

## **Hyperinsulinemic Euglycemia Therapy for Verapamil Poisoning: A Review**

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# H YPERINSULINEMIC EUGLYCEMIA THERAPY FOR VERAPAMIL POISONING: A REVIEW

By Nirav P. Patel, MD, Meredith E. Pugh, MD, Steven Goldberg, MD, and Glenn Eiger, MD

**Abstract** Treatment of patients with verapamil overdose remains challenging. Traditional decontamination and supportive measures with intravenous calcium and vasopressors are the mainstays in initial care. Recently, the successful use of rescue hyperinsulinemic euglycemia therapy has been described in multiple cases. Treatment resulted in improved hemodynamic parameters and increased metabolic efficiency in patients with a low-output, myocardial shock state. Information on clinical use of hyperinsulinemic euglycemia therapy in humans is limited to case reports and small case series; no controlled clinical trials have been done. Hyperinsulinemic euglycemia therapy should be considered for patients with calcium channel blocker overdose who do not respond to initial supportive therapy. (*American Journal of Critical Care*. 2007;16:498-503)

**T**he calcium channel blocker (CCB) verapamil has been implicated in a number of intentional and unintentional overdoses. Like other CCBs, verapamil inhibits the influx of calcium into myocardial and vascular tissues via L-type channels. By antagonizing L-type calcium channels in the myocardium, verapamil has negative inotropic and chronotropic effects, and overdoses of this drug can lead to decreased cardiac output, hypotension, and shock.<sup>1</sup>

Verapamil's effect on vascular smooth muscle can potentiate hypotension with decreased systemic vascular resistance and shock.<sup>1</sup> Hyperinsulinemic euglycemia (HIE) therapy is a relatively new method in which insulin infusions, often with concomitant glucose administration to prevent hypoglycemia, are used to treat life-threatening CCB overdose. It is well known that calcium plays an intricate and crucial role in regulation of cellular movement and transport, electrical activation of excitable cells, and various enzymatic reactions throughout the body.<sup>2</sup> In myocytes, calcium influx via calcium channels promotes intracellular release of calcium by the sarcoplasmic reticulum, allowing a coupling with troponin and thereby facilitating the contraction of myocardial cells.

Cardiovascular consequences of calcium channel blockade include a reduction of electromechanical contraction in atrial and ventricular myocytes, slowed pacemaker activity in the sinoatrial and atrioventricular nodes, decreased atrioventricular node conduction, and vasodilation of vascular smooth muscle.<sup>3</sup> Antagonism of calcium channels in vascular smooth muscle results in relaxation and dilatation. In addition, CCBs inhibit calcium influx into pancreatic beta cells, leading to hyperglycemia and a relative hypoinsulinemic state that impairs normal metabolism and use of carbohydrates by cardiac myocytes.<sup>4</sup>

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Overdose with CCBs results in an exaggeration of these physiological effects that can be life threatening; profound bradycardia, hypotension, metabolic acidosis, and a shock state can occur.

In this article, we review current and emerging treatments available for CCB poisoning. For a case report<sup>5</sup> of a patient with CCB poisoning who had HIE therapy, see pages 520, 518-519.

Certain CCBs are selective for peripheral rather than cardiac L-type channels; that is, dihydropyridines act predominantly on vascular smooth muscle and have few cardiac effects. This selectivity is decreased in CCB overdose.<sup>1</sup> Therefore, the clinical features of CCB overdose and the subsequent treatment strategy are similar for intoxications caused by various CCBs. Goals of management in verapamil overdose include removing the drug, improving cardiac contractility and increasing atrioventricular nodal conduction, increasing vascular tone, maintaining tissue oxygenation, and providing metabolic support.<sup>6</sup>

#### Decontamination

As with other cases of unstable hemodynamic status due to ingestions, initial therapy in CCB overdose is assessment of the airway, breathing, and circulation. The first intervention for patients with hypotension is appropriate volume replacement. Decontamination with activated charcoal or whole-bowel irrigation should be considered for patients who receive treatment in the appropriate setting and time frame. Activated charcoal can be considered for patients with a protected airway who seek treatment within 1 hour of ingestion,<sup>7</sup> although use of activated charcoal as late as 2 hours after ingestion can prevent absorption of sustained-release verapamil.<sup>8</sup> Whole-bowel irrigation with polyethylene glycol along with activated charcoal was used effectively to treat overdose with sustained-release verapamil in a patient who sought treatment several hours after ingestion.<sup>9</sup> In another case,<sup>9</sup> whole-bowel irrigation with polyethylene glycol was not effective

Overdoses of verapamil can lead to decreased cardiac output, hypotension, and shock.

Decontamination with activated charcoal or whole-bowel irrigation should be considered for patients treated in an appropriate time frame.

in a patient who had treatment approximately 24 hours after ingestion of sustained-release verapamil. No controlled trials have been done that suggest that either activated charcoal or whole-bowel irrigation improves the outcome in CCB poisonings, but these treatments should be considered when indicated as detailed in the position papers of the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists.<sup>7,10</sup>

Accurate determination of the time since ingestion is often limited by the unstable condition of patients when treatment is sought, and in turn this situation often limits the usefulness of decontamination therapy. In addition, the constipating effect of verapamil can cause difficulty with these treatments.<sup>11</sup>

CCBs are highly protein bound, extensively distributed, and rapidly metabolized by the liver. Norverapamil, a metabolite of verapamil, has 20% of the pharmacological activity of the parent agent.<sup>1</sup> The half-life of verapamil can be prolonged in patients with overdose because of the saturation of hepatic enzymes.<sup>12</sup> Treatments such as hemofiltration and dialysis are of limited value in verapamil intoxication because of the drug's highly protein

bound state.<sup>13</sup> Plasmapheresis can be used to stabilize a patient's condition and allow time for hepatic detoxification.<sup>14</sup> In 2 patients,<sup>15,16</sup> extracorporeal bypass resulted in improved blood levels of verapamil, although 1 of the patients died. Certainly this treatment can provide a bridging interval of adequate tissue and brain perfusion until drug levels are reduced.<sup>15,16</sup>

### Calcium

Calcium would seem to be a logical choice for treatment of CCB poisoning, with the aim of overcoming competitive blockade of calcium

channels in the cardiac conducting system. The efficacy of calcium in improving conduction, contractility, and hypotension has varied.<sup>17</sup> Treatment with calcium was successful in some patients<sup>18-20</sup> with CCB overdose but had transient or no effects in others.<sup>21</sup> The optimum dosage of intravenous calcium remains unclear.<sup>22</sup> Buckley et al<sup>23</sup> recommend boluses of 1 g of calcium chloride every 15 to 20 minutes, for a total of 4 doses, or 1 g every 2 to 3 minutes until an effect is achieved. Lam et al<sup>18</sup> had good effects with continuous infusions of calcium. More recently, in experiments<sup>24,25</sup> in dogs, treatment of verapamil poisoning with calcium plus digoxin had a beneficial dose-dependent effect on systolic

blood pressure and mean ventricular pressure, and treatment with calcium alone reversed the negative inotropic and hypotensive effects of low-dose CCB poisoning but was ineffective against high-dose poisoning. Thus, despite conflicting reports of its efficacy and no standardization of dosage, intravenous calcium is a reasonable early therapy in CCB overdose.

### Vasoactive Agents and Supportive Care

Various sympathomimetics, including dopamine, dobutamine, norepinephrine, and amrinone, have been used to counter the hypotensive effects of CCB overdose; the responses to all of these were mixed.<sup>17</sup> It remains unclear which agent or combination of agents is better for the treatment of CCB poisoning.<sup>17,26</sup> Atropine sulfate<sup>27</sup> and glucagon<sup>26,28,29</sup> have been used commonly, and although therapeutic effects have been reported, the clinical response has been variable. Recently, terlipressin, a long-acting analog of vasopressin, was used to treat a patient with massive felodipine overdose refractory to other catecholamine drugs.<sup>30</sup>

In experiments in swine, sodium bicarbonate reversed the low cardiac output associated with severe verapamil overdose.<sup>31</sup> The rationale underlying use of sodium bicarbonate is 2-fold: first, an increase in pH in the calcium channel microenvironment should reverse impaired contractility, and second, the reversal of sodium channel blockade with hypertonic sodium bicarbonate might allow more rapid recovery.<sup>31</sup>

Pacemaker use, indicated for marked bradycardia or high-grade conduction blocks, can result in positive responses in patients with CCB overdose.<sup>32,33</sup> The increase in heart rate alone can increase the cardiac output. In our case<sup>5</sup> and in other reports, transvenous capture is not always successful for unclear reasons. Furthermore, capture does not always improve hemodynamic status.<sup>34,35</sup>

Research<sup>36,37</sup> in the 1980s indicated that 4-aminopyridine, a potassium channel antagonist, could combat the toxic effects of verapamil by enhancing calcium influx across cell membranes. This antagonist has been used only once in a human; in that case, it improved blood pressure and cardiac conduction.<sup>38</sup> Bay K 8644, a dihydropyridine and a calcium channel promoter, has been effective in animals<sup>39</sup> but requires further evaluation. Recently, on the basis of the lipophilic properties of verapamil, findings in a rat model of verapamil poisoning suggest that therapy with the lipid emulsion Intralipid may provide a survival benefit.<sup>40</sup> Although preliminary data appear promising, the mechanism of action, safety, and efficacy of this agent in humans have not been elucidated.

## Hyperinsulinemic Euglycemia Therapy

The use of insulin to treat CCB intoxication is an exciting development in the treatment of severe CCB poisoning. The treatments described previously focus mainly on counteracting the effects of verapamil on L-type calcium channels within the myocardium and vasculature. Additional important effects include alteration in myocardial cellular utilization and metabolism of carbohydrates. CCB intoxication and blockade of L-type calcium channels in the pancreatic islet cells may have manifestations similar to those of diabetic ketoacidosis, with hyperglycemia and a shift to carbohydrate catabolism in cardiac myocytes during shock.<sup>4,41,42</sup>

Under normal conditions, myocardial cells primarily derive energy aerobically from the oxidation of free fatty acids; however, in shock, the heart becomes dependent on carbohydrate metabolism.<sup>42</sup> In CCB-induced shock, the heart cannot use carbohydrates effectively because of hypoinsulinemia (inhibition of calcium-mediated insulin secretion) and an acquired insulin resistance.<sup>43</sup> Furthermore, depressed cardiac output reduces effective delivery of insulin and glucose. This ineffective delivery appears to be instrumental in the cycle of hypodynamic shock.<sup>44</sup> Thus, the negative inotropy that occurs in verapamil overdose may not be attributable solely to calcium channel antagonism; it may also be due to derangements of carbohydrate use and metabolism by the myocardium during shock.<sup>45</sup>

Insulin has several proposed roles in improving the manifestations of CCB overdose. Insulin increases plasma levels of ionized calcium, improves the hyperglycemic acidotic state, improves myocardial utilization of carbohydrates, and exerts its own independent inotropic effect.<sup>46-48</sup> The inotropic effect is heightened in stressed myocardium, as indicated by studies in isolated rat hearts,<sup>49</sup> in piglet hearts subjected to  $\beta$ -blocker poisoning,<sup>50</sup> and in humans after coronary artery bypass grafting<sup>51</sup> and after myocardial infarction.<sup>52</sup>

## HIE Therapy in Studies in Animals

Data from studies in animals have indicated the positive effects that HIE may have in clinical CCB poisoning. In dogs with verapamil poisoning, treatment with insulin improved hemodynamic measurements.<sup>42</sup> In another study<sup>53</sup> in dogs with verapamil poisoning, insulin therapy alone, as compared with therapy with epinephrine and glucagon, was associated with a survival benefit related to improved myocardial contractility and enhanced tissue perfusion. In further research,<sup>42,54</sup> improvements were not limited to

myocardial performance but also extended to indices of carbohydrate oxidation. Standard treatments such as administration of epinephrine, glucagon, and calcium enhanced oxidation of free fatty acids and caused a transient increase in contractility at the expense of increased myocardial consumption. In contrast, administration of insulin improved myocardial uptake of carbohydrates and was correlated with improved function. These animal models suggest a scientific model for determining the benefit of HIE therapy in humans.

## HIE Therapy in Humans

In 13 reported cases<sup>55-62</sup> in which HIE therapy was used in severe CCB overdose in humans, all of the patients had hypotension, and many had conduction disturbances, acidosis, and coma. In 12 of the 13 cases, HIE therapy improved hemodynamic measurements.<sup>58</sup> In some cases, improvements in blood pressure and discontinuation of or weaning from vasopressor therapy occurred within 15 minutes<sup>59</sup> to 5 hours<sup>60</sup> after initiation of insulin/glucose therapy.

In contrast to the increase in blood pressure associated with HIE therapy in these patients, in previous experiments in vivo in animals, HIE therapy had a vasodilatory effect. In dogs, insulin had positive inotropic effects without marked increases in mean arterial pressure.<sup>53,54</sup> Of note, the studies in dogs differ from the case reports in an important way: in all of the human cases, insulin was used as adjunctive therapy to other measures (eg, decontamination attempts; administration of vasoactive agents, glucagon, or atropine). Possibly, the improvements in blood pressure with HIE therapy in humans were due to its additive effects to vasoactive therapies.

HIE therapy consistently improved mean arterial pressure in all but one of the reported cases, but its effects on conduction abnormalities were more variable. Although some patients had conversion to normal sinus rhythm after initiation of insulin therapy, as in our case,<sup>5</sup> other patients<sup>55,58,59</sup> had persistence of bradycardia or conduction delays.

In 1 case,<sup>58</sup> that of a 58-year-old man with hypotension, hyperglycemia, metabolic acidosis, a left bundle-branch block pattern on electrocardiograms, and hypotension unresponsive to various inotropic agents, HIE therapy was not effective. After several hours, verapamil poisoning was suspected, and after an unknown number of hours into the hospitalization, therapy with various inotropic agents, calcium chloride, bicarbonate, glucagon, and an unspecified dosage of

In 12 of 13 reported cases, HIE therapy improved hemodynamic measurements.

Glucose and electrolytes should be closely and regularly monitored during HIE therapy.

insulin/dextrose was started. Despite these interventions, the patient died. The delay of initiation of HIE therapy in this case<sup>58</sup> may account for the lack of clinically significant effect of insulin therapy.

The dose and duration of HIE therapy used in the 13 cases varied. A single bolus dose of insulin was used in 2 cases, but the size of the bolus varied widely: a 20-U bolus in 1 case<sup>59</sup> and a 1000-U bolus in the other.<sup>60</sup> In the cases reported by Yuan et al,<sup>55</sup> 5 patients received bolus insulin doses of 10 to 20 U and then received insulin infusions. In 11 of the 13 cases reported,<sup>55,57,61</sup> the dosage of insulin infused ranged from 0.1 to 1.0 U/kg per hour, with a duration of 6 to 96 hours. In 1 case report,<sup>58</sup> the dosing regimen for insulin/dextrose therapy was not included. The insulin dose of 0.25 U/kg per hour used in the case<sup>5</sup> we reported was within the dosage range cited in other case reports. In addition, the 24-hour duration of HIE therapy in our case was similar to the duration of insulin therapy in other reported cases. In the 5 cases reported by Yuan et al,<sup>55</sup> the mean duration of therapy was 27 hours.

Attention must be given to the danger of hypoglycemia in HIE therapy. In several of the cases reported,<sup>55,57-59,61,62</sup> boluses or infusions of dextrose were administered to maintain euglycemia during insulin therapy. No adverse outcomes due to hypoglycemia occurred when regular bedside capillary testing of blood glucose levels and supplemental glucose were used. The risk of hypokalemia with high-dose insulin therapy also must be considered; however, no adverse events due to hypokalemia occurred in the cases reported.<sup>55-62</sup> None of the reports

mentioned other electrolyte complications, including hypomagnesemia and hypophosphatemia. Magnesium and phosphorus levels should be monitored during HIE therapy, because the levels of both may decrease in patients receiving insulin therapy.

## Conclusions

HIE therapy appears to be beneficial for treatment of life-threatening CCB overdose. Currently, all available information on HIE is limited to case reports and series in which it was used as an adjunctive or salvage therapy in patients with refractory shock. No prospective clinical trials on the use of HIE as a first-line therapy in CCB overdose have been done. Therefore, when the efficacy of HIE therapy for CCB poisoning is considered, the limitations of the 13 case reports<sup>55-62</sup> must be recognized.

First, as in our case,<sup>5</sup> many of the reported cases involve the ingestion of multiple substances that can confound the clinical picture of CCB overdose and response to medical therapy. Second, many patients in the cases reported were treated with various additional therapies (eg, vasoactive agents, intravenous calcium, intravenous atropine) for variable lengths of time before HIE was started, and in several cases these other therapies were continued during HIE therapy. Because of this lack of uniformity among cases, delineating the precise indications for HIE therapy is difficult. Third, in the cases reported, both the route of administration (bolus alone vs infusion alone vs bolus followed by infusion) and the dosage varied widely; no standard regimen for HIE therapy exists. In addition, monitoring for and treatment of the hypoglycemia and hypokalemia that may accompany HIE therapy are not standardized.

In a review of 5 experiences with CCB poisoning, Boyer et al<sup>63</sup> propose a protocol for the dosing and monitoring of HIE therapy. The protocol has not been prospectively validated in clinical trials, but it can be used as a guide for clinicians considering HIE therapy in CCB overdose when hypotension persists despite adequate fluid replacement and administration of high-dose calcium and vasopressors.

## FINANCIAL DISCLOSURES

None reported.

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