hr IV Titrate. Starting today
Dextrose Orders, initiate with insulin infusion	
D50W 25 gm IV PRN to maintain blood glucose 100 – 200 mg/dL	25 gm IV, PRN based on blood sugar. Starting today
D10W IV infusion to maintain blood glucose greater than 100 mg.dL. Start with insulin infusion.	At 100 mL/hr IV. Titrate starting today.

Novel Therapies

- Insulin
  - High Dose-Euglycemia (0.5-1.0 unit/kg/hr)
  - *Super* High Dose (>1.0 unit/kg/hr)
- Lipid Emulsion
  - Fat soluble drugs
- Levosemendan for Ca^{++} Channel Blockers


Ca++
(a)
Ca++
CCB
EPI
(b)
β
BB
Glucagon
(c)
Gs
AC
ATP
(d)
PKA
cAMP
PDE
Amrinone
ATPase
Troponin
Ca++
Ca++
Sarcoplasmic reticulum
Actin
Myosin
K+
Antiinflammatory effects
Aerobic metabolism
Glucose
K+
Insulin
(e)
Glucose

Ranges of Therapy and Toxicity



Hemodynamic Effects of *High Dose* Insulin

- Myocardial Performance
  - Calcium dependent
  - Calcium independent
    - Cellular / mitochondrial energetics
- Vascular Smooth Muscle Relaxation
  - Systemic, coronary & pulmonary vessels
  - Endothelial NO synthase (eNOS) activation
    - PI3K pathway?

Insulin *Cardiovascular* Therapy

- Ischemia-Reperfusion
- Hypoxia
- Congestive Heart Failure (?)
- Post-Pump Cardiac Dysfunction
- Myocardial Ischemia
- Cardio-Toxic Overdosage / Poisoning
  - β-Blockers
  - Ca^{++} Channel Blockers
  - Bupivicaine
    - Other Na^{+} Channel Blockers?

Research Hypotheses

- Insulin's effects on *hemodynamics* continue into a dosing range far above that which achieves *glucose* homeostasis.
- Off-setting insulin's depression of glucose and potassium levels may allow safe exploitation of insulin's inotropy and vasodilatory properties into this high-dose range.

RESULTS SUMMARY

- INSULIN
  - 100% *Survival to 4hrs*
  - Resolution of Hypotension
  - Dramatic Increase in CO with small improvement in HR
- VASO/EPI
  - 100% death by 2hrs
  - Worsening hypotension
  - An early dramatic increase in SVR then a drop in SVR as death approached
  - CO decreased as SVR increased

CONCLUSIONS

- INSULIN
  - Improved survival in β-Blockade is due to CO recovery primarily from INOTROPIC effects
  - Insulin euglycemia therapy should be considered early in the treatment of beta-blocker induced hypotension
- VASO/EPI
  - Early death is due to lack of cardiac inotropy that is unable to overcome the VASOPRESSOR effects
  - Vaso/EPI should be avoided in beta-blocker OD

Clinical Translation of HDI ?

- 65 y.o. woman multi-drug overdose / ingestion
- No prior cardiovascular or pulmonary disease
- Atenolol, Venlafaxine, ***Amitriptylene*****
- Refractory to pressors and **moderate** dose insulin, Glucagon, Epi, Atropine, Calcium

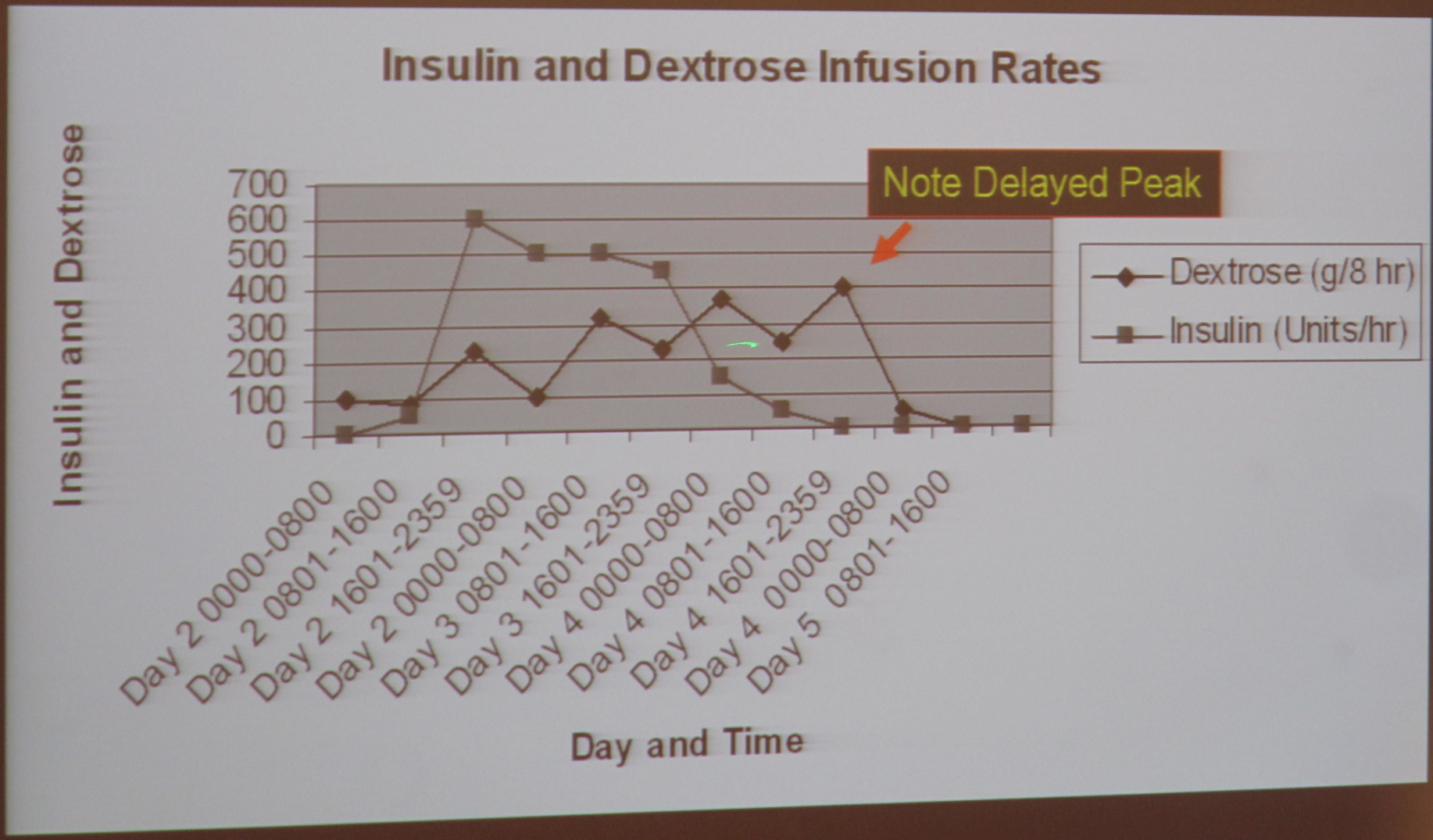
Holger J, ***J Clin Tox*** 2009

Clinical Translation of HDI ?

- "Terminal Shock" after several minutes of cardiac arrest
- ***Very*** high dose insulin begun
  - 1 u/kg/hr increments q 10 min
  - Near immediate improvement in urinary flow, skin temperature and metabolic acidosis
  - Cardiac Output rose from 3.5 to 11 L/min
  - Normal CVP and Wedge
- High Functioning Survival

Holger J, ***J Clin Tox*** 2009

Glucose Requirement



Consecutive HDI Case Series

- Twelve Consecutive patients were treated with HDI protocol. Age range: 19-65 years (mean 43).
- Primary toxins: β-blocker (BB) in 5, Ca^{++} channel blocker (CCB) 1, combined BB/CCB (4), TCA (1), polydrug (1).
- Two patients had pulseless electrical activity (PEA) cardiac arrest prior to HDI.
- Six patients failed pre-existing vasopressor therapy, and 5 of these were tapered off vasopressors while on HDI; 1 completed therapy with HDI and a vasopressor.
- IV fat emulsion 2 patients; initiation of HDI during cardiac arrest, and unresponsive to HDI at 10 units/kg/hr.

Consecutive HDI Case Series

- An initial HDI bolus was used in all 12 patients.
- Mean maximum HDI infusion rate: 8.4 units/kg/hr (range: 0.5-21).
- Mean duration HDI 25.5 hrs (range 4-60).
- Mean duration of glucose infusion *post*-HDI: 21 hrs.

Clinical Outcomes

11 of 12 patients survived. One patient expired 9 hours into HDI therapy from cardiac arrest shortly after the HDI infusion was stopped and a vasopressor was re-initiated (protocol deviation).

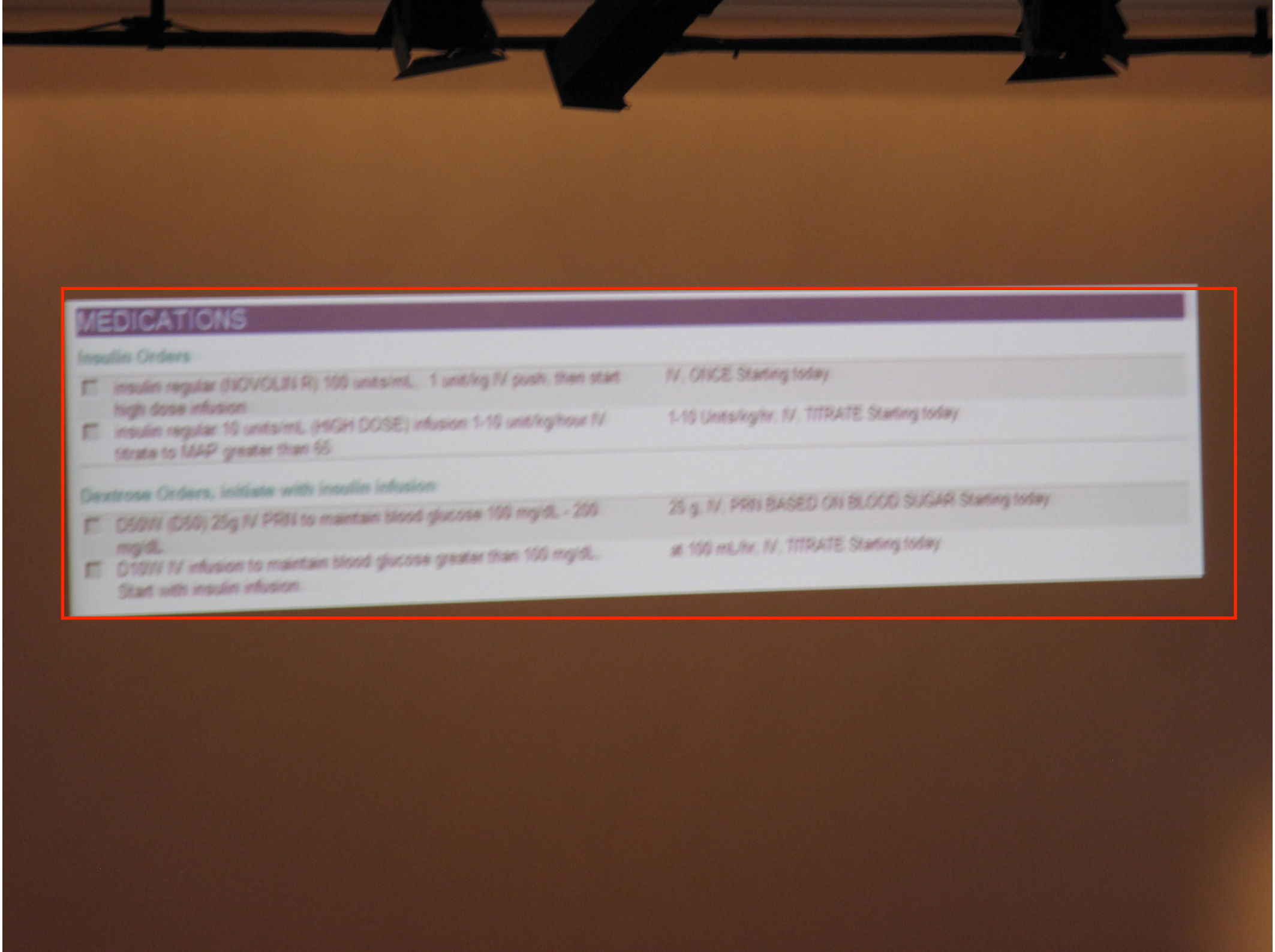
Necrotic digits in one patient with prior clotting disorder. High dose NE and INR reversal with FFP were administered prior to HDI therapy.

One patient was discharged with mild anoxic injury thought due to prolonged PEA arrest prior to HDI therapy.

Conclusion

HDI therapy, using a pre-established protocol that urges avoidance of vasopressors, was effective in the treatment of Toxin-Induced Cardiogenic Shock.

HDI related adverse events were mild and infrequent. Known adverse sequelae were not related to HDI therapy.


MEDICATIONS
Insulin Orders
insulin regular (HOVOLIN R) 100 units/mL - 1 unit/kg IV push, then start high dose infusion
IV, ONCE Starting today
insulin regular 10 units/mL (HIGH DOSE) infusion 1-10 unit/kg/hour IV titrate to MAP greater than 65
1-10 Units/kg/hr, IV, TITRATE Starting today
Dextrose Orders, initiate with insulin infusion
D50IV (D50) 25g IV PRN to maintain blood glucose 100 mg/dL - 200 mg/dL
25 g, IV, PRN BASED ON BLOOD SUGAR Starting today
D10IV IV infusion to maintain blood glucose greater than 100 mg/dL. Start with insulin infusion
at 100 mL/hr, IV, TITRATE Starting today

A Few Key Points

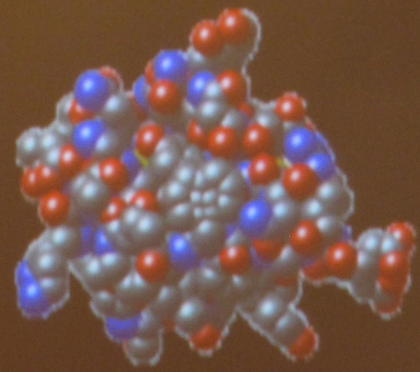
- Monitor *Cardiac Output Continuously*
  - Non-Invasive
  - BP is not an adequate monitor
- *Titrate* to Effect *Decrementally*
- *Central* Monitoring of *Glucose* and Potassium
- Consider "Lipid Sink" co-Treatment

Summary

- Insulin in doses much higher than needed for glucose control has potent *hemodynamic* actions
  - Inotropic
  - Vasodilatory
- Glucose and potassium requirements
  - do *not* increase in direct proportion to insulin dosage
  - tend to rise with shock *resolution*
  - Are manageable
- Because HDI bridges across a spectrum of cardiotoxic mechanisms and merits further investigation as an early 'first-line' approach to mixed drug overdoses of uncertain composition

Conjecture

- Other ICU conditions characterized by transient and potentially reversible hemodynamic compromise may benefit from HDI inotropic action, alone or in combination with vasopressors
  - Sepsis
  - Myocardial ischemia



Hemodynamic Effects Of *High Dose* ** Insulin

- Myocardial Contractility--*Strong*
- Vasodilation---*Moderate*

- Heart Rate and Rhythm—*Negligible*
  - A possible rationale for simultaneous lipid infusion and levosemendan

** *1-10 units/kg/hr*

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ARTICLE

High dose insulin in toxic cardiogenic shock

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Objective. To report the successful use of high dose insulin (HDI) in previously unreported insulin dosing ranges in a patient with severe myocardial toxicity due to an amitriptyline and citalopram overdose. *Case Report*. A 65-year-old female presented in respiratory arrest, which was followed by bradycardic pulseless electrical activity after ingesting multiple medications. After a prolonged resuscitation, the patient was maintained only on infusions of norepinephrine (40 mcg/min), vasopressin (4 units/h), insulin (80 units/h), and sodium bicarbonate. Due to a deteriorating clinical condition and limited prognosis, the insulin infusion was titrated incrementally upwards to 600 units/h (6 units/kg/h) over a 5 h time period while simultaneously completely weaning off both vasopressors. She developed brisk pulses and warm extremities, and her cardiac output nearly tripled. After 2 days of stabilization the insulin was slowly tapered, and the patient recovered. *Discussion*. HDI as a single cardiovascular agent significantly improved clinical and cardiovascular parameters after the failure of vasopressor therapy in severe cardiovascular toxicity. Higher doses of insulin than previously recommended may be needed in toxic poisonings when severe myocardial depression is present.

Keywords Insulin; Overdose; Cardiogenic shock; Tricyclic antidepressant; High dose insulin

Introduction

High dose insulin (HDI) therapy has been recommended in the treatment of overdoses due to calcium channel blocker (CCB) and β-blocker (BB) medications when conventional measures fail to improve hemodynamic status.[1,2] We report a patient who ingested a cardiotoxic overdose of the tricyclic antidepressant (TCA) amitriptyline and citalopram resulting in cardiopulmonary arrest. Initial treatment with vasopressors resulted in ischemic extremities and evidence of organ hypoperfusion. Clinical improvement was evident with the initial dose increase of HDI therapy and increasing doses allowed for complete withdrawal of vasopressor drugs.

Case report

A 65-year-old woman (100 kg) was brought to our Emergency Department (ED) hypotensive, comatose, and intubated after having ingested multiple medications at an unknown time. The patient was known to be taking atenolol, citalopram, enalopril, and venlafaxine. Preexisting medical problems were hypertension and depression with past suicidal attempts. Paramedics found the patient unresponsive and in an idioventricular rhythm with brief episodes of ventricular tachycardia. Brief seizure activity was also noted. On arrival to the ED the patient had dilated pupils, a Glasgow Coma Score of 3, a blood pressure (BP) of 79/43 mmHg, a heart rate (HR) of 70 beats/min, and an idioventricular rhythm with a QRS interval of 320 ms. Deterioration to pulseless electrical activity quickly ensued, with a ventricular rate of 40 beats/min. Resuscitation medications were bolus administration (totals) of sodium bicarbonate (250 mEq), atropine (3 mg), epinephrine (8 mg), and calcium chloride (1 g) over 40 min, which resulted in return of palpable pulses. Bradycardia and hypotension persisted. Boluses of glucagon (total 6.5 mg), dextrose 50% (25 g), and insulin (10 units) were given intravenously (IV). Normal saline and sodium bicarbonate infusions were started. An epinephrine infusion, which delivered 1 mg over the next 30 min, was stopped due to dropping BPs. Norepinephrine (NE) was then started at 8 mcg/min and titrated to 40 mcg/min over the next 20 min. A bolus of 80 units of insulin was given IV and an insulin infusion started at a rate of 80 units/h due to the possibility of a severe BB overdose (patient was thought to weigh 80 kg). The echocardiogram (ECG) in the ED after initial resuscitation showed a wide complex bradycardia at a rate of 56, with a QRS interval of 200 ms and a QTc interval of 646 msec. Bedside point-of-care testing during initial resuscitation revealed a pCO_2 >130 mmHg, Na of 143 mmol/L, K of 3.4 mmol/L, ionized calcium of 1.56 mmol/L (normal 1.0–1.3 mmol/L), and a pH of 6.80. After resuscitation, laboratory testing results revealed a Na of

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138 mmol/L, K 3.5 mmol/L, Cl 102 mmol/L, CO_2 25 mmol/L, Blood urea nitrogen (BUN) 20 mg/dL, creatinine 1.1 mg/dL, magnesium 2.1 mg/dL, calcium 10.6 mg/dL, blood ethanol level <0.01 gm/dL, normal cardiac enzymes, and a lactate of 9.8 mmol/L (reference 0.7–2.1 mmol/L).

Within 2 h the patient was transferred to the Intensive Care Unit (ICU) with BP 79/44 mmHg, HR 73 beats/min, and respiratory rate 16 breaths/min. Vasopressin (VP) at 4 units/h was started. The ECG showed sinus rhythm with a QRS duration of 200 ms and a QTc of 699 ms. An ECG demonstrated an ejection fraction of 55% and mild left ventricular hypertrophy. The QRS remained >160 ms despite maintaining the arterial pH between 7.50 and 7.55 with a sodium bicarbonate infusion. Cool extremities, nonpalpable peripheral pulses, and markedly delayed capillary refill developed. The HR improved to 80–90 beats/min. Noninvasive cardiac output (CO) monitoring by a NICO® monitor (Respironics, Murphysville, PA, USA) on day 2 measured the patient's CO at 4 L/min with a low calculated cardiac index of <2.5 L/min/m^2. At this time (approximately 12 h after arrival) due to concern for a diminishing prognosis secondary to decreased peripheral perfusion with ischemic extremities, inadequate inotropic function, and urine output of 0.6 mL/kg/h, her clinicians attempted to improve cardiac inotropic function and peripheral perfusion by using higher doses of insulin. Based on our own laboratory experience along with previous animal studies that support the use of HDI in doses up to 10 units/kg/h, the insulin infusion was increased progressively in 1 unit/kg/h increments (100 units/h increases) on an hourly basis.[3,4] Insulin was infused in a concentration of 10 units/mL. Clinical improvement first manifested as improved extremity warmth and capillary refill time was appreciated after the first increase in insulin dose. This response prompted us to wean off the NE first followed by the VP over a 5-h interval while concomitantly increasing the insulin dose with the goal to maintain a minimum mean arterial pressure (MAP) of 65 mmHg. During this time the patient developed brisk peripheral pulses and warm extremities. From this time point on, insulin was the only cardiovascular agent used to support the patient. At a dose of 600 units of insulin/h (6 units/kg/h) both vasopressors had been discontinued. The HR remained unchanged. CO measurements made from a pulmonary artery catheter improved from the previously noted 4 L/min to 11.3 L/min. Urine output increased to 2 mL/kg/h. Hemodynamic data and medication infusions are graphed in Fig. 1. The maximum quantity of glucose required to maintain a serum level >100 mg/dL was 50 g/h (Fig. 2).

After 36 h of the insulin infusion at or above 500 units/h, the insulin infusion was weaned by 50 units/h increments as tolerated to keep MAP >65 mmHg. No hypoglycemic events occurred. The ECGs showed no evidence of a rightward terminal 40-ms frontal plane QRS axis (R prime wave in lead aVR of greater than 3 mm or a deep S wave in lead I) at any time. Pulmonary emboli complicated the patient's later course. The patient recovered to a clinical state consistent with residual mild anoxic injury (confusion regarding recent events and unsteadiness requiring assistance with transfers) and was discharged to a transitional care unit.

Toxicology testing on serum samples collected 2 h after ED presentation identified the TCA amitriptyline and citalopram (Table 1). The combined level of amitriptyline and

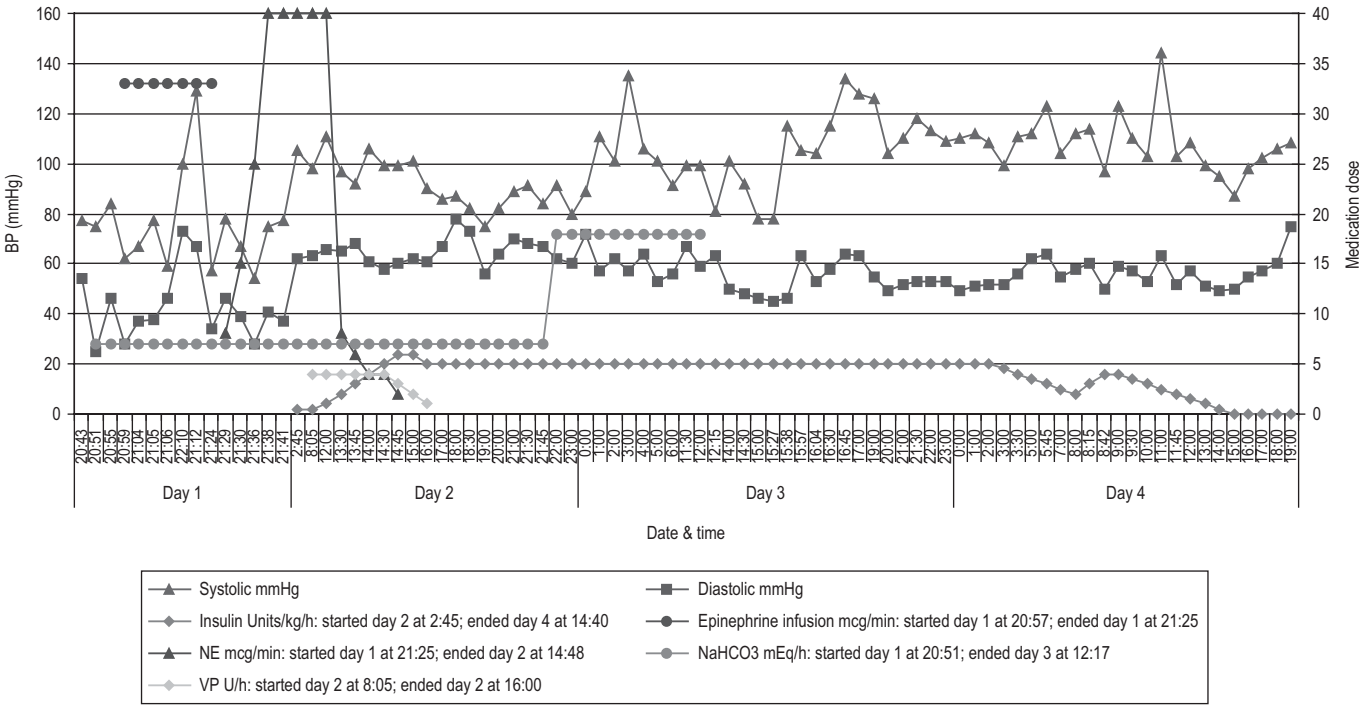

Fig. 1. Medications and blood pressure versus time.

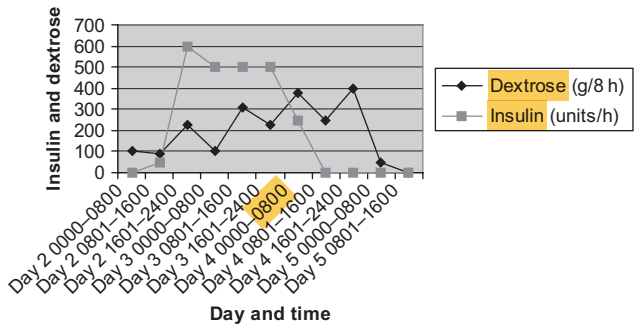

Fig. 2. Insulin and dextrose infusion rates.

Table 1. Comprehensive drug testing results by GC/MS

Drug	Actual level (ng/mL)	Therapeutic range
Venlafaxine	500	100–500 ng/mL
Desmethylvenlafaxine	280	200–400 ng/mL
Atenolol	336	200–500 ng/mL
Citalopram	197.3	Up to 120 ng/mL
Desmethylcitalopram	82.3	1/3 of citalopram level
Amitriptyline	1,150	50–150 ng/mL
Nortriptyline	378	50–150 ng/mL
Amitriptyline and nortriptyline (total)	1,528	75–250 ng/mL

nortriptyline was 1,528 ng/mL. TCA levels >1,000 ng/mL are consistent with severe toxicity.[5] The citalopram level was 197 ng/mL (therapeutic levels up to 120 ng/mL). Venlafaxine, desmethylvenlafaxine, and atenolol levels were within therapeutic ranges. Knowledge that the patient also had access to amitriptyline was not revealed until later while the patient was in the ICU.

Discussion

Since the 1930s insulin has been known to have positive cardiac inotropic properties although the mechanism(s) is not fully understood.[6] Insulin promotes cellular glucose uptake by activating glucose transporters on the cell membrane. Increasing glucose as an energy substrate during myocardial stress improves myocardial energy production by activating calcium and potassium channels, regenerating cytosolic ATP levels and enhancing aerobic metabolism.[1] The phosphatidylinositol 3-kinase (PI3K) pathway (one of the three major intracellular signaling pathways that insulin is known to activate) facilitates glucose uptake and affects the synthesis of glycogen and lipids. This pathway is known to be suppressed in CCB toxicity and can be re-activated *in vitro* by insulin in high concentration.[7]

In addition to being a potent inotrope insulin dilates the systemic, coronary, and pulmonary vasculature. The mechanism of this is likely due to the activation of endothelial nitric oxide synthase (eNOS). Microvascular recruitment (blood flow becoming less heterogeneous) at the terminal arterioles and capillary level is also improved, an effect that is likely due to the effects of the PI3K pathway on eNOS.[8] This enhances perfusion in vascular beds.

Over the past 20 years animal models investigating BB and CCB toxicities in conjunction with anecdotal clinical experiences have led to guidelines recommending using insulin infusions up to 1.0 unit/kg/h after fluids, calcium, atropine, catecholamine vasopressors, and glucagon have failed.[1,9–11] Our recently published experience with a highly cardiotoxic propranolol porcine model compared HDI (an inotropic approach) to a vasopressor approach.[4] When systemic vascular resistance (SVR) is raised by vasopressors in this state of myocardial depression, CO drops continuously until death occurs. In contrast, HDI increased CO markedly due to an inotropic effect accompanied by a decreasing SVR, which resulted in a marked increase in survival. This is a key concept that may have been instrumental in the survival of this patient. The effect of vasopressors depressing CO when severe myocardial depression exists cannot be simply measured by observing BP and pulse. Measuring CO and the response to cardiovascular support therapy is essential for optimizing treatment in patients with severe myocardial toxicity, and can be accomplished noninvasively. If CO is low or decreases in the presence of hypotension and signs of hypoperfusion an inotropic approach to therapy should be considered as first-line pharmacologic therapy. Decreasing or eliminating vasopressor therapy in the presence of severe myocardial depression may enhance this approach, as was evident in our patient. Persistent vasopressor therapy in these circumstances may theoretically increase the dose of insulin required to overcome the high SVR induced by these medications.[4]

HDI was employed when evidence of the vasopressor approach failed clinically, in hopes of overcoming myocardial depression, inadequate CO, and the resulting hypoperfusion. Clinical improvements were associated with increasing HDI titration and weaning of vasopressors. This corresponded to increases in CO and resulted in a decreased SVR, and evidence of improved perfusion (Table 2). In our patient our BP goal was to maintain an MAP >65 mmHg. The optimum target level for MAP in the treatment of shock is unknown. The titration of MAP to 65 mmHg has been demonstrated to preserve tissue perfusion, and this level has been shown to be physiologically equivalent to higher BPs (MAP >85 mmHg).[12,13] Cerebral perfusion was not calculated in this patient as intracranial pressure was not measured; however, cerebral blood flow should be maintained at this level of MAP due to protective autoregulation. No previous case reports have utilized HDI in known TCA overdoses, have used insulin as a sole cardiovascular agent, or employed doses of HDI in toxicology cases higher than 2 units/kg/h. All other case reports have used insulin in combination with other vasoactive or inotropic medications after the initial approach was inadequate.

Table 2. Insulin levels and hemodynamic values

Date	Time	Insulin (μIU/mL)	CO (L/min) normal range (4.0–8.0 L/min)	CI (L/min/m^2) normal range (2.5–4.0 L/min/m^2)	SVR (dyn-s/cm^5)	PVR (dyn-s/cm^5)	HR (beats/min)
Day 3	1859	>3,000	11.3	5.3	435	64	98
Day 3	2310	>3,000					
Day 4	0900		10.3	4.8	466	70	93
Day 4	1027		9.4	4.4	502	145	97
Day 4	1100	608					
Day 4	1324		6.3	2.9	584	152	94
Day 4	1400	Insulin stopped					
Day 4	2134		6.0	2.8	733	187	92
Day 5	0445	43					
Day 6	1622		5.6	2.6	671	86	94

Initial CO output (prior to HDI therapy) was 4 L/min and rose with insulin titration. At a maximum insulin infusion of 600 units/h, the CO was noted to be 11.3 L/min. Further documentation correlating increasing insulin doses with CO was not documented. The figure above documents decreasing insulin levels with hemodynamic parameters.

- Therapeutic levels of insulin are <17 μIU/mL (micro-international units/mL).
- Normal SVR is 900–1,300 dyn-s/cm^5.
- Normal PVR is 155–255 dyn-s/cm^5.
- Normal CO is 4.0–8.0 L/min.
- Normal CI is 2.5–4.0 L/min/m^2.

Figure 2 illustrates the prolonged need for dextrose infusion for 24 h after discontinuation of the insulin infusion, which correlates well with our patient's increased measured serum insulin levels during this time period (Table 2). The onset of inotropic effects from IV bolus or infusion of HDI is not known. Clinical effects have been reported within minutes (in this case) and up to 45 min in other case reports.[14] This variation may be due to bolus versus infusion administration or may even be a dose-dependent effect.

The toxicologic effects of TCAs include a myocardial depressant effect due to sodium channel blockade, which can usually be overcome with the use of hypertonic sodium bicarbonate by maintaining a pH of 7.50–7.55.[15] Approximately 33% of patients with TCA overdose and a limb lead QRS complex ≥100 ms develop seizures and 14% develop ventricular dysrhythmias.[16] However, no ventricular dysrhythmias occurred in patients with a QRS duration <160 ms. Our patient had seizure activity and dysrhythmias early in her presentation when the QRS interval was 320 ms, which is consistent with TCA toxicity. The metabolite didesmethylcitalopram shares a toxic mechanism with TCAs in its blockade of sodium and potassium channels; the effects from which could explain the prolonged cardiovascular toxicity (QRS >120 ms for more than 36 h) seen in our patient.[17–19]

Limitations of this case report include the lack of toxicokinetic data, which could have helped correlate drug toxicity to the patient's hemodynamic and clinical course. Other limitations include lack of more invasive cardiac hemodynamic documentation early in the patient's presentation. Incapacitation of the patient and limited family knowledge delayed discovery of etiological agents in this case until quantitative drug levels could be confirmed.

Conclusions

This case demonstrated the effectiveness of using HDI to increase CO and peripheral perfusion in a patient with myocardial depression from a TCA overdose. This case also demonstrates the clinical and physiological effects when an inotropic approach replaces a vasopressor approach to therapy. This treatment hopefully prevented end-organ dysfunction and death secondary to hypoperfusion. To our knowledge, this is the highest dose of insulin yet reported in the medical literature and significantly greater than the currently recommended maximum HDI dose of 1 unit/kg/h. Our experience also suggests that HDI might be considered earlier in drug overdoses resulting in myocardial depression when hypotension and hypoperfusion result secondary to decreased CO. Further research is needed to define the mechanism of insulin's cardiovascular actions in the setting of poisonings with myocardial depression, and the interrelationship of the cardiovascular effects between vasopressors and HDI.

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CRITICAL CARE

High-dose insulin: A consecutive case series in toxin-induced cardiogenic shock

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Context. Cardiovascular medication overdoses can be difficult to treat. Various treatment modalities are currently recommended. *Objective.* To describe patient outcomes and adverse events of high-dose insulin therapy in consecutive overdose patients in cardiogenic shock after implementation of a high-dose insulin protocol (1–10 U/kg/h, while avoiding or tapering off vasopressors). *Methods.* This is an observational consecutive case series of patients identified from a registry. Data were collected by retrospective chart review of patients treated by our toxicology service with this protocol from February 2007 until March 2010. *Results.* Twelve patients were treated with high-dose insulin. The mean age was 36.5 years (SD 11.7). Seven patients had pre-existing vasopressor therapy, and all were tapered off vasopressors while on insulin. Two patients experienced pulseless electrical activity cardiac arrest prior to high-dose insulin therapy. Intravenous fat emulsion was given to two patients. The mean maximum insulin infusion rate was 8.35 U/kg/h (mean = 8.35, SD 6.34). The mean duration of insulin infusion was 23.5 h (SD 19.7). The mean duration of glucose infusion post-insulin was 25.2 h (SD 17.7). The primary toxins were β-blocker in five, calcium channel blocker in two, combined β-blocker/calcium channel blocker in two, tricyclic antidepressant in one, and polydrug in 2. *Clinical outcomes.* Eleven of 12 patients survived. One patient expired 9 h into insulin therapy from cardiac arrest shortly after the insulin was stopped and a vasopressor re-initiated (protocol deviation). *Adverse events.* Six patients experienced a total of 19 hypoglycemic events. Hypokalemia (defined as < 3.0 mEq/L) developed in eight patients. *Adverse sequelae.* Necrotic digits occurred in one patient with known clotting disorder after receiving high-dose norepinephrine and INR reversal with fresh frozen plasma prior to insulin therapy. One patient was discharged with mild anoxic injury thought due to pulseless electrical activity arrest prior to insulin therapy. Three of these 12 patients have been previously described in published case reports. *Conclusion.* High-dose insulin therapy based on a 1–10 U/kg/h dosing guideline and recommending avoidance of vasopressors appears to be effective in the treatment of toxin-induced cardiogenic shock. Hypoglycemia was the most frequent adverse event, followed by hypokalemia. Adverse events did not lead to adverse sequelae.

Keywords High-dose insulin; Overdose; Cardiogenic shock; Calcium channel blocker; Beta blocker

Introduction

Significant cardiovascular toxicity manifested by hypotension and bradycardia may result from an overdose of a variety of medications. This syndrome is most commonly caused by ingestion of calcium channel blockers and β-blockers; however, overdoses involving tricyclic antidepressants, clonidine, antidysrhythmics, and other xenobiotics may also cause this toxidrome. Animal studies, case reports, and case series demonstrate increasing evidence for the role of high-dose insulin as a primary therapeutic approach, particularly when precipitated by calcium channel blockers and/or β-blocker ingestions.[1–3]

Since the initial successful case reported in 1999, high-dose insulin has been typically used late in the course of resuscitation after other treatments have been tried or failed, and in a general dose range of 0.5–2.0 U/kg/h.[4,5] Our group first reported the successful use of a much higher range of insulin infusion (6 U/kg/h) in what was initially thought to be a β-blocker-induced cardiogenic shock that ultimately proved to be due to a tricyclic antidepressant ingestion.[6] Based on this experience, published case reports, and together with experience in our laboratory, we developed a protocol to treat toxin-induced cardiogenic shock using high-dose insulin as a primary therapeutic modality, in a range up to 10 U/kg/h. An important caveat of this protocol was to avoid the use of vasopressor drugs, or, if already implemented, to taper off these medications. We justify this approach using direct and indirect animal study evidence that these medications may not be helpful and may be harmful in moderate to severe toxicities in these conditions.[7–9]

In this case series, we report the characteristics, medications ingested, adjunctive treatments, adverse events, and outcomes of patients treated and managed by our toxicology service using this protocol as a guideline.

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Methods

This is an observational consecutive case series with data collected from a registry and by retrospective chart review of all patient consultations maintained by the toxicology service at Regions Hospital in St Paul, MN. The patients were identified by examining this registry beginning in February 2007 (when the initial case referenced above occurred and this protocol was devised) until March 2010, representing a 3-year experience. All patients with toxin-induced cardiogenic shock were treated with this protocol as a guideline. Cardiogenic shock was defined as a patient showing objective signs or clinical symptoms of organ hypoperfusion. There were no pre-specified minimum blood pressure or mean arterial pressure requirements for inclusion. Patients that needed only intravenous fluids and observation without pharmacological interventions were excluded. The care of patients occurred in conjunction with emergency department and intensive care unit resident, fellow, and attending physicians. Patients were only included if our toxicology service was present in person to participate in patient management, which is our standard protocol (telephone advice to off-site hospitals are not included in the registry). The toxicology service did not maintain a bedside presence throughout the entirety of each patient's care. This protocol represents the direct clinical application and translation of knowledge gained in the animal care laboratory, where insulin doses up to 10 U/kg/h are routinely used, including our experience and those of many others.[8–10] Steps such as calcium goals and the definition of hypokalemia as < 3.0 mmol/L within the context of this treatment are arbitrarily derived from incomplete evidence. While not specifically addressed, vasopressor infusions are encouraged to be titrated downwards and eventually tapered off while implementing insulin therapy. The protocol is outlined in Fig. 1.

Adverse events were defined as episodes of hypoglycemia (glucose < 60 mg/dL), hypokalemia (defined as K + < 3.0 mmol/L), and arrhythmias (other than sinus bradycardia) during high-dose insulin therapy. Adverse sequelae were defined as death, neurological deficits at discharge, or any other outcomes noted during retrospective chart review by consensus of the treating physicians or internal review that may have been attributable to high-dose insulin.

Results

During this time period, 12 patients were evaluated and treated for toxin-induced cardiogenic shock. All were treated with high-dose insulin using this protocol as a guideline. No patients were treated with vasopressors or other inotropes, such as glucagon alone, as their primary pharmacologic treatment. Eleven patients were treated at Regions Hospital; one was treated at another hospital with a toxicology consultation member present. Patient data are presented in Table 1. Three of these patients have been previously described in published case reports.[6,11,12]

The age range was 19–65 years (mean = 36.5, SD 11.7). The primary toxins were β-blockers in five patients (patients 2, 3, 5, 7, and 10), calcium channel blockers in patients 4 and 8, combined β-blocker/calcium channel blockers in patients 1 and 6, primarily a tricyclic antidepressant in patient 11 (also polydrug), and polydrug in patients 9 and 12. Confirmation by serum drug level testing was performed in patient 11 (amitriptyline, venlafaxine, atenolol, citalopram). Seven patients had pre-existing vasopressor therapy, and all were tapered off vasopressors while on high-dose insulin (patients 3, 5, 7, 8, 9, 11, and 12). Patients 10 and 11 had pulseless electrical activity cardiac arrest prior to high-dose insulin therapy. Both of these patients lived and were discharged.

An initial insulin bolus was used in all 12 patients (column 8 in Table 1). The mean maximum insulin infusion rate was 8.35 U/kg/h (mean = 8.35, SD 6.34). The mean duration of insulin infusion was 23.5 h (SD 19.7). The mean duration of glucose infusion after insulin discontinuation was 25.2 h (SD 17.7).

Step 1: Fluid bolus with 20-40 ml/kg Normal Saline over the first hour. Goal for maintenance fluids is minimum urine output of 0.5 ml/kg/hr.

Step 2: Infuse calcium IV with an ionized goal of 2 mmol/L (12 mg/dL, total) (especially in calcium channel blocker ingestions).

Step 3: Administer 50ml of dextrose 50% IV if blood glucose is <200gm/dL.

Step 4: Regular insulin bolus at 1 U/kg IV push.

Step 5: Insulin infusion at 1 U/kg/hour (10 U/ml in Normal Saline) with a 10% dextrose infusion at 100 ml/hour, to maintain glucose > 100 mg/dL (dextrose 50% infusion via central line preferred to avoid fluid overload).

Step 6: Increase insulin infusion 1–2 U/kg/hour (maximum 10 U/kg/hr) every 10–15 minutes to clinical response.

Step 7: Maintain K+ >3.0 mmol/L and <4.5 mmol/L.

Fig. 1. Goal of therapy: maintain/improve cardiac output and tissue perfusion.

Clinical outcomes

Eleven of the 12 patients lived and were discharged from the hospital. Patient 7 expired due to a pulseless electrical activity/asystolic cardiac arrest within 1 h after the cessation of a 9-h insulin infusion and the re-administration of norepinephrine at a dose rate of 12–14 mcg/min. This management decision was made by intensive care unit staff without consultation with toxicology staff. The patient was demonstrating clinical signs of adequate perfusion while on high-dose insulin; however, the mean arterial pressure was thought to be inadequate. We presume that, at the time of the cardiac arrest, the physiological effects of insulin were likely to be present due to the persistence of high serum levels. The addition of the vasopressor might have caused a reflexive decrease in cardiac output in a depressed myocardium, resulting in further cardiac failure. This patient's hypokalemia was treated from a level of 2.3 to 3.0 mmol/L prior to cardiac arrest. The contribution of hypokalemia as a

Table 1. Patient Data.

Pt. No.	Age/sex	Drug(s) ingested	Initial BP; HR	BP nadir	Post-bolus BP; HR	Time, ingestion to HDI (h)	HDI bolus (IU)	HDI drip range (IU/h)	Max drip (IU/kg/h)	Total HDI time (h)	Total K + given (mEq)	Serum K + nadir (mmol/L)	Dextrose given (g)	Serum glucose range (mg/dL)	ICU LOS (days)
1	32F	Amlodipine, metoprolol	109/58; 34	79/38	93/45; 102	6	80	160–2100	13.8	16	0	3.2	805	57–240	3
2	19F	Propranolol	109/63; 53	68/48	102/50; 47	1	60	60–733	14.1	46	100	2.6	1578	36–389	6
3	37F	Citalopram, propranolol, bupropion	129/79; 78	54/27	83/55; 64	7	70	70–770	11	18	0	2.4	926	77–448	6
4	37F	Amlodipine, carbamazepine, tramadol, loxapine, warfarin	95/49; 121	53/47	80/39; 106	8–10	30	130–1300	10	53.5	425	3.2	2082	47–349	30
5	36M	Carvedilol, furosemide, lisinopril	86/49; 75	81/45	81/45; 74	3	70	10–70	1	7	220	2.3	289	21–442	2
6	34M	Metoprolol, quetiapine	75/40; 45	66/41	81/43; 42	10.5	70	70–700	9	18	0	2.8	475	46–283	2
7	49M	Quetiapine, metoprolol, buproprion, lisinopril, diphenhydramine	94/47; 69	78/29	90/39;69	U	80	80–250	2.8	15.5	80	2.3	1509	79– > 600	1 (died)
8	58F	Verapamil	107/77; 59	32/22	92/62; 74	U	80	82–84	1	4	335	2.7	587	61–574	2
9	21F	Quetiapine	76/27; 99	70/21	97/40; 114	12.5	50	13–24	0.5	10	455	3.4	135	47–426	5
10*	48M	Baclofen, nebivolol	98/61; 71	0	89/42; 75	U	100	50–1310	21	32	100	2.4	1258	68– > 600	7
11*	65F	Amitriptyline, atenolol, venlafaxine, escitalopram, quinapril	82/43; 72	73/60	113/58; 72	U	80	20–600	6	60	470	2.8	2050	63– > 600	15
12*	30F	Metoprolol, diltiazem, amiodarone	89/46; 73	64/41	64/41; 70	9	50	50–500	10	2	0	3.9	25	> 123	5

Pt = patient, BP = blood pressure (mmHg), HR = heart rate, IU = international units, HDI = high-dose insulin, U = unknown, K = potassium, ICU LOS = intensive care unit length of stay. BP nadir in column 5 is lowest recorded BP in chart. Post-bolus measures in column 6 are next recorded BP and HR in patient's chart after insulin bolus.
*Patients 10, 11, and 12 have been have been previously described in published case reports.[6,11,12]

potential cause of cardiac arrest is unknown. Internal review of this case prompted the addition to our guideline of non-invasive cardiac output monitoring whenever possible to help assess response to treatment changes.

Adverse events

Six patients experienced a total of 19 hypoglycemic events. The lowest recorded glucose was 21 mg/dL in a patient who experienced a total of eight hypoglycemic events (patient 5). Dosing ranges in patients 1, 2, and 10 above 10 U/kg/h were protocol deviations due to calculation error; these prompted educational efforts but not protocol changes. Hypokalemia (< 3.0 mmol/L) developed in eight patients (minimum 2.3 mmol/L). KCl was infused in six of these patients. No excessive potassium rebound was found on cessation of the insulin infusion. No adverse arrhythmias (excluding the expected toxicity-induced bradycardia) were recorded as a result of the treatment protocol.

Adverse sequelae

Patient 11 was discharged to a transitional care unit with mild anoxic injury. This was likely secondary to a prolonged pulseless electrical activity arrest prior to high-dose insulin therapy. At the time of discharge from the hospital, she had confusion regarding recent events and unsteadiness requiring assistance with transfers. No hypoglycemic events were recorded during her therapy with insulin.[6] Necrotic digits requiring partial digit amputation occurred in patient 4 with a prior clotting disorder after receiving high-dose norepinephrine and coagulation reversal with fresh frozen plasma prior to insulin. This patient was weaned off the initial treatment of norepinephrine (40 mcg/min) and vasopressin on day 1 while treated with high-dose insulin for 53.5 h. Cardiac output was maintained in the 10–11 L/min range while on insulin therapy. The necrotic digits were attributed to disseminated intravascular coagulation unrelated to high-dose insulin therapy by consulting physicians. No patients were discharged with adverse sequelae secondary to hypoglycemia.

Two patients were treated with an intravenous fat emulsion. Patient 10 experienced cardiovascular collapse in the intensive care unit following an intentional overdose of primarily nebivolol along with baclofen and diazepam.[11] Hypotension and bradycardia developed which deteriorated into an asystolic cardiac arrest. High-dose insulin was started during the brief arrest period, and a perfusing cardiac rhythm occurred after a bolus administration of the intravenous fat emulsion. An intravenous fat emulsion infusion followed and the insulin dose escalated following recovery from the arrest. The insulin infusion in this case actually peaked over 21 U/kg/h, in part due to a caregiver calculation error. Patient 12 was a 30-year-old female who developed cardiogenic shock after an intentional ingestion of diltiazem, metoprolol, and amiodarone.[12] This patient had an underlying hypertrophic cardiomyopathy (for which her medications were prescribed). The insulin had been titrated up to 10 U/kg/h and a progressively deteriorating mental status was evident with an inadequate mean arterial pressure. Intravenous fat emulsion bolus and infusion were administered to this patient with subsequent recovery and without further adverse events. High-dose insulin may have been ineffective or even deleterious due to an induced obstructive pathology known to occur when inotropes and vasodilators are used in this condition. We consider this patient a high-dose insulin treatment failure.

Discussion

This series represents a large consecutive case series using high-dose insulin as a primary pharmacologic intervention in toxic-induced cardiogenic shock. We report these results from a single toxicology service using a protocol as a guideline that allows much higher than the usual recommended doses of insulin while emphasizing the avoidance of vasopressor therapy. The range of toxicity was broad, from moderate to severe, including two patients who manifested cardiac arrest early in their treatment course.

The published literature contains few case series for comparison to our outcomes, with no direct comparisons for mixed etiologies of toxic cardiogenic shock and treatment approaches. Kern summarized the case report and case series literature and found a survival rate of 88% when insulin was used in resuscitation.[1] He notes that no direct outcome comparisons can be made to standard therapies. Shephard and Klein-Schwartz published a 13-patient case series with calcium channel blocker toxicities collected from the literature (12 survived). All patients received multiple treatments prior to high-dose insulin, and the maximum dose of insulin was 1 U/kg/h. They note that this literature likely suffers from underreporting and publication bias (non-responders or deaths not reported or accepted).[13] Greene et al. presented a prospectively collected seven-patient case series with severe calcium channel blocker toxicity with treatment advised by their poison center (six survivors). Insulin was infused at rates from 1 to 2 U/kg/h and all were treated with vasopressors. No adverse sequelae were reported in the survivors.[14] Lastly, Megarbane et al. recently reported a mortality of 8% (5 of 65 patients) in their series of admitted verapamil-poisoned patients. Multiple treatment modalities were used, and insulin was used in 15% of patients.[15]

Insulin is well known to have inotropic and vasodilatory properties.[16,17] It is not a vasopressor. Cardiac output is increased by the combination of these effects, and is further enhanced by augmenting ventricular relaxation. Microcirculatory dysfunction is a hallmark of many forms of cardiogenic shock that results in heterogeneous blood flow at the terminal arteriole and capillary level and results in tissue ischemia.[18] Insulin has also been shown to enhance microvascular recruitment (blood flow becoming less heterogeneous) at the terminal arteriole and capillary level, an effect that is likely due to increasing nitric oxide production. Capillary flow can achieve perfusion density similar to that of exercising muscle.[17] The goal of our high-dose insulin protocol is to increase cardiac output and maintain perfusion of essential organs. Based on these physiological effects and laboratory

data that suggest that the use of vasopressors is ineffective or possibly harmful in this form of cardiogenic shock, we developed our protocol to maximize insulin therapy and de-emphasize the use of vasopressors.[7–9]

When treating patients with this clinical condition, we stress the importance of achieving clinical parameters (mental status, skin warmth and color, urinary output, etc.) rather than a rigid goal of obtaining a minimum mean arterial pressure. We have previously shown in an animal model of β-blocker toxicity that increasing mean arterial pressure with the use of a vasopressor may depress cardiac output and have deleterious outcomes. This effect cannot be ascertained by simple observation of blood pressure and heart rate.[8] Individual patient responses to therapy with high-dose insulin are variable, and may depend on the severity of the toxicity, the type of medications ingested, and host factors, such as age, pre-existing cardiovascular conditions, and reserve. Determining a minimum mean arterial pressure goal to ensure vital organ perfusion is difficult, especially in severe toxicity. If high-dose insulin is unable to sustain clinical signs of perfusion, the addition of vasopressors should be done judiciously, preferably with the ability to monitor cardiac output to assess responses to treatment. Consideration of other therapeutic approaches, such as intravenous fat emulsion, ventricular assist devices, aortic balloon pumps, and temporary pacemakers, are also warranted.

We are not aware of any studies that have assessed the dose/response effects of insulin levels in toxin-induced cardiogenic shock or any form of shock in which it has been used therapeutically. The downstream intracellular signaling effects initiated by the binding of insulin to the membrane-bound insulin receptor are highly complex and incompletely understood. The concept of "saturation" is a fluid process involving phosphorylation of the receptor with subsequent internalization into endosomes, which then may either degrade the activated receptor or reprocess it back to the cell membrane.[19] The relevance of insulin dose to receptor saturation in unknown. Intracellular glucose transport does increase with higher serum levels of insulin in cardiac and skeletal muscle by translocation of intracellular Glut 4 complexes to the cell membrane. This mechanism, however, is unlikely to be the primary mechanism responsible for the various mechanisms of enhanced cardiovascular effects.[20] Insulin in high concentrations effects several intracellular mechanisms that contribute to the inotropic effects, many of which involve calcium handling. The onset of these effects can be measured within 5 min in explanted human myocardium.[21] We maximized insulin doses at 10 U/kg/h in our animal studies as others have, and utilized this dose in our guideline.

Conclusions regarding the safety and efficacy of high-dose insulin in this case series are limited by the relative infrequency of these clinical events, which makes a large case series difficult to collect. This also limits the feasibility of performing a prospective randomized trial. Rigorous adherence to the guideline did not occur, as would be expected due to individual care provider variation and preferences (by both toxicology and intensive care personnel), especially when introducing a novel protocol. This was not measured quantitatively. The assessment of clinical responses to treatment can be difficult and are subject to variable clinical impressions when quantitative parameters (such as cardiac output monitoring) are lacking. Adverse sequelae may not have been detected due to the lack of long-term follow-up assessments. Most of these cases lacked analytical confirmation of ingested drugs. This series, however, represents a spectrum of moderate to severely poisoned patients with toxin-induced cardiogenic shock.

Conclusions

High-dose insulin therapy based on a 1–10 U/kg/h dosing guideline and recommending the avoidance of vasopressors appears to be effective in the treatment of toxin-induced cardiogenic shock in this case series. Hypoglycemia was the most frequent adverse event, followed by hypokalemia. Aggressive surveillance and treatment for these conditions are indicated. Adverse events did not lead to known adverse sequelae.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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REVIEW

High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning

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Introduction. High-dose insulin therapy, along with glucose supplementation, has emerged as an effective treatment for severe beta-blocker and calcium channel-blocker poisoning. We review the experimental data and clinical experience that suggests high-dose insulin is superior to conventional therapies for these poisonings.
Presentation and general management. Hypotension, bradycardia, decreased systemic vascular resistance (SVR), and cardiogenic shock are characteristic features of beta-blocker and calcium-channel blocker poisoning. Initial treatment is primarily supportive and includes saline fluid resuscitation which is essential to correct vasodilation and low cardiac filling pressures. Conventional therapies such as atropine, glucagon and calcium often fail to improve hemodynamic status in severely poisoned patients. Catecholamines can increase blood pressure and heart rate, but they also increase SVR which may result in decreases in cardiac output and perfusion of vascular beds. The increased myocardial oxygen demand that results from catecholamines and vasopressors may be deleterious in the setting of hypotension and decreased coronary perfusion.
Methods. The Medline, Embase, Toxnet, and Google Scholar databases were searched for the years 1975–2010 using the terms: high-dose insulin, hyperinsulinemia–euglycemia, beta-blocker, calcium-channel blocker, toxicology, poisoning, antidote, toxin-induced cardiovascular shock, and overdose. In addition, a manual search of the Abstracts of the North American Congress of Clinical Toxicology and the Congress of the European Association of Poisons Centres and Clinical Toxicologists published in Clinical Toxicology for the years 1996–2010 was undertaken. These searches identified 485 articles of which 72 were considered relevant.
Mechanisms of high-dose insulin benefit. There are three main mechanisms of benefit: increased inotropy, increased intracellular glucose transport, and vascular dilatation.
Efficacy of high-dose insulin. Animal models have shown high-dose insulin to be superior to calcium salts, glucagon, epinephrine, and vasopressin in terms of survival. Currently, there are no published controlled clinical trials in humans, but a review of case reports and case series supports the use of high-dose insulin as an initial therapy.
High-dose insulin treatment protocols. When first introduced, insulin doses were cautiously initiated at 0.5 U/kg bolus followed by a 0.5–1 U/kg/h continuous infusion due to concern for hypoglycemia and electrolyte imbalances. With increasing clinical experience and the publication of animal studies, high-dose insulin dosing recommendations have been increased to 1 U/kg insulin bolus followed by a 1–10 U/kg/h continuous infusion. Although the optimal regimen is still to be determined, bolus doses up to 10 U/kg and continuous infusions as high as 22 U/kg/h have been administered with good outcomes and minimal adverse events.
Adverse effects of high-dose insulin. The major anticipated adverse events associated with high-dose insulin are hypoglycemia and hypokalemia. Glucose concentrations must be monitored regularly and supplementation of glucose will likely be required throughout therapy and for up to 24 h after discontinuation of high-dose insulin. The change in serum potassium concentrations reflects a shifting of potassium from the extracellular to intracellular space rather than a decrease in total body stores.
Conclusions. While more clinical data are needed, animal studies and human case reports demonstrate that high-dose insulin (1–10 U/kg/hour) is a superior treatment in terms of safety and survival in both beta-blocker and calcium-channel blocker poisoning. High-dose insulin should be considered initial therapy in these poisonings.

Keywords High-dose insulin; Beta-blocker; Calcium-channel blocker; Poisoning

Introduction

Beta-blocker and calcium-channel blocker overdoses may be the result of unintentional or suicidal ingestions, medication errors, or drug interactions.[1] Overdose is associated with a high incidence of morbidity and mortality due to cardiovascular toxicity including profound hypotension and

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conduction disturbances.[1–4] In addition to supportive care, potential interventions include fluids, calcium, glucagon, atropine, catecholamines, inotropes, vasopressors, and mechanical supportive measures such as extracorporeal bypass.[1,3] Unfortunately, these interventions may not improve hemodynamic parameters or ensure survival in severely intoxicated patients.[1]

Recent experimental data and clinical experience suggest high-dose insulin (HDI) may have a greater effect on hemodynamic stability than conventional measures.[5] Treatment failures with HDI have been reported when HDI has been used as a rescue therapy after other pharmacological measures have failed.[5] This may be a result of delayed HDI administration, underlying pathophysiology incompatible with HDI's mechanism of action, and/or ineffective dosing.[6,7] In some situations, the initial selection of pharmacological measures may impact the efficacy and dosing of HDI therapy. It has been theorized that higher doses of HDI may be required when vasopressors are employed initially.[8]

HDI's wide availability, inexpensive cost, and minimal adverse event profile further support its use. Adverse events are predictable and can be effectively managed with glucose and potassium supplementation. This review provides a synopsis of case reports, summarizes efficacy data, and describes current dosing strategies in order to characterize HDI's role in poisoning by these drugs.

Presentation and general management

Hypotension, bradycardia, decreased systemic vascular resistance (SVR), and cardiogenic shock are characteristic features of beta-blocker and calcium-channel blocker poisoning. Hypotension is a result of decreased inotropy, conduction defects, and peripheral vasodilation. Other clinical findings may include hyperglycemia (calcium-channel blockers), bronchospasm (beta-blockers), tachycardia due to myocardial compensation of peripheral vasodilation (dihydropyridine calcium-channel blockers), metabolic acidosis, pulmonary edema due to pre-capillary vasodilation and increased transcapillary hydrostatic pressure, ischemia, bowel infarction/ileus, and cardiogenic shock.[1–3,9–11]

Initial treatment is primarily supportive including consideration of gastrointestinal decontamination and saline fluid resuscitation which is essential for resultant vasodilation and low cardiac filling pressures. Conventional therapies often fail to improve hemodynamic status in severely poisoned patients.[3,4] Glucagon produces a transient increase in inotropy that may not be maintained throughout treatment.[12] Glucagon may cause vomiting resulting in aspiration and airway obstruction in patients with decreased mental status. Case reports of glucagon failures have also been published.[13–15] Catecholamines can increase blood pressure and heart rate, but they also increase SVR which may result in decreases in cardiac output and perfusion of vascular beds. The increased myocardial oxygen demand that results from catecholamines and vasopressors may be deleterious in the setting of hypotension and decreased coronary perfusion.[1]

Calcium salts are used to partially or completely reverse the hemodynamic effects of beta-blockers and calcium-channel blockers by overcoming inhibited calcium channels and increasing inotropy.[16,17] Calcium salts should be considered as initial therapy but may have variable success in severe intoxications.[18–20] Atropine can be used for symptomatic bradycardia in moderate toxicity, but its effects are variable and short-lived. Variable results and failures in severe poisonings have led clinicians toward alternative therapies including HDI.

Methods

The Medline, Embase, Toxnet, and Google Scholar databases were searched for the years 1975–2010 using the terms: high-dose insulin, hyperinsulinemia–euglycemia, beta-blocker, calcium-channel blocker, toxicology, poisoning, antidote, toxin-induced cardiovascular shock, and overdose. In addition, a manual search of the Abstracts of the North American Congress of Clinical Toxicology and the Congress of the European Association of Poisons Centres and Clinical Toxicologists published in *Clinical Toxicology* for the years 1996–2010 was undertaken. These searches identified 485 articles of which 72 were considered relevant. These included animal studies, case reports, and case series; no clinical trials were available.

Mechanisms of HDI benefit

There are many proposed and proven mechanisms for the major salient effects of HDI in beta-blocker and calcium-channel blocker poisoning and cardiogenic shock induced by these drugs. In general, these fall into three categories: (1) increased inotropy, (2) increased intracellular glucose transport, and (3) vascular dilatation. HDI is not a vasopressor. To the contrary, insulin is a vasodilator of the systemic, coronary, and pulmonary vasculature. These vasodilatory effects are due to enhancement of endothelial nitric oxide synthase (eNOS) activity by its effects on PI3K (a major insulin intracellular signaling pathway). Microvascular dysfunction is a hallmark of cardiogenic shock, and insulin enhances microvascular perfusion at the capillary and pre-capillary concentration. These effects appear to be rapid, occur independently of changes in total blood flow to the vascular bed, and can achieve perfused capillary density similar to that of exercising muscle.[21] In cell culture systems, supraphysiological doses of insulin are required to increase eNOS activity above basal concentrations, consistent with the need for a higher insulin dosing range to elicit these beneficial vascular effects. Decreasing vascular resistance by these mechanisms (independent of inotropy) results in enhanced cardiac output.

Intracellular transport of glucose in cardiac and skeletal muscle is greatly enhanced by insulin and has been implicated as an essential component of its inotropic

properties. Stressed myocardium primarily uses glucose as the preferred energy substrate, while preferring fatty acid oxidation under normal conditions.[5] These glucose transport mechanisms that enhance inotropic function have been demonstrated in human explanted hearts.[22] This mechanism, however, is unlikely to be the primary mechanism responsible for the various mechanisms of enhanced cardiovascular effects. Insulin in high concentrations affects several intracellular mechanisms that contribute to the inotropic effects, many of which involve calcium handling and the PI3K pathway.[22,23] The onset of these effects can be measured within 5 min in explanted human myocardium.[24] These inotropic effects have also been shown to occur while increasing coronary blood flow without increasing O_2 requirements, in contrast to catecholamine agents.

Efficacy of HDI

Experimental studies

Kline et al.[25–28] performed studies using HDI in verapamil poisoning in dogs. In the 1993 study, the dogs were treated with either: normal saline (2 ml/min), epinephrine (1 mcg/kg titrated to response), glucagon (0.2–0.25 mg/kg bolus followed by 150 mcg/kg/min infusion), calcium chloride (20 mg/kg bolus followed by 0.6 mg/kg/h infusion), or HDI (19.8–27.5 U/kg/h with 20% dextrose). Survival rates were 0/6 in the normal saline control, 4/6 in the epinephrine group, 3/6 in the glucagon and calcium chloride groups, and 6/6 in the HDI group. While there was no significant improvement in mean blood pressure or heart rate, dogs treated with HDI had significantly improved maximum elastance at end systole, left ventricular (LV) end diastolic pressure, ventricular relaxation, and coronary artery blood flow.[24] When assessing the same treatments in another canine study,[26] HDI increased myocardial contractility and improved the ratio of myocardial oxygen delivery/work. They also found that HDI increased myocardial glucose concentrations.[24,27–29] Overall, Kline et al.[24–28] ascertained that HDI therapy increased survival in comparison to high-dose epinephrine, glucagon, and calcium therapy in a canine verapamil poisoning model.

Krukenkamp et al.[30] induced myocardial depression using 0.2 mg/kg propranolol in 13 dogs. Myocardial depression was defined by the lack of response to a 1 mcg/kg IV bolus of isoproterenol. The subjects were given a 33.3–50 U/kg insulin bolus followed by a 10–15 U/kg/h continuous insulin infusion. Glucose concentrations were monitored every 5 min and dogs were given 50% dextrose and potassium to maintain plasma glucose concentrations greater than 100 mg/dL (5.6 mmol/L). Insulin concentrations in the control group were 22 $\pm$ 7 U/mL and increased in the treatment group to 5660 $\pm$ 60 and 4730 $\pm$ 480 U/ml after the bolus and 30 min into the continuous infusion, respectively. Insulin reversed the myocardial depression to 80 $\pm$ 2% of the baseline cardiac function and produced a statistically significant increase in peak blood pressure without changing myocardial oxygen consumption.

Kerns et al.[31] compared insulin, glucagon, and epinephrine for propranolol poisoning (0.25 mg/kg/minute) in a canine model. Each group received either 4 U/min insulin, 50 mcg/kg glucagon bolus followed by a 150 mcg/kg/h continuous infusion, or 1 mcg/kg/min infusion of epinephrine. The insulin group was found to have increased CO and contractility and decreased SVR. While the epinephrine group showed increased contractility over 30–90 min, contractility steadily declined over the remainder of the study. Epinephrine also transiently increased blood pressure, but this was not maintained. The overall survival rate was significantly higher in the insulin-treated group with 6/6 insulin, 4/6 glucagon, and 1/6 epinephrine-treated dogs surviving for the 240-min study duration.

Holger et al.[32] compared HDI (10 U/kg/h) to a combination of vasopressin and epinephrine in a porcine model of propranolol poisoning. The insulin group demonstrated decreased SVR, while maintaining mean arterial pressure and increasing cardiac output. The increased cardiac output was thought to be due to a combination of increased inotropy and vasodilatation. Vasopressin/epinephrine treatment increased mean arterial pressure and SVR initially, followed by a steady decline until death, similar to the findings by Kerns et al.[31] Cardiac output and heart rate steadily decreased from the initiation of therapy. A significant difference in survival rates was found, with 5/5 of the HDI treatment group and 0/5 of the vasopressin/epinephrine group surviving, leading to early study termination.

Studies have found either no advantage or antagonism may occur when HDI therapy is used in conjunction with vasopressors. Engebretsen et al.[33] hypothesized that the addition of phenylephrine, an alpha-adrenergic agonist, would overcome the peripheral vasodilation seen in dihydropyridine calcium-channel blocker poisoning and improve survival, cardiac index, mean arterial pressure and SVR. Pigs were given nifedipine until mean arterial pressure $\times$ cardiac output had decreased by 25% of baseline. The pigs were then treated with either fluids (control), insulin (titrated from 2 to 10 U/kg/h) alone or insulin and phenylephrine (titrated from 2.4 to 3.6 mcg/kg/h). No differences were seen in survivability, cardiac index, SVR, heart rate, mean arterial pressure, peripheral vascular resistance, or base excess with the addition of phenylephrine to HDI therapy. These results are consistent with other studies showing that vasopressors are not beneficial in calcium-channel blocker poisoning.

Holger et al.[8] theorized that even higher insulin doses are required in the presence of vasopressors to overcome increased SVR and decreased cardiac output. There does not appear to be any strong evidence that the use of vasopressors in drug-induced cardiogenic shock is beneficial and an attempt to wean vasopressor therapy off if already initiated should be strongly considered.[8,34]

Clinical experience

While there have been no clinical trials comparing the use of HDI to other treatments in humans, many case reports report the beneficial effects of HDI therapy in calcium-channel blocker and beta-blocker poisoning and in cardiogenic shock induced by these and other drugs.[2,10–11,35–59] Insulin boluses ranged from 0.1 to 10 U/kg. Continuous insulin infusion rates ranged from 0.015 to 22 U/kg/h with the majority of patients receiving between 0.5 and 2 U/kg/h. Two patients did not require a continuous infusion after the insulin bolus due to rapid improvement.[2,10,35–59] Treatment continued up to 49 h in one case report.[37]

A few HDI case reports have used insulin doses outside of the typical range of 0.5–1 U/kg/h. Hasin et al.[11] reported on a combined verapamil and metoprolol overdose that responded to very low doses of insulin (0.015 U/kg/h). However, insulin was started more than 48 h after presentation and toxicity from the overdose may have been resolving. More recent case reports and some institutions are reporting the safe and effective use of insulin doses greater than 10 U/kg/h to stabilize the patient's clinical condition and cardiac output.[7,35,47]

Engebretsen et al.[42] reported on a mixed beta-blocker/calcium-channel blocker overdose that was treated with HDI. Instead of titrating up to a maximum of 10 U/kg/h, the insulin rate was inadvertently increased to 16.7 U/kg/h. This patient did experience one episode of hypoglycemia (57 mg/dL), but it was rapidly corrected and the patient did not exhibit any clinically significant symptoms.

A nebivolol overdose reported by Stellpflug et al.[48] also inadvertently received a continuous infusion of insulin at 22 U/kg/h for 2 h. After identification of the therapeutic error, the insulin infusion was titrated down but required insulin infusion rates greater than 10 U/kg/h for more than 7 h. The patient continued to receive HDI therapy for a total of 36 h. The patient recovered and no apparent adverse effects were noted.[42] Finally, Place et al.[41] reported on a verapamil overdose patient that was intended to receive a 1 U/kg insulin bolus. The patient, however, received a 10 U/kg bolus in error, which led to rapid hemodynamic improvement and no reported adverse effects.

A few reports of treatment failure with HDI have been reported. One case of amlodipine ingestion remained hypotensive and developed oliguric renal failure despite HDI and vasopressor therapy.[45] Treatment failure could have been due to a number of possibilities including concomitant administration of vasopressors resulting in increased afterload and decreased cardiac output, inadequate insulin dosing, delayed administration of HDI, inadequate duration of therapy, or underlying pathophysiology unresponsive to inotropic therapy.[6,7]

HDI treatment protocols

IV saline resuscitation is an essential initial intervention as central venous pressures (CVP) and LV filling pressures are decreased in drug-induced cardiogenic shock. Prior to initiating HDI therapy, glucose concentrations need to be determined. Patients with concentrations less than 200 mg/dL (11.1 mmol/L) should be supplemented with intravenous dextrose (adults: 25 g dextrose; children: 0.25 g/kg dextrose, given as 10–25% dextrose).

Most clinicians recommend an initial insulin bolus of 1 U/kg followed by a 0.5–1 U/kg/h continuous infusion.[3–5,9–11] In one of the more aggressive HDI protocols, insulin doses as high as 10 U/kg/h have been used in refractory cases.[34] This protocol suggests initiating a 1 U/kg/h continuous infusion after a 1 U/kg bolus. The infusion rate may be increased by 2 U/kg/h every 10 min to a maximum of 10 U/kg/h if no increase in cardiac output or clinical improvement is seen.

Although the onset of action of HDI has been stated as 15–45 min, we could not find any studies that actually studied or measured the onset of action clinically in patients. Human and canine myocardial studies have demonstrated measurable inotropic improvements in 5 min.[60] Traditionally, HDI therapy has been reserved for refractory cases. In order for HDI to be of greatest benefit, it should be used early on in therapy rather than as rescue therapy.[59]

The recommended goals of HDI therapy are to maintain perfusion of essential vascular beds and organs not by increased BP or mean arterial pressure alone. This can be assessed by monitoring mental status, skin warmth and color, peripheral pulses, urine output and vital signs. Insulin is an inotrope and a vasodilator, with minimal effects on systolic blood pressure. Traditional hemodynamic parameters such as maintaining a mean arterial pressure >65 mmHg, a systolic blood pressure >90 mmHg and a HR >50 may not be obtainable. Maintaining adequate perfusion by assessing clinical parameters is likely more important than these traditional hemodynamic targets, especially when shock is defined at the microcirculation/oxygenation concentration.[61] Non-invasive cardiac output monitoring, if available, will add significant data to assess the effects of HDI therapy. Measuring response by blood pressure and pulse alone may be misleading, especially when vasopressors are used, as these values do not reflect cardiac output and perfusion. Vital signs may provide a false sense of security by looking as if they "improved", while underlying increases in SVR may decrease tissue perfusion and result in decreased survival.[32] Biochemical parameters and lactate concentrations may also be helpful when monitoring therapeutic response.

At the beginning of therapy, a dextrose infusion should be initiated in order to prevent hypoglycemia. Shepherd et al.[9] suggest administering 10% dextrose and ½ normal saline at a rate equal to 80% maintenance, while others suggest infusing 5–10% dextrose to maintain glucose concentrations above 100 mg/dL (5.6 mmol/L). However, concentrated glucose infusions greater than 10% through a central line may be required to maintain normal glucose concentrations and should be implemented without delay to minimize risk of fluid overload. During initiation and titration of insulin,

glucose concentrations should be checked every 10 min to see if additional boluses of dextrose and/or increased rates of infusion are needed. Once the insulin dose is stable, glucose concentrations may be checked every 30–60 min.[9] Potassium concentrations should be checked every hour during insulin titrations and then every 6 h once stable. Most recommend supplementing potassium once concentrations fall below 2.8–3.0 mEq/L (2.8–3.0 mmol/L).[4,5,9] In addition, magnesium and phosphorous concentrations should be monitored as concentrations may decrease during HDI therapy.[62]

There are currently no studies illustrating the best way to decrease HDI therapy after cardiac function has improved. Once the hemodynamic parameters have stabilized, the insulin infusion may be gradually tapered and discontinued. Alternatively, the infusion may be stopped abruptly allowing elevated insulin concentrations to self-taper due to gradual release of insulin from lipid stores. Dextrose supplementation may be required for up to 24-h post-insulin discontinuation due to elevated insulin concentrations.[62] Potassium concentrations should also be assessed after insulin discontinuation due to cellular shifts.[62]

Further studies are underway in our laboratory to look at the effectiveness of different insulin doses as a true dose/response study has not been reported. A study by Bechtel et al.[63] found that the degree of glucose uptake inhibition differs by calcium-channel blocker class. The strongest glucose uptake inhibition was seen with nifedipine and verapamil and least with diltiazem. The effects of HDI reversed the PI3K pathway defect, while physiological doses of insulin had no effect. Further studies should investigate insulin dosing requirements to see if higher concentrations are beneficial. In addition, the maximum beneficial dose of insulin has not been established.

Adverse effects of HDI

The most common adverse effects of HDI include hypoglycemia and electrolyte imbalances especially hypokalemia. Although high doses of insulin have been used, no irreversible adverse effects have been reported. Greene et al.[59] prospectively reviewed adverse drug reactions in seven severe calcium-channel blocker (verapamil, diltiazem, or amlodipine) overdoses, where HDI therapy was used. In this review of patients, serum glucose and potassium concentrations were monitored every 30 min until patients stabilized and then every 1–2 h. Potassium concentrations were maintained between 3.8 and 4.0 mEq/L (3.8–4.0 mmol/L) and glucose concentrations between 65 mg/dL (3.6 mmol/L) and 110 mg/dL (6.1 mmol/L). No patient had clinically significant hypoglycemia or hypokalemia. One patient experienced a blood glucose concentration of <65 mg/dL (3.6 mmol/L), but it was rapidly corrected. The mean blood glucose concentrations at the time of presentation and during therapy were 207 mg/dL (11.5 mmol/L) and 210 mg/dL (11.7 mmol/L), respectively. Two patients had potassium concentrations of <3.5 mEq/L (<3.5 mmol/L), but neither had ECG signs of hypokalemia or arrhythmias. Average potassium supplementation during therapy was 2.7 mmol/h.[59] Other studies found that many patients do not require potassium supplementation.[5]

Holger et al.[34] reported on adverse effects in 12 patients receiving HDI therapy for treatment of drug-induced cardiogenic shock. Six patients experienced a total of 19 hypoglycemic events. The lowest recorded glucose was 21 mg/dL (1.2 mmol/L) in a patient that experienced a total of 8 hypoglycemic events. Hypokalemia (<3.0 mEq/L; <3.0 mmol/L) developed in seven patients (minimum 2.3 mEq/L); potassium was infused in these patients. No adverse arrhythmias were recorded. No patients were discharged with adverse sequelae determined to be due to hypoglycemia.

In other case reports, incidences of hypoglycemia and hypokalemia have also been clinically insignificant and have resolved easily. Yuan et al.[37] reported on five calcium-channel blocker overdoses requiring HDI therapy. Four of the patients experienced hypoglycemia but glucose concentrations were only checked hourly. All patients had reported potassium, phosphate, and/or magnesium abnormalities but no reported signs/symptoms of deficiencies.

Conclusions

HDI is a promising treatment for severe beta-blocker and calcium channel-blocker poisoning. Its use is supported by experimental evidence and case reports. HDI has been shown to increase cardiac output without increasing myocardial oxygen demand. Animal studies show higher survival rates in comparison to glucagon, epinephrine, and vasopressin in beta-blocker and calcium-channel blocker poisoning. Current evidence suggests using an insulin bolus of 1 U/kg followed by a continuous infusion of 1–10 U/kg/h early in therapy. A concentrated dextrose infusion should be initiated at the start of HDI therapy. While HDI therapy has been associated with minimal clinically significant adverse events, glucose and potassium concentrations need to be monitored carefully and rapidly corrected if they do occur.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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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.

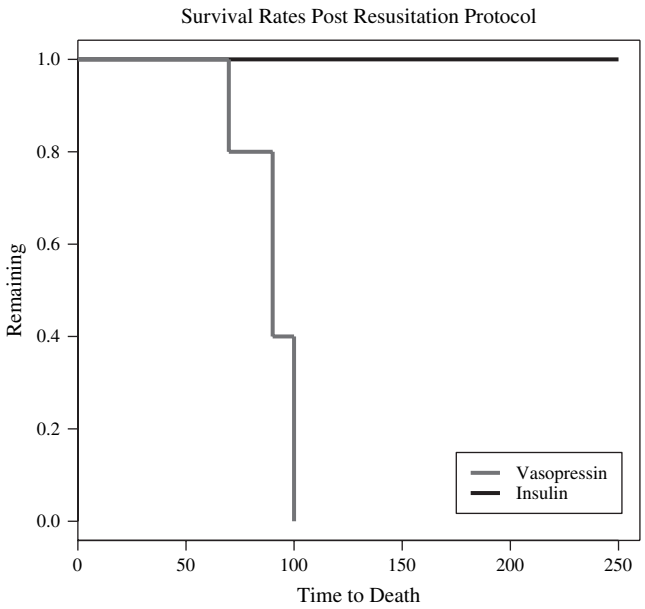

Fig. 1. Kaplan-Meier survival curve.

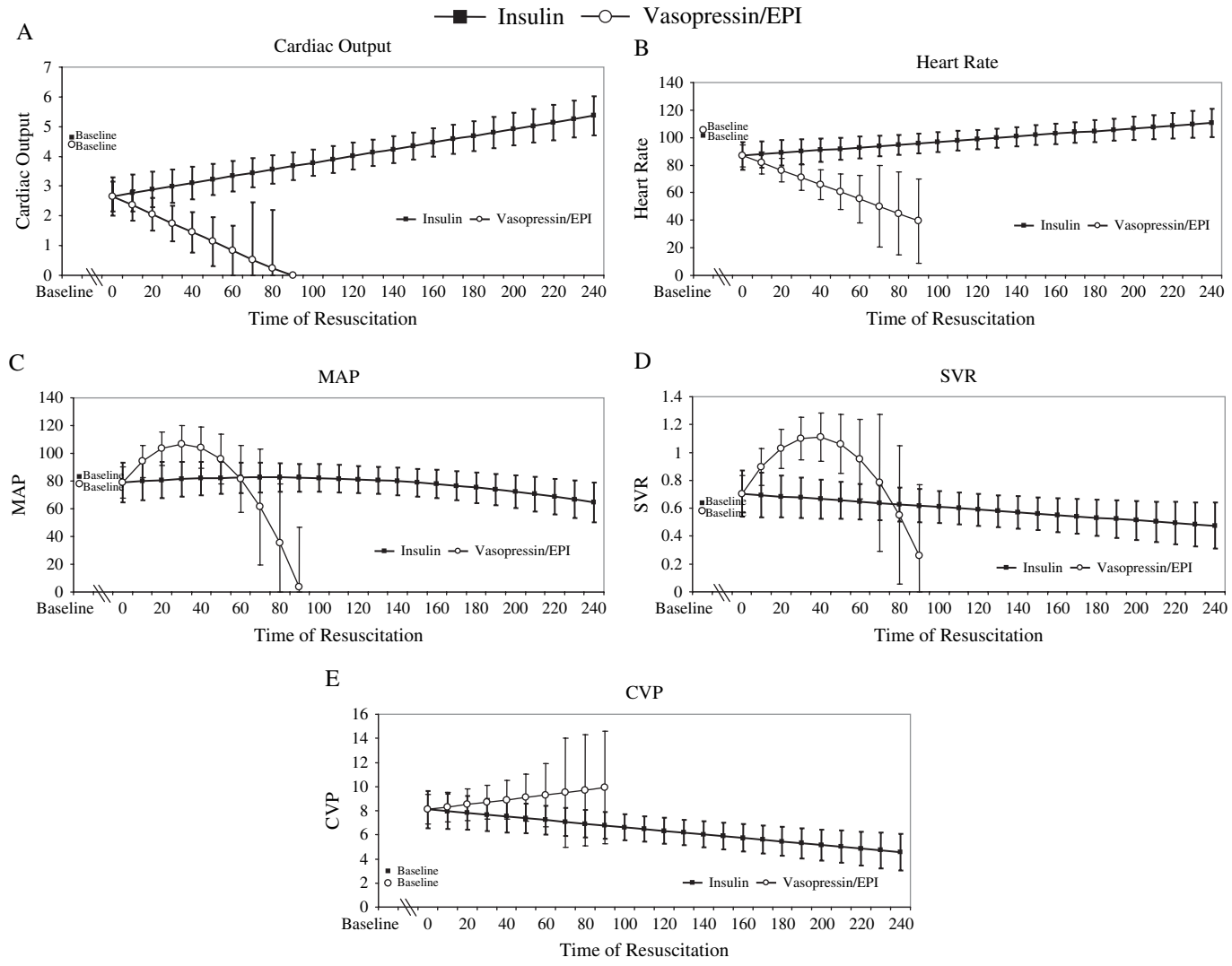

Fig. 2. Mean hemodynamic measurements with 95% confidence intervals.

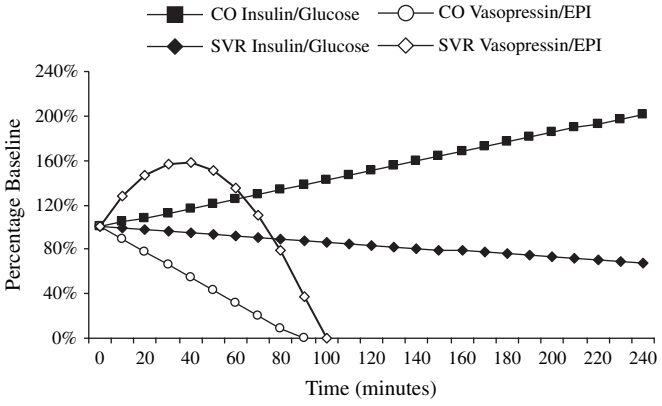

Fig. 3. Relationship of cardiac output and SVR.

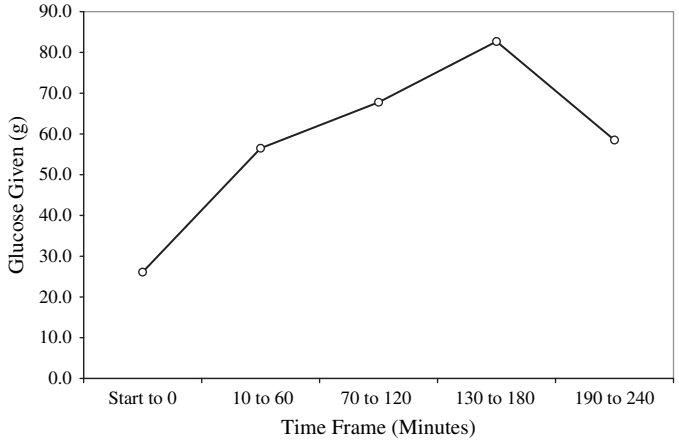

Fig. 4. Glucose requirements per hour in the insulin-glucose group.

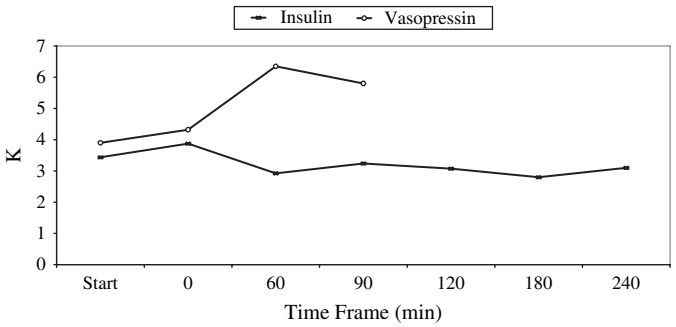

Fig. 5. Comparison of mean potassium levels during resuscitation.

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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RESEARCH ARTICLE

A blinded, randomized, controlled trial of three doses of high-dose insulin in poison-induced cardiogenic shock

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Background. High dose insulin (HDI) has proven superior to glucagon and catecholamines in the treatment of poison-induced cardiogenic shock (PICS) in previous animal studies. Standard recommendations for dosing of insulin vary and the optimal dose of HDI in PICS has not been established. Our hypothesis was a dose of 10 U/kg/hr of HDI would be superior to 1 U/kg/hr with cardiac output (CO) as our primary outcome measure in pigs with propranolol-induced PICS. *Methods.* This was a blinded, prospective, randomized trial with 4 arms consisting of 4 pigs in each arm. The arms were as follows: placebo (P), 1 U/kg/hr (HDI-1), 5 U/kg/hr (HDI-5), and 10 U/kg/hr (HDI-10). Cardiogenic shock was induced with a bolus of 0.5 mg/kg of propranolol followed by an infusion of 0.25 mg/kg/min until the point of toxicity, defined as 0.75 x (HR x MAP) was reached. At this point the propranolol infusion was decreased to 0.125 mg/kg/min and a 20 mL/kg bolus of normal saline (NS) was administered. The protocol was continued for 6 hours or until the animals died. *Results*. 2 pigs died in the P arm, 1 pig died each in the HDI-1 and HDI-5 arms, and all pigs lived in the HDI-10 arm. There was a statistically significant difference in dose by time interaction on CO of 1.13 L/min over the 6 hr study period ($p = < 0.001$). There was also a statistically significant difference in dose by time interaction on MAP, HR, and systemic vascular resistance (SVR). No statistically significant difference was found between any of the arms regarding glucose utilization. *Conclusion.* HDI was statistically and clinically significantly superior to placebo in this propranolol model of PICS. Furthermore a dose response over time was found where CO increased corresponding to increases in doses of HDI.

Keywords High dose insulin; Cardiogenic shock; Beta blockers

Introduction

Poison-induced cardiogenic shock (PICS) is a cause of serious morbidity and mortality, and thus, the knowledge on effective treatment of this clinical scenario is vital for clinical toxicologists or other physicians managing drug overdoses. Beta-blockers are the commonly encountered causes of PICS.[1] The 2010 American Association of Poison Control Centers' National Poison Data System Annual Report revealed 23,091 beta-blocker exposures in the United States. This included 842 cases categorized with moderate or major toxicity outcomes and five deaths due to intentional or accidental ingestion.[1] Treatment for patients with moderate or major toxicity focuses on attempting to reverse both macro- and microhypoperfusion that occurs with these exposures. This hypoperfusion is often the result of a combination of bradycardia, decreased inotropy, and peripheral vasodilation.[2] With beta-blocker toxicity specifically, cardiogenic shock results from bradycardia, decreased inotropy, and occasionally conduction defects.[3–5] As beta-blockers are but one cause of PICS, a new or improved therapy would likely benefit patients who also ingest calcium channel blockers, anti-dysrhythmics, cyclic anti-depressants, and other xenobiotics known to cause PICS.

Various pharmacologic modalities have been suggested, subsequently studied and/or used clinically for attempted reversal of PICS. These include volume expansion, calcium salts, atropine, glucagon, catecholamines (vasopressors and/or inotropes), methylene blue, levosimendan, and high-dose insulin (HDI).[3,6,7] Volume expansion and administration of calcium salts have sound reasoning in their favor and little downside, but there is a controversy regarding the use of glucagon or catecholamines.[2] Glucagon may be transiently effective for PICS from beta-adrenergic blockers, but prolonged treatment may not be effective, and there are several case-reported failures.[8–11] Catecholamines can increase blood pressure and heart rate, but they also increase systemic vascular resistance (SVR). This increase in SVR increases afterload against the already stressed myocardium resulting in decrease in cardiac output (CO) and subsequently decreased perfusion of vascular beds (microperfusion).[12] The increased myocardial oxygen demand that results from catecholamines may be deleterious in the setting of hypotension

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and decreased coronary perfusion as well. Evidence exists that HDI is more effective than catecholamines for the treatment of PICS from both beta-adrenergic blockers[13] and calcium-channel blockers,[14] and it is likely related to its difference in physiological effects as compared to vasopressors. HDI functions as a powerful inotropic agent and as a vasodilator in addition to increasing myocardial glucose transport.[2] Several studies have illustrated the differences in physiologic effects of placebo, glucagon, vasopressors, and HDI in the setting of severe PICS, with HDI resulting in reduced mortality in comparison with other arms.[14–16] There is mounting positive human experience with HDI in this setting as well.[15,16]

Despite the growing evidence that HDI should be a standard treatment for PICS, there is no universal dosing recommendation, in part because there has been no previously performed dose comparison studies. In human case experience with correlating recommendations, insulin boluses ranged from 0.1 to 1 U/kg while continuous insulin infusion rates ranged from 0.015 to 22 U/kg/h; a majority of patients received between 0.5 and 2 U/kg/h.[17,18] A 1994 review of beta-blocker and calcium channel blocker toxicity recommended an initial bolus of 1 U/kg followed by an infusion starting at 0.5 U/kg/h, titrated up every 30 min as needed.[18] The same author offered updated and reiterated recommendations in a standard Toxicology textbook in 2011; those recommendations included starting insulin dosing with a bolus of 1 U/kg followed by an infusion starting at 0.5–1 U/kg/h.[19] This reference text also goes on to say that the maximum dose has not been established in humans. With no maximum HDI dose established, deaths reported after use of low doses of HDI, and good outcomes without adverse effects after use of as high as 22 Units/kg/h,[15] and it is apparent that an analysis of HDI dose–response was needed. As propranolol has previously been demonstrated to account for a disproportionate number of poisonings and deaths,[20] we chose it as our agent to induce cardiogenic shock. The purpose of this study was to determine whether a difference in cardiac output exists in swine with propranolol-induced PICS treated with placebo (P) or insulin infusions of 1 Unit/kg/h (HDI-1), 5 Units/kg/h (HDI-5), or 10 Units/kg/h (HDI-10). This swine model primarily evaluated the role of HDI, dose, time, and the interaction of dose and time in the determination of cardiac output.

Methods

Our Institutional Animal Care and Use Committee approved this project. The supervision of the animals was in accord with the American Association for Accreditation of Laboratory Animal Care guidelines. Healthy Yorkshire swine, ranging in weight from 32 to 44 kg, were sedated with the short-acting agents tiletamine and zolazepam for instrumentation and anesthetized for the entire protocol with a combination of 30% nitrous oxide and isoflurane. Reflexes were monitored to minimize cardiovascular depressant effects. A tracheostomy was performed, and the animal was placed on a ventilator. An incision on the right upper neck of the pig was made, and a Swan-Ganz catheter was placed via cutdown method for the determination of cardiac output (CO) measurements as determined by the thermodilution technique, pulmonary artery pressures, and central venous pressure measurements. A femoral arterial line was placed for continuous arterial blood gas and pH determinations, and for continuous systolic, diastolic, and mean arterial pressure monitoring. Animals were ventilated with 30% O2 and monitored to maintain the pCO2 near the baseline. Femoral venous access was allowed for medication, fluid, and venous blood sampling. Electrocardiogram electrodes were attached for continuous monitoring. A suprapubic urinary catheter was placed. Each animal was placed on a heating pad to maintain baseline temperature. A stabilization period of 30 min was observed before induction of toxicity.

Baseline measurements were taken on each pig prior to the experimental protocol. The following measurements were recorded every 10 min: cardiac output, cardiac index, systolic blood pressure, mean arterial blood pressure (MAP), central venous pressure (CVP), SVR (calculated), pulmonary vascular resistance (PVR, calculated), arterial blood gasses, base excess, and glucose. Serum lactate and potassium concentrations were recorded at baseline, at the point of toxicity, and at 60-min intervals until the end of the study. The total amounts of infused glucose and potassium were also recorded. Measured potassium concentrations less than 2.5 mEq/L were administered 10 mEq of intravenous potassium chloride.

Induction of toxicity in the pigs was complicated by model development. Initially, we attempted to replicate a model of toxicity first described by Leppikangas et al.,[8] in which toxicity was induced in the swine with a 1 mg/kg intravenous bolus of propranolol followed by an infusion of 0.5 mg/kg until the point of toxicity was reached. Toxicity was defined in this study as 40% of baseline cardiac output for a period of 15 min before resuscitation was initiated. Despite extensive laboratory experience among the investigators, we were unable to replicate this model; the swine enrolled in this protocol died before we could begin resuscitation.

Next, we attempted a model of toxicity used in our previous work.[21] In this model, toxicity was induced with a 1 mg/kg intravenous bolus of propranolol followed by an infusion of 0.25 mg/kg until the point of toxicity was reached. Toxicity in this model was defined as a 25% reduction in the product of the initial MAP x HR. This point of toxicity was previously defined and validated in work by Kerns[13] and Kline.[14] Twelve animals were enrolled under this protocol in four arms; placebo, 1 U/kg/h, 5 U/kg/h, and 10 U/kg/h of HDI. No animals survived, and an interim analysis revealed no difference between any of the HDI arms. Again, we concluded that our model was too toxic to make any meaningful conclusions.

We then moved to a model we had previously used[12] that was developed in response to editors' concerns that our previous research model had been too toxic to find subtle differences in treatment arms. In this study, the propranolol bolus was reduced to 0.5 mg/kg. The point of toxicity was identical. Induction of toxicity was brought about by the same 0.25 mg/kg/min infusion of propranolol; however, upon reaching the point of toxicity, the infusion was reduced

Table 1. Comparisons between treatment arms at baseline.

	Placebo		1 U/kg/hr		5 U/kg/hr		10 U/kg/hr		Overall
Variable	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	P value
Weight (kg)	39.6	2.9	38.8	0.8	42.3	1.8	40.4	2.0	0.67
Time to toxicity (min)	14	1.2	21	2.6	16	2.4	20	2.9	0.17
Cardiac output (L/min)	2.8	0.3	3.6	0.8	3.6	0.7	2.9	0.5	0.78
Cardiac index (L/min/m^2)	3.4	0.4	4.4	1.0	3.8	0.8	3.4	0.5	0.75
Heart rate (bpm)	69	3.8	73	7.8	72	2.1	70	6.2	0.94
Mean arterial pressure (mm Hg)	49	2.4	48	1.3	53	3.5	52	4.4	0.75
SVR (dyne-sec/cm^5)	1262	116	1125	287	1174	274	1389	247	0.87
Venous O2 saturation (%)	52	2.4	50	2.8	46	3.8	44	8.0	0.68
Base Excess	4.9	0.9	6.3	1.0	4.2	1.6	5.4	1.7	0.73
Potassium Concentration (mEq/L)	3.7	0.1	3.3	0.4	4.0	0.2	3.8	0.1	0.20

to 0.125 mg/kg/min. Resuscitation was carried out for 6 h or until death of the animals. Sixteen swine were enrolled under this protocol and randomized to one of the same 4 arms: placebo, 1 U/kg/h, 5 U/kg/h, and 10 U/kg/h of HDI. Randomization was performed utilizing www.randomization.com. The randomization results were delivered blinded to the central pharmacy in our institution and study drug was mixed there. Investigators were blinded to the treatment arm. After the point of toxicity was reached, each animal received a 20 mL/kg bolus of 0.9% sodium chloride. Glucose concentrations were measured in all subjects at baseline, at the point of toxicity, and at every 10 min after the point of toxicity until the end of the protocol. A glucose concentration less than 60 mg/dl was treated with 25 g of intravenous glucose; if the glucose concentration was less than 40 mg/dl, the subject was treated with 50 g of intravenous glucose. Upon administration of the first bolus of glucose, an infusion of glucose was started at a rate of 12.5 g/h. On every occasion, an additional bolus of glucose was given, and the glucose infusion rate was increased by 12.5 g/h. D50 was used as the glucose fluid of choice for this study.

We described each treatment arm at baseline using the mean and standard error of several important prognostic factors. Equivalence at baseline in each of these factors between treatment arms was assessed using ANOVA. Our primary aim, which was to determine whether the rate of change in CO in measures observed over time was proportional to the dose of HDI, was addressed using a linear mixed-effects regression model in SAS PROC MIXED. Like the previous analyses of CO over time that have been conducted by our group,[12,22,23] this model featured CO as a function of time, quadratic time, a time by CO interaction, and a random effect for each subject to account for correlation between observations taken from the same animal. Analogous regression models were used to assess whether the change over time for CI, HR, MAP, SVR, and venous oxygen saturation was associated with higher doses of insulin. We used multiple imputation to correct for truncation of data in animals that expired, assuming that after expiration, unobserved values of cardiometric variables were proportional to the average values for that subject, as well as to the values of the variable observed in other subjects, using the method of Rubin[24] to account for imputation error. Mortality was analyzed using Kaplan–Meier survival rates, and the association between randomization group and survival was assessed using a log-rank test. Survival analysis was performed using the statistical software R, version 2.9.1, while all other analyses and data manipulations were performed using SAS 9.1. All hypothesis tests were two-sided, with $\alpha = .05$.

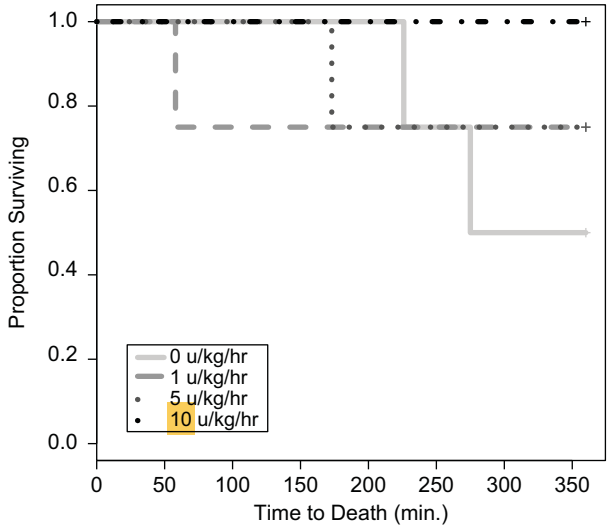

Fig. 1. Post-resuscitation survival.

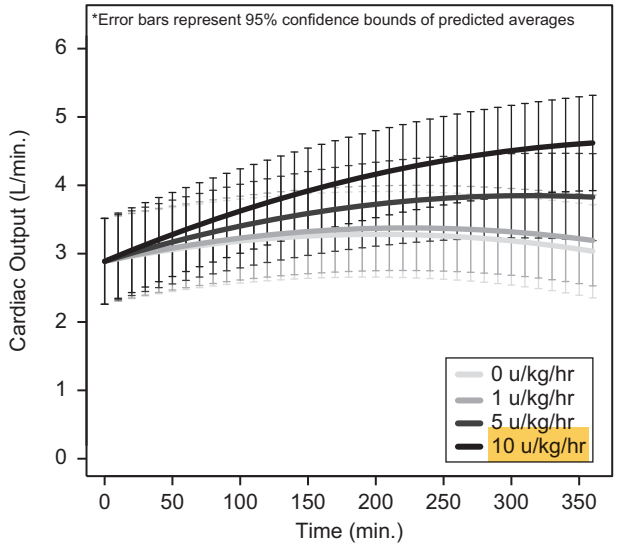

Fig. 2. Cardiac output (Pred. Avgs.).

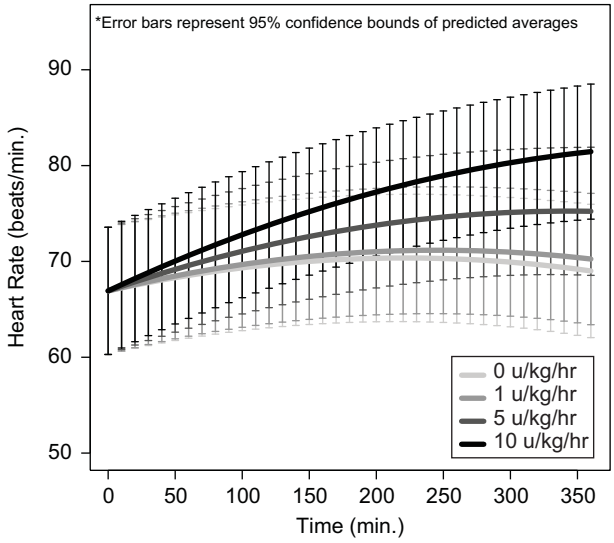

Fig. 3. Heart rate (Pred. Avgs.).

We performed a power analysis, which indicated that under the assumed conditions, our study would have an 85% chance of correctly identifying a real increase in CO of 0.45 L/min per every 1 U/kg/h increase in HDI dose, if such an effect existed. The assumptions made regarding study conditions were that the sixteen subjects would be measured an average of 24 times apiece, that CO would vary significantly within each subject (ICC = 0.01), that the effect of insulin upon the change in CO over time was linear with increasing dose, and that our tolerance for type I error would be 5%.

Results

No baseline differences prior to induction of toxicity were found between the four arms in weight, CO, CI, HR, MAP, SVR, venous oxygen saturation, base excess, or serum potassium concentration (Table 1). No difference was found with respect to time to toxicity between any of the arms (p = 0.17).

Mortality

Two pigs died in the P arm, one pig each died in the HDI-1 and HDI-5 arms, and no pigs died in the HDI-10 arm. Survival was not statistically different between the 4 arms as the study was not powered for mortality as a primary outcome. However, a dose-related trend in mortality was noted. The Kaplan–Meier method was used for analysis of this variable (Fig. 1).

Cardiovascular parameters

Cardiac output

Little difference between the 4 arms in terms of CO was observed at any point during the 360-min protocol. However, a linear mixed-effects regression found a small but statistically significant dose by time interaction, in which CO improved an average of 0.00035 L/min/min for every 1 U/kg/h of insulin ($p < 0.001$). Thus, while there was no difference in groups at any single point in time, there is evidence of a difference in the trajectory that the group average CO followed over the 360-minute study interval that is proportional to the dose of insulin received (Fig. 2). Because we assumed a linear effect, this difference can be calculated for any of the cardiovascular variables between any of the 4 arms in the study using the following formula:

(dose/time interaction (for CO, 0.00035 L/min/min) × 360 min × HDI dose) – (dose/time interaction × 360 min × HDI dose)

The difference in projected averages between the HDI-10 arm and the HDI-1 arm at the end of a 6-hour resuscitation is (0.00035 L/min/min × 360 min × 10) – (0.00035 L/min/min × 360 × 1) = 1.26 L/min – 0.126 L/min = 1.13 L/min.

Heart rate

At no single points were average heart rates for any two groups statistically different from one another. However, as with CO, a statistically significant dose by time interaction effect upon heart rate was observed ($P < 0.0001$). On

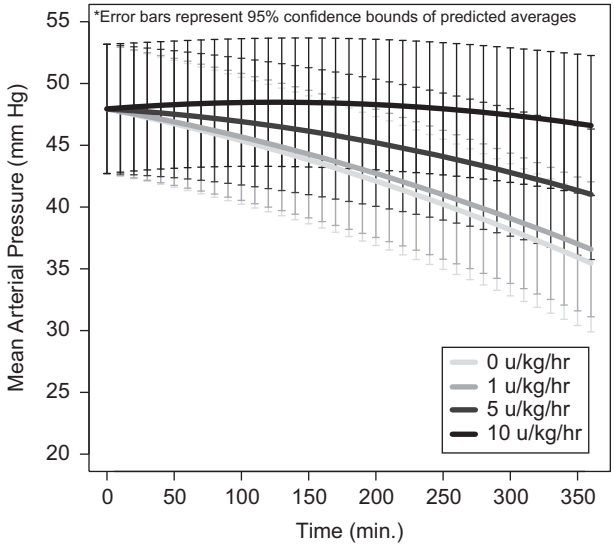

Fig. 4. Mean arterial pressure (Pred. Avgs.).

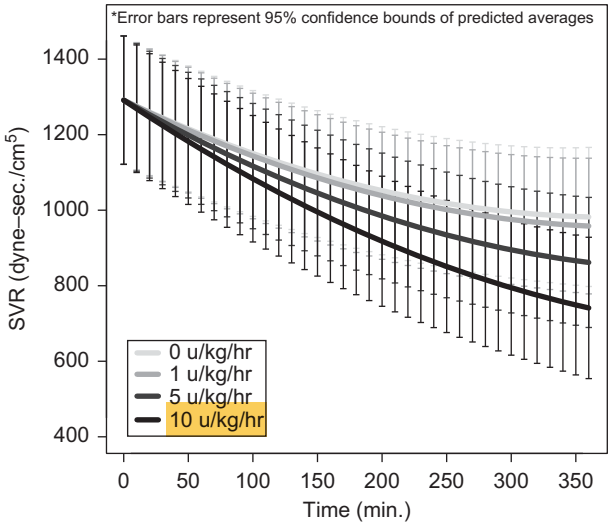

Fig. 5. Systemic vascular resistance (Pred. Avgs.).

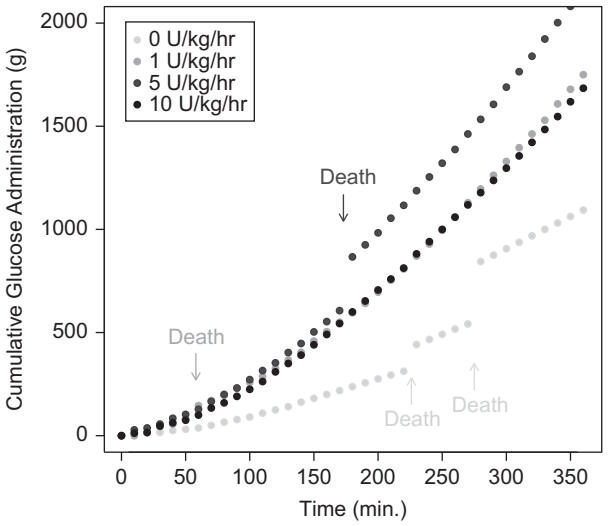

Fig. 6. Cumulative glucose administration.

average, heart rate increased by 0.0028 bpm/min each minute for every 1 U/mg/kg of insulin (Fig. 3). Thus, the difference in projected averages between the HDI-10 and the HDI-1 arm at the end of a 6-hour resuscitation is (0.0028 bpm/min × 360 × 10) – (0.0028 bpm/min × 360 × 1) = 10.08 – 1.008 = 9 bpm.

Mean arterial pressure

Similarly, MAP did not exhibit significant differences between group averages at any point of measurement over the duration of the study, but the trend over time was significantly different ($P < 0.001$). As is somewhat visible from the projected plot of MAP vs. time, the HDI-10 arm maintained an average MAP that was more or less stable, while the other three groups experienced a monotone downward trend (Fig. 4). Thus, assuming a linear dose by time interaction trend, the effect of 1 U/mg/kg of insulin is to raise MAP by 0.0024 mmHg every minute, which given the observed degree of uncertainty, is statistically nonzero ($< p = 0.001$). The predicted effect is such that MAP would be 8 mmHg higher in the HDI-10 arm than in the HDI-1 arm at the end of the 360 min.

Systemic vascular resistance

In keeping with the pattern, SVR was not significantly different by dose at most of the measured time intervals, but a linear mixed effects model indicated that SVR decreased faster over time in groups receiving higher doses of insulin ($p < 0.001$). This was expected as HDI is not a vasopressor, rather it is a vasodilator.[22] This interaction effect was estimated to be a decrease of approximately 0.067 dyne-s/cm^5 per minute, for every 1 U/mg/kg of insulin. Thus, SVR would be predicted to decrease by 217 dyne × sec/cm^5 over the entire 360-min study interval in the HDI-10 arm compared to the HDI-1 arm (Fig. 5).

Table 2. Average glucose cumulative administration (grams) across all time points in the study.

Placebo	HDI-1	HDI-5	HDI-10	Overall	p-value
271	632	742	680	586	>0.0001

Metabolic parameters

Glucose administration

Graphical representation for cumulative glucose administration per arm is shown in Fig. 6. The average glucose administration over the entire resuscitation in each arm, adjusted for mortality by calculating the average glucose administration per 10-min interval, was as follows: P = 271 g, HDI-1 = 632 g, HDI-5 = 742 g, HDI-10 = 680 g (Table 2). There was a statistically significant difference in glucose administration between the P arm and all the HDI arms ($P < 0.0001$, Table 2). We found no statistically significant difference between any two individual arms in terms of glucose administration (Table 3); however, no power analysis was done prior to obtaining data as glucose administration was a secondary outcome. Of note, glucose administration in the P arm was particularly affected by one pig that had four hypoglycemic events but did not consume glucose at a significantly higher rate as the animal was hyperglycemic for much of the resuscitation. As we did not determine a priori what to do if a pig stopped utilizing glucose, we did not decrease the glucose infusion when the pig became hyperglycemic; thus, the P arm's glucose administration is somewhat inflated. The average number of hypoglycemic events per arm (measurements of glucose < 60 mg/dL while on the glucose protocol described above, not accounting for mortality) were as follows: P = 1.75, HDI-1 = 4.25, HDI-5 = 5.75, HDI-10 = 5.25.

Potassium concentration

Only thrice did potassium concentration drop below 2.5 mEq/L. Two measurements of 2.4 mEq/L were observed in one animal in the HDI-1 arm that had a baseline potassium concentration of 3.1 mEq/L. One measurement of 2.4 mEq/L was observed in the HDI-10 arm. All three instances responded to a single dose of 10 mEq of intravenous potassium chloride.

Lactate concentration

We observed no clinically significant changes in lactate measurements over time during the resuscitation. However,

Table 3. Group average cumulative glucose administration (grams) among pigs alive at time *t*.

Time (min)	Placebo	HDI-1	HDI-5	HDI-10	p-value
60	37.5	109	128	100	0.291
120	125	292	353	309	0.134
180	238	563	750	600	0.104
240	463	896	1138	941	0.169
300	763	1296	1573	1297	0.379
360	950	1717	2044	1684	0.145

a sharp rise in lactate concentration seemed to coincide with the ultimate terminal event. Measurements were not taken often enough to make a meaningful statistical conclusion regarding this parameter.

Discussion

In this model of Poison-Induced Cardiogenic Shock, there was a statistically significant increase in the cardiac output of 0.13 L/min for every increase in dose of HDI of 1 U/kg/h between placebo and 10 U/kg/h. Thus, there is a difference of 1.13 L/min of CO between the HDI-10 and HDI-1 arms over the 6-hour resuscitation. Given the average CO nadir of the pigs in this study, this represents a 57% increase in CO between the HDI-10 and HDI-1 arms. As we measured an increase in heart rate with increasing doses of HDI, some of the increase in CO appears to be via an increase in HR. This increase in HR, however, dose not account for the entire change in CO; thus, we can infer that stroke volume also increases with increasing doses of HDI. As expected, SVR tended to fall as HDI dosing increased demonstrating the vasodilatory effect of HDI. Though the concept of giving a vasodilator to a patient in cardiogenic shock may alarm some clinicians, in fact MAP actually rose with increasing doses of HDI. This suggests that while the vasodilatory effect of HDI is in fact present, the increased inotropy from HDI actually overcomes the vasodilatory effect on MAP, resulting in an overall higher macroperfusion as well as an increased microtissue perfusion.

Our findings are consistent with our clinical observation that some patients do not respond to lower doses of HDI and that, in fact, higher doses are required to maintain perfusion.[17] We did not study doses higher than 10 U/kg/h and did not see a plateau effect in our study and therefore cannot comment on a ceiling dose. A review of the literature reveals no previous work establishing a dose–response with HDI. Out data support a dose–response for HDI in Poison-Induced Cardiogenic Shock does in fact exist.

Regarding glucose administration, our study was not powered to detect a difference between arms. No difference was found between the three HDI arms in terms of glucose administration when death was accounted for. Perhaps, a more clinically useful measurement regarding glucose use would be a number of hypoglycemic episodes that occurred, on average, at each HDI dose. While on average there was one less hypoglycemic episode per resuscitation in the HDI-1 arm, there appears to be no difference between the HDI-5 and HDI-10 arms; in fact the HDI-5 arm averaged slightly more hypoglycemic episodes. While we cannot make definitive conclusions regarding glucose utilization, our data show no difference between any of the HDI arms in terms of glucose administration.

Metabolic parameters outside glucose administration were not particularly revealing. Only three episodes of hypokalemia were observed. At no time did any pig experience a dysrhythmia consistent with hypokalemia. In these three instances, potassium was replaced uneventfully. Measured serum lactate was also unrevealing other than elevated levels likely coinciding with the terminal event; this is consistent with previously published clinical data.[25]

Our study is not without limitations. Data derived from an animal model may not accurately represent toxicity in a human. We attempted to replicate continued absorption of propranolol via a constant infusion of propranolol; however, this may not simulate what truly occurs in a human oral overdose. The duration of monitoring lasted only 6 h. While this is longer than much of the previous animal work,[12,13,14,23] it is conceivable that the difference we found is no longer present further into a patient's toxicity. Animal cardiovascular models may have inherent myocardial depression due to anesthesia, and this model is no different; however, we believe that the combination of nitrous oxide and low-dose isoflurane minimizes these effects. Lastly, this model used propranolol to induce cardiogenic shock. Propranolol induces cardiogenic shock via both beta-adrenergic blockade and sodium-channel blockade. It is conceivable other mechanisms that cause PICS, such as calcium-channel blockade, may not exhibit the same dose–response we found with the propranolol.

Though our data support a dose–response effect of HDI in PICS, we did not observe a ceiling effect. This is consistent with our clinical observation as well.[15] Further work is required to establish a true ceiling effect of HDI.

Conclusion

In this model of Poison-Induced Cardiogenic Shock, there was a dose–response over time where cardiac output increased corresponding to the increases in HDI dosing. When using HDI, clinical toxicologists should be mindful, a ceiling dose has not been established, and higher doses of HDI appear to be more effective than lower doses with likely minimal additional risk.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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BRIEF COMMUNICATION

Intentional overdose with cardiac arrest treated with intravenous fat emulsion and high-dose insulin

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Introduction. Nebivolol, a beta blocker with 3–10 times more β_1 cardioselectivity than metoprolol, has caused hypotension and bradycardia in overdose. We report a nebivolol-induced cardiac arrest in the setting of a polydrug ingestion, successfully resuscitated with intravenous fat emulsion (IFE) and high-dose insulin (HDI). *Case report*. A 48-year-old man was brought to the emergency department after ingesting nebivolol and ethanol, along with possibly diazepam and cocaine. He had a heart rate of 71/min and a blood pressure of 98/61 mmHg. The initial ECG showed sinus rhythm with a QTc of 483 ms and a QRS of 112 ms. Over the subsequent 4 h, he became bradycardic and hypotensive and developed bradyasystolic cardiac arrest. Standard resuscitation including epinephrine had no effect. Spontaneous circulation returned 30 s after a 100 mL bolus of 20% IFE, and the patient then became briefly hypertensive and tachycardic with heart rate and blood pressure measured as high as 123/min and 251/162 mmHg, respectively. His care included IFE infusion along with HDI bolus and infusion with doses as high as 21.8 units/kg/h. With subsequent hypotension, vasopressors were withheld in favor of HDI and supportive care. He was discharged with baseline neurologic function. *Discussion*. We hypothesize that after the administration of IFE the epinephrine was able to exert its effect on receptors previously occupied with the nebivolol. This would be congruent with the lipid sink theory of IFE mechanism. *Conclusion*. We report an overdose involving nebivolol in a polydrug ingestion resulting in cardiac arrest, successfully treated with IFE and a very HDI infusion.

Keywords Beta-blocker; Intravenous lipid emulsion; Intralipid; HDI; Nebivolol

Introduction

Nebivolol is a third-generation beta adrenergic receptor antagonist, approved by the FDA in December of 2007 for the treatment of hypertension.[1] It has been used in Europe since 1999 for the treatment of hypertension and heart failure, and at therapeutic doses it is the most cardioselective β_1 antagonist available.[2] It has caused hypotension and bradycardia in overdose.[3] Ethanol, diazepam, baclofen, and cocaine have been reported to precipitate hypotension, bradycardia, and/or bradyasystolic arrest.[4–7] We report a cardiac arrest likely because of nebivolol ingestion with possible contribution from ethanol, diazepam, baclofen, and cocaine. The patient was successfully resuscitated with a combination of intravenous fat emulsion (IFE) and high-dose insulin (HDI). The maximum infusion rate of HDI was 21.8 units/kg/h.

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Case report

A 48-year-old man was brought to the emergency department (ED) by ambulance after being found unresponsive in his wheelchair. His past medical history included hypertension and paraplegia. His known medications were baclofen, diazepam, and nebivolol. His fingerstick glucose was 100 mg/dL, and his vital signs included blood pressure (BP) 92/52 mmHg, heart rate (HR) 72/min, respiratory rate 22/min, and O_2 saturation of 96% on 15 L/min O_2 through nonrebreather mask. Physical examination revealed a patent airway, shallow breath sounds, palpable pulses, Glasgow coma score of 3, sluggishly responsive pupils bilaterally (3 mm), and no signs of trauma. ECG showed sinus rhythm with QRS of 112 ms and QTc of 468 ms. His ED course included endotrachial intubation, a normal head computed tomography, and chest X-ray; abnormal laboratory studies included a serum ethanol of 110 mg/dL and a positive urine immunoassay for benzodiazepines and cocaine metabolites (confirmed by GC–MS). In his 4 h in the ED, his HR and systolic BP remained essentially 70/min and 90 mmHg. The patient's home nurse reported that he had left a suicide note next to three bottles of medicine prescribed the day before: half empty bottles of baclofen (2,700 mg prescribed) and diazepam (75 mg prescribed), and an empty bottle of nebivolol (300 mg

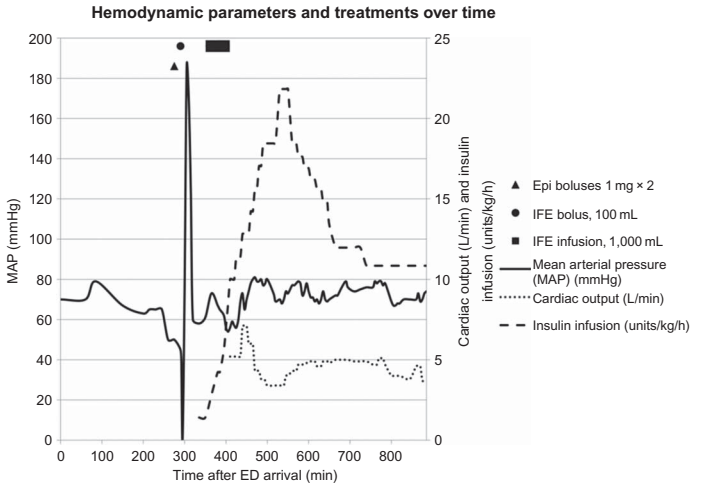

Fig. 1. Representation of a time course of documented hemodynamic parameters and treatments.

prescribed). The time of ingestion was unknown, but was within 3 h before arrival.

Within the hour after the patient arrived to the intensive care unit, his HR declined to 35/min and his systolic BP fell to 50 mmHg. During this time he was given intravenous (IV) normal saline boluses totaling 3 L and 18 mEq calcium. He developed a bradyasystolic cardiac arrest. Figure 1 shows resuscitation medications and time frame. His resuscitation included CPR and two boluses each of atropine 1 mg and epinephrine 1 mg, 4 min apart. One minute after the second dose of epinephrine, a 100 mL bolus of 20% IFE was administered IV over a few seconds. Thirty seconds after the IFE bolus, a pulse returned with organized sinus rhythm, and 30 s later the patient developed a HR and BP measured as high as 123/min and 251/162 mmHg, respectively. Over the ensuing 20 min, bradycardia and hypotension returned. At this point a 20% IFE infusion was started at 0.25 mL/kg/min and was continued for 1 h (1 L total infused), and the patient received a bolus of 100 units of regular insulin IV, which was followed by HDI infusion. The infusion quickly reached doses in excess of 21 U/kg/h because of administration error and was slowly tapered over the subsequent 36 h although maintaining perfusion parameters. Supportive care included calcium (117 mEq total) and dextrose (485 g total) to maintain euglycemia. Although the patient's mean arterial pressure was less than 60 mmHg for 50 min, as per toxicology recommendations no pressors were used. No evidence of impaired end organ perfusion was evident by clinical exam or laboratory tests. He was discharged on day 11 with no neurologic change from his previous baseline.

Discussion

This is a case of cardiac arrest as an outcome in a nebivolol overdose. A previous nebivolol overdose is reported, in which the patient demonstrated hypotension, bradycardia, hypoglycemia, and respiratory failure.[3] Our case is unique because of the cardiac arrest but also because of the successful IFE resuscitation. The IFE bolus was given 1 min after the last 1 mg epinephrine bolus. A prevalent mechanistic hypothesis for IFE is the lipid sink theory, in which IFE sequesters lipophilic drugs into the serum and away from their target receptors.[8] Additionally, there is evidence that IFE also modifies energy metabolism in the cardiac myocyte.[9] The theory of IFE creating a sequestering pool for lipophilic agents to be pulled away from receptors is congruous with the immediate response in our patient. He transitioned from being pulseless to being hypertensive and tachycardic immediately after the IFE bolus. We hypothesize that after IFE administration epinephrine was able to exert its effect on the receptors previously occupied by nebivolol. Nebivolol has a volume of distribution between 151 and 200 L/kg.[10] It is highly lipophilic, much more so than epinephrine, thus the epinephrine would be more available to the receptor after IFE treatment.[10–12] Of note, baclofen and diazepam are also quite lipophilic, so it is possible that the IFE may also have caused withdrawal of either of these xenobiotics.[13,14] The insulin infusion dose given to this patient reached 21.8 units/kg/h. It was slowly tapered and was kept over 10 units/kg/h for several hours. There is no evidence of a dosing ceiling for HDI. There is not a consensus standard for dosing, but recommendations are typically in the range of 0.5–1 units/kg/h.[15,16] Animal studies show increasing efficacy at much higher doses and human case reports of good outcomes at higher doses as well.[17–19] This patient tolerated the very high doses of insulin without hypoglycemia and/or clinically significant hypokalemia. Our case adds support that current recommendations for HDI dosing are not aggressive enough for maximal patient benefit. Report limitations include the unavailability of serum nebivolol levels and the possibility that the paraplegia or other medications played an important role.

Conclusion

We report a polydrug overdose involving nebivolol resulting in cardiac arrest, successfully treated with IFE and a very HDI infusion.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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COMMENTARY

Premises, Premises (Poisoning-induced cardiogenic shock and High-dose Insulin)

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A *premise* is a statement that an argument claims will induce or justify a conclusion.[1] In other words, a premise is an assumption that something is true.

Poisoning-induced cardiogenic shock (PICS) is a very broad term. It is a much broader term than calcium channel block(CCB)-induced cardiogenic shock or beta blocker(BB)-induced cardiogenic shock or sodium channel block(NCB)-induced cardiogenic shock. So one must assume that the phrase PICS encompasses shock caused by any or all poisons. End-stage shock caused by many drugs will have a similar clinical picture. But the mechanism of toxicity that causes shock is different in each of the individual drugs, for example, channel block (we do not even approach shock caused by drugs that block channels the same way – initial treatment of NCB toxicity is very different from initial treatment of CCB toxicity). The physiology of early shock is varied enough that initial treatments are different. But is the physiology similar enough that we can approach PICS as a single entity and therefore look for a best or universal treatment?

Before we knew much about the sodium channel, scientists tried for years to determine which component of plasma alkalinization improved hemodynamic instability and outcome in tricyclic antidepressant (TCA) overdose. There were many papers published (bench and animal experiments, and case studies) indicating it was the sodium, or the bicarbonate, or the pH, etc. It was important to determine which component so that we could find the best universal treatment. But as research increased our understanding of the sodium channel, it became clear that the component of the sodium bicarbonate that decreased the drug's affinity for the sodium channel was drug dependent and different for each drug. One size does not fit all.

Now, we are looking for the best universal treatment for PICS in the same way we looked for the best universal treatment of NCB poisoning. Again, we are looking for the one size that fits all.

We must be very careful in how we present the evidence. For instance, the authors state that high-dose insulin (HDI) is more effective than catecholamines and that HDI decreases mortality in several studies that compare glucagon, vasopressors, and HDI for treatment of PICS.[2] And although these studies are appropriately referenced, the text does not mention that the "several studies" are two experiments in canines, one with beta blockers and one with verapamil.[3,4] The authors add that there is mounting human experience, referencing a single case report of a beta blocker overdose treated with HDI and intravenous fat emulsion[5] as well as an observational case series with data collected from a registry.[6] They then state that despite growing evidence that HDI should be standard treatment for PICS, there are no universal dosing recommendations, and their study is addressing the dosing issue.

So from animal experience and a few case reports and case series, which do not include analytical confirmation,[3–6] it has been suggested that there is a standard treatment for PICS (i.e., HDI). Premise number one – there is a standard treatment for PICS. Premise number two – HDI is the standard treatment (we just do not know the dose). Premise number one and premise number two have led to premise number three – there must be an universal dosing regimen for HDI. That might seem logical but may not reflect the reality.

The ability to translate animal experiment results to the bedside has plagued us for years. First is the issue of developing a model of toxicity. The authors tried two different models, but no animals survived in either model, so a third model was developed. (This exemplifies the diligence of the authors and the difficulty of the task.)

Premise number four – results from intravenous (IV) administration of drug to animals until they demonstrate toxicity simulate the toxicity of oral ingestion of the same drug in humans. The authors correctly note that data derived from an animal model may not accurately represent human toxicity. Pharmacologically, IV administration followed by constant infusion causes a rapid distribution of the drug, which does not occur with oral ingestion. IV administration also avoids any first-pass effects, which vary from drug to drug. IV infusion maintains a constant serum drug concentration, which certainly does not occur following oral ingestion. How important are these differences? And how does one know the threshold of clinical importance – in this case in cardiac output (CO)? Clinically, is there a linear effect of insulin dosing and CO improvement?

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Premise number five – side effects of HDI are the same regardless of the poisoning drug. The number of hypoglycemic episodes occurring in each arm of the study is recorded. The issue of hypoglycemia with HDI administration in poisoning other than CCB should not be underestimated. CCB causes insulin resistance. Hyperglycemia is a marker of the degree of calcium channel block and is prognostic in these overdoses.[7] There is little concern about hypoglycemia when administering HDI to these patients. But what about hypoglycemia caused by drugs that do not cause insulin resistance? This is a key issue. If a patient is paralyzed and ventilated, hypoglycemia may go unnoticed. How often should one check a bedside glucose? In a hemodynamically unstable patient, hypoglycemia has the potential to increase mortality. In overdoses in which there is not insulin resistance, the benefit of HDI versus the potential to increase mortality (or neurologic deficits) caused by unrecognized hypoglycemia has not been evaluated.

There are many clinical issues that are difficult to address with animal studies. Take age, for instance; Young patients do so much better than older patients following an overdose. Their healthy adrenals respond to hypoperfusion with an outpouring of catecholamines (no wonder exogenous catechols do not work so well), and the young have sensitive receptors. A verapamil overdose in a 14-year-old patient is an entirely different clinical entity than an ingestion of exactly the same amount of verapamil in a 55-year-old patient.

It is so important that we have animal experiments to increase our knowledge about these poisonings. But we have to realize the limitations of these experiments and use the data from them to increase our understanding. We cannot use the data to make far-reaching conclusions until we have more clinical evidence. Read the cases of the various treatments of digoxin overdose prior to the release of antibody therapy. It will make you be very wary of evidence from case series and animal studies, even if everyone is doing it.

HDI is part of every toxicologist's armamentarium. And the authors are to be congratulated on an animal study that has added information to our knowledge base. As noted by the authors, in clinical medicine, HDI does not always work. Why? Is it because cardiogenic shock caused by one of the ingested poisons does not respond to HDI and it has nothing to do with dose response; the HDI dose is wrong; the patient ingested a fatal dose of drug, or is it a reason that we have yet to understand? It is the combination of further experiments and clinical evidence that holds the answer and allows us to replace premises with evidence.

Declaration of interest

The author reports no declarations of interest. The author alone is responsible for the content and writing of the paper.

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