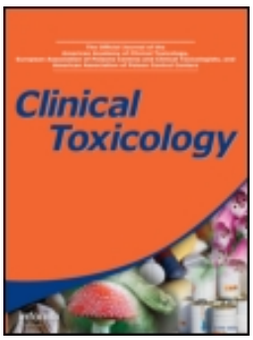

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REVIEW

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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