

## Review

# Bench-to-bedside review: Hyperinsulinaemia/euglycaemia therapy in the management of overdose of calcium-channel blockers

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## Abstract

Hyperinsulinaemia/euglycaemia therapy (HIET) consists of the infusion of high-dose regular insulin (usually 0.5 to 1 IU/kg per hour) combined with glucose to maintain euglycaemia. HIET has been proposed as an adjunctive approach in the management of overdose of calcium-channel blockers (CCBs). Indeed, experimental data and clinical experience, although limited, suggest that it could be superior to conventional pharmacological treatments including calcium salts, adrenaline (epinephrine) or glucagon. This paper reviews the pathophysiological principles underlying HIET. Insulin administration seems to allow the switch of the cell metabolism from fatty acids to carbohydrates that is required in stress conditions, especially in the myocardium and vascular smooth muscle, resulting in an improvement in cardiac contractility and restored peripheral resistances. Studies in experimental verapamil poisoning in dogs have shown that HIET significantly improves metabolism, haemodynamics and survival in comparison with conventional therapies. Clinical experience currently consists only of a few isolated cases or short series in which the administration of HIET substantially improved cardiovascular conditions in life-threatening CCB poisonings, allowing the progressive discontinuation of vasoactive agents. While we await further well-designed clinical trials, some rational recommendations are made about the use of HIET in severe CBB overdose. Although the mechanism of action is less well understood in this condition, some experimental data suggesting a potential benefit of HIET in β-adrenergic blocker toxicity are discussed; clinical data are currently lacking.

Pathophysiological bases, as well as experimental data and clinical observations, suggest that HIET might be useful in cases of severe overdose of calcium-channel blockers (CCBs). Conventional measures that consist of intravenous fluids, calcium salts, dopamine, dobutamine, noradrenaline (norepinephrine), phosphodiesterase inhibitors or glucagon often fail to improve the haemodynamic condition of the patient, so that more invasive procedures such as intra-aortic balloon counterpulsation or extracorporeal circulatory support may be needed [1-3]. Until now, HIET has mainly been used as a rescue therapy and as an alternative to invasive procedures. However, HIET seems to ensure a more favourable energetic balance in the myocardium than other conventional treatment. It has few side effects provided that glycaemia is frequently checked, and it uses only widely available and relatively inexpensive medications. Because HIET failures have mainly been reported when it was introduced late as a rescue measure, it seems rational to propose its earlier use in patients with hemodynamic compromise associated with CCB overdose.

Some promising experimental data also suggest potential for HIET in overdose of β-blockers but clinical experience is lacking as yet.

## Introduction

Hyperinsulinaemia/euglycaemia therapy (HIET) consists of the infusion of high-dose regular insulin (most commonly 0.5 to 1 IU/kg per hour). Of course, frequent blood glucose monitoring by bedside capillary testing is needed to minimise the likelihood of hypoglycaemia. Glucose infusion is adapted to maintain euglycaemia (6 to 8 mmol/l, or 110 to 150 mg/dl). Adults may require 15 to 30 g of glucose per hour (as glucose 10% or more), associated with potassium supplements to maintain normokalaemia.

## Pathophysiological bases

Severe CCB toxicity consists mainly of hypotension or shock due to cardiac dysfunction (bradycardia, conduction delay and negative inotropy) and peripheral vasodilation [1,2]. Poor tissue perfusion results in metabolic lactic acidosis. The cardiovascular disorders related to CCB toxicity are thought to be a direct consequence of an excessive blockade of the L-type calcium channel in myocardial and vascular smooth muscle membranes: by preventing calcium influx into cells, CCBs decrease cardiac inotropy, dromotropy and

CCB = calcium-channel blocker; EES = elastance at end systole; HIET = hyperinsulinaemia/euglycaemia therapy; i.v. = intravenous; LVEDP = left ventricular end diastolic pressure.

chronotropy, as well as vascular tone. Conventional treatments of CCB overdose consist of attempts to increase transmembrane calcium flow either by increasing extracellular calcium concentration (calcium salts) or by increasing intracellular cAMP concentration, which can be achieved by adenylate cyclase stimulation (with adrenaline or glucagon) or phosphodiesterase inhibition (with amrinone or milrinone) [3]. None of these antidotes has been shown to reverse CCB cardiovascular toxicity reliably: no controlled clinical trial has been conducted and treatment successes or failures have been reported in almost equal measure [4-9].

Hyperglycaemia is another common feature in CCB poisoning [10-13] and can even result from therapeutic doses [14]. Indeed, blockade of L-type calcium channels impairs insulin release by the pancreatic  $\beta$ -islet cells [15] and impairs glucose uptake by tissues by altering sensitivity to insulin [16,17]. Hypoinsulinaemia and insulin resistance could be cornerstones in the pathophysiology of CCB cardiovascular toxicity, beside the direct effect of calcium channel blockade. Indeed, under normal aerobic conditions, myocardial cells oxidise free fatty acids (non-esterified fatty acids) as the main energy substrate. Conversely, in poor haemodynamic or aerobic conditions (such as those induced by CCB toxicity), myocardial cells switch to glucose utilisation for the main fuel. However, the decreased perfusion impairs glucose delivery to tissues. Furthermore, hypoinsulinaemia and insulin resistance obviate the uptake of glucose, especially by myocardial and vascular muscle cells, thereby preventing its adequate use as main energy substrate. The lack of fuel and energy stores further compromises the cardiovascular condition already impaired by the blockade of calcium channels. These mechanisms give rise to the hypothesis that high-dose insulin therapy could be beneficial in the management of CCB overdose by overcoming hypoinsulinaemia and insulin resistance and thereby breaking the vicious circle of haemodynamic deterioration leading to shock and death. Although both animal experience and clinical observations seem to confirm that HIET is able to improve inotropy and peripheral vascular resistance, to reverse acidosis and to increase survival, the exact mechanism underlying these actions still remains controversial. Nevertheless, because the beneficial haemodynamic effects of insulin are probably related to changes in cellular metabolism, they are unsurprisingly delayed, frequently occurring within 30 to 45 minutes of starting HIET.

## Supporting experimental data

A model using verapamil toxicity in dogs has been used because it produces comparatively greater haemodynamic depression *in vivo* than other CCBs.

Kline and colleagues [18] demonstrated that HIET improved heart function in anaesthetised dogs in which severe CCB toxicity (hypotension or complete atrioventricular dissociation) was induced by the intravenous (i.v.) administration of

verapamil. In this model, various treatment protocols were compared: (1) normal saline (2.0 ml/min); (2) adrenaline (starting at 1.0  $\mu$ g/kg per minute, titrated to maintain left ventricular pressure at basal values); (3) HIET (4.0 IU/min insulin with 20% glucose, arterial glucose clamped); or (4) glucagon (0.2 to 0.25 mg/kg bolus followed by an infusion at 150  $\mu$ g/kg per minute). Another study added a fifth treatment group with calcium chloride (20 mg/kg bolus, then 0.6 mg/kg per hour) [19]. Treatments were continued until death or 240 minutes. Surviving animals then received a 3.0 mg/kg additional bolus of verapamil. All controls died within 85 minutes. Four out of six survived after adrenaline, three out of six after glucagon and calcium chloride, and six out of six in the HIET group. All treatments tended to improve haemodynamic status. Although HIET did not significantly increase mean blood pressure and heart rate, it significantly improved maximum elastance at end systole (EES), left ventricular end diastolic pressure (LVEDP) and coronary artery blood flow compared with other treatments. Only the six HIET-treated animals survived the additional bolus of verapamil.

The same group of authors subsequently performed several studies to elucidate the underlying mechanisms of these HIET-related beneficial effects. They demonstrated that during verapamil toxicity, the myocardial glucose uptake doubled despite a decrease in cardiac work, and the myocardial respiratory quotient increased [19]. Net myocardial lactate uptake also increased significantly, excluding myocardial ischaemia. However, plasma insulin concentration did not increase despite hyperglycaemia. HIET produced a larger improvement in myocardial contractility and ratio of myocardial oxygen delivery to work than did calcium chloride, adrenaline or glucagon, and these effects, which were correlated with the myocardial glucose uptake, probably explain the improved survival even when an additional bolus of verapamil was administered [19].

For better simulation of an oral overdose, another canine model of verapamil toxicity was developed in which cardiogenic shock was induced in awake dogs by graded intraportal infusion of verapamil [20]. Animals were treated with one of the following: (1) saline (3.0 ml/kg per minute); (2) adrenaline (5  $\mu$ g/kg per minute); (3) glucagon (10  $\mu$ g/kg per minute); or (4) HIET (1 IU/min with glucose to clamp arterial glycaemia to  $\pm 10\%$  of basal concentrations). One dog died early with glucagon treatment before the first death in the saline-treated group. Once again, insulin provided superior improvement in systolic and diastolic heart function than other treatments. The myocardial efficiency (ratio of left ventricular minute work to myocardial oxygen consumption) also increased. Conversely, both adrenaline and glucagon decreased mechanical efficiency in comparison with saline controls. In contrast with adrenaline and glucagon, HIET did not improve cardiac function by increasing catecholamine concentration but rather through direct effects on myocardial metabolism. HIET increased myocardial lactate consumption

but not glucose uptake, whereas both adrenaline and glucagon increased myocardial fatty acid consumption without increasing lactate uptake.

In the same model, Kline and colleagues [16] have further studied the effect of insulin treatment on myocardial use of lipid and carbohydrate. HIET alone induced sevenfold and threefold increases in myocardial glucose and lactate extractions, respectively. However, no change in myocardial blood flow or EES was detected. Verapamil toxicity was shown to produce a decrease in myocardial extraction of free fatty acids without a change in arterial concentration of free fatty acids, whereas myocardial glucose extraction was doubled with an increase in arterial glucose. No change in myocardial blood flow was observed, but EES decreased. In comparison with saline controls, HIET improved the EES and survival of verapamil-intoxicated dogs, but neither myocardial glucose nor lactate extraction increased significantly.

These studies in dogs show that verapamil toxicity produces a decrease in myocardial contractile efficiency by a combination of metabolic synergistic effects and calcium channel blockade. Although the availability of free fatty acids is maintained, myocardial extraction is decreased, making the heart dependent on carbohydrates as an energy supply. In contrast, verapamil toxicity results in both blockade of insulin release by pancreatic cells and systemic insulin resistance [17] that impedes insulin-stimulated myocardial glucose uptake and renders the tissues' carbohydrate uptake dependent on glucose concentration.

In verapamil toxicity, HIET increases myocardial contractility, but this effect does not seem to be related to an increase in glucose transport. Whether these effects can be extrapolated to the toxicity of all other CCBs, including dihydropyridine and benzothiazepine agents, is unknown.

## **Supporting clinical data**

### **Adult clinical experience**

In 1999, Yuan and colleagues [21] reported the case of a 31-year-old male who developed sustained hypotension, bradycardia and complete heart block after ingesting an overdose of extended-release verapamil. The ejection fraction was estimated at 10% on the basis of an echocardiogram. Because the condition failed to improve with respiratory support, activated charcoal, i.v. fluids, calcium chloride, glucagon and atropine, HIET was started (10 IU of insulin bolus plus 25 g of glucose, followed by a continuous insulin infusion of up to 4 to 10 IU/h, along with 8 to 15 g/h glucose). Blood pressure improved within 15 minutes, the patient converted to normal sinus rhythm within an hour and ejection fraction was measured at 50% 3 hours later. However, dopamine had to be infused because of persistent oliguria. Dopamine and insulin infusions were discontinued at 18 and 22 hours, respectively. The same paper documented the clinical courses of two other adult patients with verapamil

overdose and one patient with amlodipine–atenolol overdose who developed hypodynamic circulatory shock unresponsive to conventional treatment. HIET also produced an improvement in hemodynamic status and all patients survived.

Two other cases of HIET use were reported by Boyer and Shannon [22]. A 48-year-old man was admitted with haemodynamic instability after ingesting an unknown amount of extended-release diltiazem; he failed to respond to calcium, i.v. fluids, dopamine and dobutamine. An insulin infusion (0.5 IU/kg per hour plus 10 g/h glucose) markedly improved the blood pressure and allowed the discontinuation of vasoactive agents within 30 minutes. The insulin infusion was maintained for 5 hours. The other patient was a 34-year-old woman who developed shock 1 hour after ingesting amlodipine tablets. Conventional therapies failed to improve haemodynamic condition so that insulin infusion at the same rate was started. Although the patient was non-diabetic, her initial capillary glucose was 325 mg/dL: it was cautiously measured every 15 to 30 minutes but she never needed supplemental glucose. Haemodynamic status improved within 30 minutes. Dopamine, noradrenaline and glucagon were stopped 45 minutes after starting HIET, which was discontinued 6 hours later.

Similar cases have been reported by Rasmussen and colleagues [23], Marques and colleagues [24], Ortiz-Munoz and colleagues [25] and Place and colleagues [26], including elderly patients with previous cardiovascular disease, and have been collected with more details elsewhere [27,28].

The case reported by Min and Deshpande [29] is especially interesting because haemodynamic data were obtained from a right heart catheter before and during HIET in a 59-year-old female after ingestion of slow release diltiazem together with sedatives. HIET (0.5 IU/kg per hour and 50% glucose infusion) was started because the patient remained dependent on the infusion of vasoactive drugs after 15 hours of treatment (i.v. fluids, adrenaline, noradrenaline and vasopressin). An increase in mean arterial pressure was observed within 30 minutes of starting HIET, and all vasoactive agents were discontinued within 60 minutes. The predominant haemodynamic effect of HIET surprisingly seemed to be an increase in peripheral vascular resistance rather than an inotropic effect.

Whatever the main haemodynamic effect involved, these observations support the value of HIET in patients with CCB intoxication and circulatory compromise and suggest that this therapy should probably be considered earlier in the management of the condition rather than being used as a rescue option. Indeed, some cases in which HIET was introduced late in the treatment and failed to improve the patient's condition have also been reported [30-32]. The effectiveness of HIET is often limited to an improvement of hypotension and acidosis that is observed within 30 to

45 minutes of starting insulin administration. Direct actions on bradycardia and cardiac conduction are variable and are hardly differentiated from effects due to the improvement of haemodynamic status.

#### **Paediatric clinical experience**

Yuan's series [21] included the case of a 14-year-old girl who developed hypotension, bradycardia and complete heart block after ingesting SR verapamil. Initial treatment with activated charcoal, calcium gluconate and atropine provided only a transient response. HIET (insulin 10 IU bolus, followed by a continuous infusion of 12 to 20 IU/h with glucose 6 g/h) was associated with an increase in blood pressure, so that no other vasoactive medication was required. Insulin and glucose were discontinued at 9 and 12 hours, respectively. Meyer and colleagues [33] also reported the history of a 13-year-old girl intentionally poisoned with SR verapamil, who developed hypotension and bradycardia. Calcium chloride, glucagon, adrenaline and noradrenaline provided only a transient improvement. HIET (insulin 0.1 IU/kg plus glucose 0.5 g/kg as a bolus, followed by continuous infusion) was started and was accompanied by marked haemodynamic improvement, so that vasoactive drugs were discontinued within 90 minutes. HIET was maintained for 26 hours.

Morris-Kukoski and colleagues [34] reported the case of a 5-month-old female infant who was inadvertently given 20 mg of nifedipine and rapidly developed hypotension. Despite ventilatory assistance, calcium chloride, glucagon, dopamine, adrenaline, phenylephrine and milrinone, severe hypotension persisted and profound acidosis developed. HIET (1 IU/kg per hour) improved the patient's blood pressure, so that glucagon and phenylephrine were discontinued 30 minutes and 2 hours later, respectively. However, adrenaline, dopamine and milrinone had to be maintained for 72 to 90 hours. Insulin administration was discontinued after 96 hours. Progress was complicated by anuric renal failure that resolved within 30 days.

#### **Adverse effects**

Hypoglycaemia and hypokalaemia are the main adverse effects that can be expected during insulin infusion.

#### **Hypoglycaemia**

Some patients with hyperglycaemia related to CCB toxicity did not require glucose supplementation during insulin infusion [22]. Administration of glucose should therefore be individually titrated according to frequent determinations of glycaemia, rather than by following standard protocols. Special attention is required in patients with altered mental status, due either to poor haemodynamic condition or to co-ingestion of sedative drugs, in whom clinical signs of hypoglycaemia may be masked.

#### **Hypokalaemia**

Most patients do not develop significant hypokalaemia. Actually, acidosis due to haemodynamic compromise may be

accompanied by mild hyperkalaemia due to an outward shift of potassium, and HIET will only shift the potassium back into cells. In Yuan's series [21], it was observed in only three out of five cases, including one with hydrochlorothiazide co-ingestion. It was not accompanied by any complication. Hypokalaemia is thought to be related to intracellular transfer of potassium during insulin infusion. Supplementation is usually not required in asymptomatic patients because potassium stores are normal. It has even been suggested that mild hypokalaemia may offer benefit by promoting cellular calcium entry and increasing the inotropic effect of insulin [21,24].

#### **Recommendations for the use of HIET in CCB poisoning**

Although there is wide variation in insulin dosing in the cases reporting the use of HIET in CCB overdose and in the duration of treatment, rational recommendations could currently consist of the administration of 1.0 IU/kg i.v. as a bolus, followed by 0.5 IU/kg per hour i.v. Glycaemia must be checked at least once every 30 minutes and hypertonic glucose must be infused to maintain blood glucose in the upper normal range. Up to 20 to 30 g/h may be needed in adults. Supplemental potassium is required only to prevent severe hypokalaemia. The duration of HIET should be guided by the clinical response, especially haemodynamic parameters: the goal should be haemodynamic stability after the withdrawal of vasoactive agents. Such rational recommendations have already been formulated by Boyer and colleagues [35] but unfortunately have never been validated prospectively in clinical trials.

HIET should not replace other therapeutic approaches but should be considered as an adjunct. However, it must be kept in mind that delaying its use in severe CCB poisoning is likely to reduce its clinical benefit markedly.

#### **Could HIET also be valuable in β-blocker overdose?**

Some experimental data from animal studies suggest that HIET could be of benefit in β-blocker toxicity and that this possibility certainly deserves further evaluation and comparison with commonly recommended therapies.

Reikeras and colleagues have studied the haemodynamic [36] and metabolic [37] effects of small and high doses of insulin during β-receptor blockade induced by 0.5 mg/kg propranolol in dogs. Insulin (0.5 IU/kg i.v. bolus followed by a continuous infusion of 0.5 IU/kg per hour and a 300 IU high-dose bolus 30 minutes later) was administered in association with glucose and potassium to maintain physiological blood concentrations. Propranolol depressed cardiac performance (increased LVEDP, decreased maximum rate of left ventricular pressure rise, left ventricular  $dP/dt_{max}$ , stroke volume and cardiac output). Only 5 minutes after low-dose insulin, performance parameters significantly improved. The high-dose insulin further improved heart function. Peripheral

resistance significantly decreased, probably by the resolution of compensatory vasoconstriction when cardiac output improved. Inotropic effects of insulin seem to be dose dependent and unrelated to adrenergic mechanisms.

In this canine model,  $\beta$ -receptor blockade was accompanied by a significant decrease in myocardial blood flow and oxygen consumption. Arterial concentrations and myocardial uptake of free fatty acids were reduced, whereas arterial concentrations and myocardial uptake of glucose and lactate remained unchanged. Improvement of heart performance induced by low-dose insulin was not accompanied by an increase in myocardial oxygen consumption. Myocardial uptake of glucose increased significantly, whereas uptake of lactate and free fatty acids was unchanged. Myocardial blood flow and oxygen consumption also remained unaltered after the high dose of insulin despite the considerable improvement in heart performance, as well as arterial concentrations and myocardial uptake of glucose, lactate and free fatty acids. The effect of insulin on heart performance thus seems to be independent of effects on substrate metabolism.

In a canine model of heart supported by cardiopulmonary bypass, high-dose insulin (aortic root bolus of 1,000 IU insulin, with a glucose clamp maintained at physiological levels) reversed the negative inotropic effect of propranolol (0.2 mg/kg) to 80% of control function and normalised heart rate without augmenting oxygen utilisation [38].

In another model [39], dogs received intravenous propranolol (0.25 mg/kg per minute) until decreased contractility and hypotension were observed. Half an hour later, animals were treated with one of the following: (1) saline (control), (2) HIET (4 IU/min insulin with glucose clamped at  $\pm 10\%$  of the baseline values by the infusion of 50% glucose), (3) glucagon (50  $\mu$ g/kg bolus and 150  $\mu$ g/kg per hour infusion) or (4) adrenaline (1  $\mu$ g/kg per minute). They were monitored until death or for 240 minutes. All animals died in the control group, whereas six out of six HIET-treated, four out of six glucagon-treated and one out of six adrenaline-treated animals survived. HIET also provided a sustained increase in blood pressure and cardiac performance (decreased LVEDP, increased stroke volume and cardiac output) compared with glucagon or adrenaline. However, HIET had no effect on heart rate and conduction. Vasodilation could result from improved cardiac function and decreased compensatory vasoconstriction. HIET-treated animals were also characterised by increased myocardial glucose uptake and decreased serum potassium [39].

HIET could thus offer a potential benefit in  $\beta$ -blocker overdose as well as in CBB toxicity. To our knowledge, no clinical experience of pure  $\beta$ -blocker overdose has been reported, but several case reports involve mixed intoxications involving both CCBs and  $\beta$ -blockers [21,25].

## Conclusion

There is growing experimental and clinical evidence of the value and the safety of HIET in the management of CCB poisoning. Although the mechanism of this beneficial action is not fully explained, HIET should be considered in patients with CBB-induced cardiovascular compromise. Although not effective in all cases, HIET often improves arterial blood pressure, myocardial contractility and metabolic acidosis, while failing to correct bradycardia or conduction defects, including heart block and intraventricular conduction delay.

Of course, additional clinical research and prospective clinical studies are needed to confirm the safety and efficacy of HIET and to support more formal guidelines and therapeutic regimens, but some rational recommendations can be made on the basis of the available data. Although HIET is still often presented as a rescue adjunct in patients who fail to respond to conventional treatments including calcium salts, glucagon or catecholamine infusion, the delayed onset of its action (30 to 45 minutes) required for metabolic actions probably justifies an earlier introduction in treatment protocols in combination with supportive measures. More invasive procedures to assist circulation could thereby be avoided. Careful monitoring of blood glucose and serum potassium concentrations is required to prevent adverse effects.

Some animal data suggest that HIET could be also beneficial in  $\beta$ -blocker poisoning, but more data are required before this therapy can be evaluated in this indication.

## Competing interests

The authors declare that they have no competing interests.

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