Overdoses of β-blockers and calcium channel blockers can produce significant morbidity and mortality, and conventional therapies often do not work as treatments for these poisonings. High-dose insulin/glucose therapy has been successful in reversing the cardiotoxic effects of these drugs in cases where the standard therapies have failed, and it appears to be relatively safe. Many successes have been well documented, but the clinical experience consists of case reports, the mechanisms of action are not completely understood, and guidelines for use of the therapy are empirically derived and not standardized. Regardless of these limitations, high-dose insulin/glucose therapy can be effective, it is often recommended by clinical toxicologists and poison control centers, and critical care nurses should be familiar with when and how the therapy is used. (Critical Care Nurse. 2016;36[2]:45-50)

High-dose insulin/glucose therapy, which is also called hyperinsulinemic/euglycemic therapy or insulin-dextrose therapy, has received considerable attention as a treatment for overdoses of β-blockers and calcium channel blockers that are refractory to conventional therapies. Clinical experience using high-dose insulin/glucose to treat cardiotoxic poisonings in humans dates to 1999, and animal experiments before that time provided the theoretical background and the impetus for extension of its use to treat calcium channel blocker overdoses and then β-blocker overdoses.

Despite many articles in medical publications and 15 years of clinical experience with its use, questions remain about how high-dose insulin/glucose therapy works and when and for whom this therapy should be applied. In addition, the dosing guidelines are not standardized. However, high-dose insulin/glucose therapy is commonly used and often recommended for treating β-blocker and calcium channel blocker poisoning, and critical care nurses should be familiar with the therapy.

This article has been designated for CE contact hour(s). The evaluation tests your knowledge of the following objectives:
1. Identify 2 clinical indications for the use of high-dose insulin/glucose therapy
2. Identify 2 mechanisms of action of high-dose insulin/glucose therapy
3. Identify 2 common complications of high-dose insulin/glucose therapy

To complete evaluation for CE contact hour(s) for test #C162, visit www.ccnonline.org and click the "CE Articles" button. No CE test fee for AACN members. This test expires on April 1, 2019.

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©2016 American Association of Critical-Care Nurses doi: http://dx.doi.org/10.4037/ccn2016370
The terms conventional and standard therapy are defined here as atropine, calcium, cardiac pacing, glucagon, intravenous fluids, phosphodiesterase inhibitors, sympathomimetics, and vasopressors. 

β-Blockers competitively block the effect of catecholamines at β-adrenergic receptors. This blockade decreases the intracellular production of cyclic adenosine monophosphate (cAMP), and this in turn reduces the amount of intracellular calcium available for cell depolarization and contraction. Calcium channel blockers act as antagonists at L-type voltage-sensitive calcium channels in the myocardium, the vascular bed, and the pancreas. Blockade of these ion channels disrupts membrane depolarization and prevents movement of calcium into the cell, which limits the release of calcium that is stored in the sarcoplasmic reticulum. For both of the drugs, disruption of calcium homeostasis causes a negative chronotropic and inotropic effect and vasodilatation. Calcium channel blocker poisoning also impairs glucose metabolism; this effect is discussed later in the article.

When taken in toxic doses, β-blockers can cause profound bradycardia and hypotension, and the mechanism of action of the drug prevents normal physiological compensation and limits the effectiveness of many standard therapies. An overdose of calcium channel blockers can cause bradycardia, hypotension, and hyperglycemia, and like β-blocker poisoning, severe poisoning due to calcium channel blockers is often refractory to standard therapies. Note: The toxicity of β-blockers is not limited to β-adrenergic blockade. Lipid-soluble β-blockers such as propranolol can cross the blood-brain barrier and may cause seizures. Acebutolol, betaxolol, and propranolol have membrane-stabilizing effects similar to the effects of quinidine and can cause prolongation of the QRS interval. These effects of β-blocker overdose are relatively uncommon and are not discussed in this article.

The toxic doses of β-blockers and calcium channel blockers are not known. The following are evidence-based guidelines that are commonly used by US poison control centers to determine how much of a specific β-blocker or calcium channel blocker may be dangerous. These are guidelines only, and each case must be evaluated individually as patients may experience toxic effects at lower or higher doses (Table 1).

Regular release β-blockers and calcium channel blockers typically begin to affect blood pressure and heart rate several hours after ingestion. The onset of effects after ingestion of sustained release (SR) preparations is variable and may be delayed. A delayed onset of
effects for more than 6 hours and up to 15 hours after ingestion of SR calcium channel blockers has been reported,24 and the maximum clinical effects produced by overdose also may be delayed.3,10 The referral guidelines for β-blockers recommend a minimum of 6 hours of observation after ingestion of an immediate-release (IR) β-blocker and a minimum of 8 hours of observation after ingestion of an SR β-blocker.1 The referral guidelines for calcium channel blockers state that asymptomatic patients who have ingested an SR product are unlikely to show toxic effects 18 to 24 hours after ingestion.5

Mechanisms of Action of High-Dose Insulin/Glucose Therapy

The common opinion is that high-dose insulin/glucose therapy works by 3 mechanisms of action to reverse cardiotoxic poisoning.2

1. Positive inotropy: The positive inotropic effects of insulin have been demonstrated in many animal experiments.15-17 These effects may be due to the effect of insulin on glucose metabolism and/or to a separate mechanism.

2. Vasodilatation: Insulin dilates peripheral vessels.18,19

3. Metabolic effects: Calcium channel blocker poisoning inhibits the L-type voltage-sensitive ion channels in the pancreas, decreasing insulin release.14,16-21 Insulin resistance is increased, as well,15,20,22,23 and hyperglycemia is a common effect of calcium channel blocker poisoning. Concurrent with these effects, the hemodynamic effects of overdose “switch” the energy substrate of the myocardium from free fatty acids to glucose,22,23,24 but the decreased insulin release and increased insulin resistance prevent glucose utilization. High-dose insulin/glucose therapy allows myocardial glucose uptake and provides a source of glucose.

These 3 physiological effects increase blood pressure and tissue perfusion in cases of β-blocker and calcium channel blocker poisoning, presumably by (1) dilating the peripheral vasculature, (2) increasing myocardial uptake of glucose, (3) providing the heart with a source of energy, and (4) acting as a positive inotropic agent.

High-dose insulin/glucose therapy has clearly been effective for treating overdoses of β-blockers and calcium channel blockers, but why it is effective is not clear.25 The positive inotropy, vasodilatation, and changes in glucose metabolism documented in the literature are from tissue and animal experiments involving calcium channel blockers or from what is known of the pharmacological and toxicologic actions of calcium channel blockers and (to a lesser degree) β-blockers. The evidence supporting these mechanisms of action appears to be good, but how—or if—these mechanisms act as the basis of the therapeutic effects of high-dose insulin/glucose therapy has not been proven.

Clinical Experience

Treatment of severely poisoned patients with the conventional therapies often fails to work,3,24-26 and inotropic agents and vasopressors can increase systemic vascular resistance and myocardial oxygen demand, effects that are not beneficial in these situations.

Holger et al19 performed a retrospective review of charts for 12 patients who had cardiogenic shock after overdose of a β-blocker, a calcium channel blocker, a combination of those drugs, a tricyclic antidepressant, or multiple drugs. High-dose insulin/glucose was used as the primary therapy. No patients were given a vasopressor or glucagon, but all 12 were initially given intravenous fluid resuscitation and calcium supplementation. Eleven of the 12 survived. Unlike other studies, a standardized insulin/glucose protocol was used for all of the patients. However, the small number of patients, differing severity of clinical presentation, and the multiple drugs ingested make interpretation of the results difficult.19

Shah et al27 reviewed the literature from 1999 to 2010 for case reports and case series, and they located 28 cases. Most cases involved poisoning with calcium channel blockers, but several involved co-ingestants. Three of the case reports were published as abstracts and 12 were part of 2 case series by Greene et al28 and Yuan and Kerns1 that are reviewed next. All of the patients had received conventional therapy at some point: the time at which conventional therapy was applied varied considerably from case to case. The survival rate was 80% (this includes the cases published by Greene et al). Two cases in which this therapy was considered to have failed were published as abstracts, and little clinical information is available. One patient actually received a low dose of insulin, 1 to 2 units per hour; this patient survived.

Greene et al28 published the results of a prospective observational study of 7 cases of calcium channel blocker
poisoning for which high-dose insulin/glucose was used. Six of the 7 survived, but the effectiveness and/or relative contribution of high-dose insulin/glucose in these cases cannot be assessed because all 7 patients had taken co-ingestants and all received other therapies such as atropine, intravenous fluids, or cardiac pacing. The authors noted that 3 of the 7 had a significant and sustained increase in blood pressure that was temporarily associated with the onset of the therapy and that adverse effects were minimal and not clinically significant.28

Shepherd and Klein-Schwartz23 reviewed the literature from 1996 to 2004. They located 13 cases of calcium channel blocker overdose for which high-dose insulin/glucose was used: all but 3 had been reviewed by Shah et al.27 Two of these 3 cases were published as abstracts; all 3 patients survived and all 3 received conventional therapy in addition to high-dose insulin/glucose.23

Many case reports about the use of high-dose insulin/glucose for the treatment of β-blocker and calcium channel blocker poisoning have been published. Most report success, but failure has been recorded,29 and underreporting of failures is always possible. Published reports do provide support for the use of high-dose insulin/glucose, but those reports cannot be used to make conclusions about (1) the effectiveness of high-dose insulin/glucose compared with conventional therapies, or (3) for whom and when high-dose insulin/glucose therapy should be used. The case reports do contain interesting and useful information. But the reports present patients with differing characteristics, a wide range of clinical presentations, co-ingestions of other potentially cardiotoxic medications, different dosing of high-dose insulin/glucose, and the use of other therapies along with high-dose insulin/glucose, so a useful interpretation of the data from these cases is quite difficult.

For obvious reasons, no clinical trials have been done to evaluate the effectiveness of high-dose insulin/glucose as a single therapy for treating severely poisoned patients. No direct comparisons of conventional therapies and high-dose insulin/glucose have been done, although animal studies suggest that high-dose insulin/glucose therapy is more effective.30,31 Some authors have stated that high-dose insulin/glucose therapy should be the first treatment used for symptomatic cases of β-blocker or calcium channel blocker overdose1 and that treatment failures may be caused by delaying its use.27 Others think that the proper use of insulin-dextrose therapy is as an adjunct.21,24,32 In a recent article, Levine et al33 concluded that overdoses of verapamil or diltiazem can be effectively and safely managed with high doses of vasopressors, and they pointed out the relative lack of experience with (and the absence of) proven dosing and administration guidelines for high-dose insulin/glucose therapy. Olson34 noted that significant evidence is lacking for the effectiveness of all the therapies used to treat calcium channel blocker overdose, and he stressed the need for attention to supportive care and the use of pharmacological interventions on a case by case basis.

### Administering and Monitoring High-Dose Insulin/Glucose

Using a pharmacological intervention properly requires you to know: (1) which patients will benefit, (2) proper dosing, (3) when to start and stop the treatment, (4) adverse effects, (5) monitoring parameters, and (6) how the intervention will be affected by other drugs or therapies that are being used.

Unfortunately, none of those requirements have been conclusively established for the use of high-dose insulin/glucose therapy. Specific dosing regimens have been used, but these regimens were empirically derived and they differ slightly from each other. But regardless of the differences, the goals of each of the dosing regimens and the monitoring parameters are the same: administration of a high dose of insulin while maintaining euglycemia, and close monitoring of serum levels of glucose and potassium. Three examples of available dosing protocols are given in Table 2. These examples are not intended to be taken as definitive guidelines for administering this therapy: decisions on dosing and therapeutic goals should be individualized for each patient. If fluid overload is or may be a concern, then the 1:1 ratio of insulin to normal saline can be changed to 10:1.

The onset of action is typically seen 30 minutes or more after the infusion has started, but a clinical response has been reported within 15 minutes.3,36 Commonly seen adverse effects are hypoglycemia and hypokalemia, but these effects have not been clinically significant and are easily corrected.19 Glucose infusions of 10% and higher...
can be irritating to the veins, so a central intravenous catheter may be needed.

No standardized guidelines specify the duration of therapy, and insulin/glucose has been used for as long as 96 hours.39 No guidelines are available for how to taper and discontinue the infusion.23 Serum glucose levels should be monitored closely after the infusion has stopped: published reports indicate that insulin levels may remain elevated for 24 hours after high-dose insulin therapy has been stopped.134 The decision to use high-dose insulin/glucose as the primary therapy or as an adjunct must be made on a case by case basis.

Conclusion

High-dose insulin/glucose therapy has been used successfully for the treatment of β-blocker and calcium channel blocker overdoses. But documentation of why this therapy works, why it fails, and specific, well-proven guidelines for its use is not available. However, the safety profile of this treatment is good and it is commonly used and prescribed; familiarity with the use of high-dose insulin/glucose should be required knowledge for critical care nurses.

Financial Disclosures

None reported.

Table 2

<table>
<thead>
<tr>
<th>Dosing protocols for high-dose insulin/glucosea</th>
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<tr>
<td>1. Give a bolus of regular insulin, 1 unit/kg.</td>
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<td>2. If the blood glucose is &lt; 200 mg/dL, give 50 mL of 50% dextrose IV.</td>
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<td>3. Dilute 500 units of regular insulin in 500 mL of 0.9% saline. Start the continuous infusion with this solution at 0.5-1.0 units/kg/hr.</td>
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<td>4. Titrate the insulin infusion to maintain a systolic blood pressure ≥ 100 mm Hg. The onset of effects may not be seen for at least 30 minutes after the therapy has been started. If there is no effect noticed after 30-60 minutes, increase the infusion rate.</td>
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<tr>
<td>5. At the same time, start an IV infusion of 10% dextrose. Titrate this and/or administer boluses of dextrose to maintain blood glucose between 100-200 mg/dL.</td>
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<td>6. Measure blood glucose every 15-30 minutes during the first 4 hours of therapy until the blood glucose has stabilized between 100-200 mg/dL for 4 hours.</td>
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<tr>
<td>7. Measure serum potassium hourly initially and then measure it every 4 to 6 hours. If the serum potassium is &lt; 2.5 mEq/L, provide supplementation.</td>
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<tr>
<td>8. Monitor serum magnesium and phosphorus, as these may be decreased during therapy.</td>
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<tr>
<td>9. Monitor the blood glucose for several hours after high-dose insulin/glucose therapy has been discontinued as reactive hypoglycemia is possible.</td>
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<td>10. The average duration of infusion has been 24-31 hours.35</td>
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Abbreviation: IV, intravenous.

Table 2 Footnotes:

a These are examples of empirically derived protocols that have been published; they are not all in agreement. There is no standardized protocol, and clinical judgment should prevail when choosing how to use high-dose insulin/glucose therapy.


