Antidotes You Should Know: Octreotide for Sulfonylurea-Induced Hypoglycemia

By James R. Roberts, MD

Author Credentials and Financial Disclosure: James R. Roberts, MD, is the Chairman of the Department of Emergency Medicine and the Director of the Division of Toxicology at Mercy Health Systems, and a Professor of Emergency Medicine and Toxicology at the Drexel University College of Medicine, both in Philadelphia.

Dr. Roberts has disclosed that he is a member of the Speakers Bureau for Merck Pharmaceuticals. All other faculty and staff in a position to control the content of this CME activity have disclosed that they and their spouses/life partners (if any) have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity. Lippincott CME Institute, Inc. has identified and resolved all faculty and staff conflicts of interest regarding this educational activity.

Learning Objectives: After participating in this activity, the physician should be better able to:
1. Explain therapeutic strategies to reverse recurrent hypoglycemia, given the decreases in glucose levels.
2. Use antidotes to reverse hypoglycemia secondary to sulfonylurea drugs.

A few specific massive pharmacological overdoses are essentially lethal sentences, even when the patient arrives awake and talking. If one takes enough calcium channel blockers, beta blockers, or tricyclic antidepressants, the scene is often set for a lethal outcome once the bolus of toxin is swallowed, regardless of physician intervention. My previous columns in this series discussed some novel, albeit nonspecific, antidotes that hold promise for reversing a heretofore-lethal overdose.

Included in a discussion of new and minimally studied potentially life-saving interventions was intravenous lipid emulsion, a tactic to literally suck up fat-soluble drugs, including local anesthetics and perhaps antidepressants, antipsychotics, and cardiovascular preparations. Another novel approach to the otherwise hopeless calcium channel blocker overdose, or perhaps even the beta blocker overdose, is high-dose insulin/glucose infusion. Similar to the data on intravenous lipid emulsion therapy, this intervention is largely supported by animal studies and case reports, and is buffered with sophisticated toxicology theory. Protocols are not FDA-approved, but both seem safe and currently have the enthusiastic support of many toxicologists. Neither are current standard interventions in the ED, but their early use, logically in the ED, has been promulgated.

This month’s column discusses the use of octreotide as an antidote for hypoglycemia secondary to sulfonylurea drugs, a common occurrence in the ED. This antidote is truly within the realm of emergency medicine, and should prompt clinician cogitation on a change in practice. Octreotide augurs to become a routine first-line intervention.

Octreotide: An Antidote for Sulfonylurea-Induced Hypoglycemia


This article is one of a modicum of small series and case reports that extol the virtues of octreotide as an antidote for hypoglycemia in patients taking sulfonylurea drugs. It reiterates the findings of many other case reports, and is a good overview of the important pharmacologic and clinical issues. (See also Ann Pharmacother 2002;36(11):1727.)

The authors retrospectively reviewed the charts of nine patients (20-65 years old) who had ingested glipizide or glyburide, two commonly used oral hypoglycemic agents. Most had normal hepatic and renal function. These drugs are often given for type 2 diabetes, but they can cause prolonged and potentially life-threatening hypoglycemia, either from overdose or from a therapeutic misadventure. The intended therapeutic mechanism of sulfonylurea agents is depolarization of pancreatic beta cells, with release of insulin into the bloodstream. If too much insulin is released, hypoglycemia ensues. The accepted initial treatment for hypoglycemia is the intravenous administration of dextrose. One should anticipate a rebound drop in serum glucose so subsequent close monitoring of blood glucose levels is required. Recurrent hypoglycemia is an often experienced conundrum because dextrose is a potent stimulus for even more insulin release from the sulfonylurea-primed pancreas. In the setting of continued sulfonylurea stimulation of insulin release, the body senses the physician's massive therapeutic glucose load as problematic and therefore releases more insulin. Rebound hypoglycemia can be recurrent, prolonged, and difficult to reverse. Often a central line is required to continually infuse hypertonic dextrose.

Octreotide is an analogue of the human hormone somatostatin. EEs may be familiar with octreotide for treating bleeding esophageal varices, where its use by continuous infusion is quite safe. Normal insulin release occurs via G-protein mediated calcium entry into pancreatic cells. Octreotide, acting like a quintessential calcium channel blocker itself, inhibits this calcium inflow, halting insulin release. Seasoned clinicians will remember a similar use for dantrolene, one of the first IV calcium channel blockers. As a reminder, a calcium channel blocker overdose often causes hyperglycemia, via a similar mechanism, and hyperglycemia may be a diagnostic clue to this overdose.

Octreotide functions as an antidote for hypoglycemia because it inhibits the release of insulin, blocking the physiology of excess pancreatic stimulation by sulfonylureas. These authors aimed to determine whether glucose requirements and the number of hypoglycemic episodes would be reduced if octreotide treatment were instituted for sulfonylurea-induced hypoglycemia.

In this report, the number of hypoglycemic episodes and the amount of dextrose required before and after treatment with octreotide were analyzed. To be eligible for inclusion, patients had to experience hypoglycemia from the sulfonylurea, been treated with glucose, and then given octreotide at some time in their course. Patients had either unintentional overdose or a suicide attempt, but patient characteristics did not appear to have significant importance for the outcome. All were admitted to a monitored inpatient service (including the ICU), and all were eventually discharged without neurologic complications.

The number of hypoglycemic episodes that occurred prior to octreotide therapy ranged from one to six. The number of ampules of D50 administered prior to octreotide therapy ranged from one to seven. The dose of octreotide varied from 40 mcg to 100 mcg, administered one to three times simultaneously. One patient received a continuous octreotide infusion (125 mcg/hr for nine hours). As one might intuit, there was no consensus on octreotide use by the clinicians in this retrospective study. Some tolerated numerous recurrent bouts of hypoglycemia before considering octreotide; others gave it a multidose vial of octreotide (administered SC, IV, or by continuous infusion) and an ampule of 50% dextrose are both antidotes for sulfonylurea-induced hypoglycemia. Glucose is initially required, but if used alone, it can be counterproductive because hypertonic glucose will stimulate even more insulin release from the sulfonylurea-primed pancreas. This sets the stage for recurrent and prolonged hypoglycemia. Octreotide so nicely breaks the cycle that it seems like an ideal low-risk, high-reward intervention after the first episode of hypoglycemia is under control. Prolonged observation, frequent glucose checks, and repeat doses of octreotide are usually the norm. Considering the therapeutic lag of octreotide’s onset of action, accomplish the first bedside Accu-Chek in 20 to 30 minutes.
before the first episode of recurrent hypoglycemia was documented.

Of the nine patients, two had a single recurrent episode of hypoglycemia after octreotide. These occurred long after the octreotide effect had dissipated (14 and 36 hours post last octreotide dose). This emphasizes the prolonged hypoglycemic effect of these oral diabetic drugs and describes inadequate octreotide dosing or premature cessation of therapy rather than pharmacologic failure of the intervention.

As a final outcome of octreotide use, the number of hypoglycemic episodes recurring after octreotide therapy was markedly reduced, as was the need for additional glucose supplementation.

The risk of recurrent hypoglycemia before octreotide was 27 times the risk after octreotide. The antidiote stabilized glucose concentrations after prevention of rebound hypoglycemia. When used properly, octreotide therapy essentially halted recurrent hypoglycemia. There were no significant consequences or side effects of intervention. Because this regimen was highly efficacious and safe, the authors suggest considering octreotide after initial glucose administration as routine first-line therapy for hypoglycemia secondary to sulfonylurea exposure.

Comment: Every EP is familiar with altered mental status, syncope, diaphoresis, confusion, or coma in patients exposed to sulfonylureas, either via overdose or as a therapeutic misadventure. Many times the exact reason for previously well tolerated diabetic therapy to suddenly produce hypoglycemia cannot be ferreted out in the ED. Likewise, most clinicians are also familiar with repeating the glucose level after an amp of D50 only to find that hypoglycemia has returned. Treating recurrent hypoglycemia with more glucose, although initially required, often results in literally chasing one’s tail with regard to glucose-hypoglycemia-more glucose. In essence, the required glucose makes the situation worse when the sulfonylurea is still exerting its effect on the pancreas. The cycle is interrupted effectively and safely with the use of octreotide. I have used this drug many times, and have never seen it fail. It’s a common recommendation by our toxicology service. I have encountered patients who have received multiple ampules of glucose, with clinicians going as far as starting a central line to deliver hypertonic glucose in gargantuan amounts, only to be continually frustrated when they can’t get the hypoglycemia under control.

Of course, identifying hypoglycemia in the first place is a difficult challenge in the ED. We are all still humbled by missing a case now and then. Unknown patients with unknown problems are on unknown medications, and they present with confusion, seizures, bizarre mental status, coma, agitation, and delirium. Any case of altered mental status must be considered to be hypoglycemia until proven otherwise. This is especially paramount when you think you know the diagnosis, and quickly relate the altered mental status to drug overdose, head trauma, alcohol withdrawal, sepsis, stroke, or end-stage cancer. Even when the paramedics report the glucose to be normal, the Accu-Chek must be repeated in the ED. One does not want to wait for a seizure in the CT scanner or a report from the laboratory with the critical value to check the serum glucose. A reassuring sign that I bungled was a chlorpropamide overdose in a prisoner who presented in coma after a fight in jail, complete with a seemingly classic Battle’s sign and a seizure. I congratulated myself on an expedited CT scan, only to have him seize again in the scanner. The lab reported a glucose of 10 soon after. Turns out he thought he was scoring methadone from a guard, only to be poisoned by the guard’s own sulfonylurea. Octreotide is expensive ($11 for 100 mcg per this study), and there appears to be no contraindications to its use. Normal individuals experience no significant side effects from doses as high as 1000 mcg. Normal volunteers do not become hyperglycemic. In my experience, the small doses of octreotide used for this indication are very benign.

Oral diabetic drugs are metabolized primarily by the liver, with some renal excretion of active metabolites. The normal duration of action of therapeutic doses can be as long as 24 hours. Many EPs will automatically opt for admission of a patient with any degree of hypoglycemia secondary to an oral agent. It’s difficult if not impossible to determine whether the hypoglycemic culprit is an overdose, just too much medication, worsening hepatic or renal dysfunction, simply lack of eating, or a drug-drug interaction. Drug-drug interactions are not well recognized by most physicians, but it is known that sulfonylurea activity is enhanced by a load of medications, including aspirin, NSAIDs, sulfonamides, warfarin, beta blockers, florpropionolones, and antifungals; the last is extensive.

From a pediatric standpoint, ingestion of a single oral hypoglycemic tablet mandates admission of the asymptomatic/egyptic child for 24 hours because hypoglycemia is often delayed for many hours.

Other treatments for hypoglycemia include giving the patient a hearty meal. One ampule of D50 has only 100 calories, less than a can of soda and not enough calories to stave off recurrent hypoglycemia with even a minimal overdose. One simply cannot administer significant calories intravenously, and a calorie-laden hospital meal should be the first order after the patient wakes up.

Be careful with IV hypertonic glucose because inadvertent extravasation into the soft tissues can cause a tissue slough that cannot be reversed. Hurried attempts at pushing D50 via a small dorsal hand vein can cause trouble. Skin grafting may follow. Lower concentrations are suggested for children because of their sensitive skin, and one should probably totally avoid IV 50% dextrose in children. Diluting an ampule of D50 with saline, about 3-4:1, is suggested. Even a prolonged infusion of 10% dextrose, another reflex action for recurring hypoglycemia, can cause significant venous irritation or a peripheral vein.

One may be tempted to discharge a stable patient after the oral-agent hypoglycemia is reversed, and the patient remains euglycemic for six to eight hours. Trying to determine the exact etiology of hypoglycemia or relying on drug half-life in these patients to formulate a disposition plan is a waste of time. You may be able to finesse discharge in an ideal patient (clued in, observable, able to have glucose checked frequently), but that requires a lot of ducks to line up. In my ED clientele, this is best accomplished by hospital admission.

As a target octreotide dose, 50 mcg SC or IV every six to eight hours is a reasonable starting point. A continuous infusion is usually unnecessary, and the IM and oral route are not used. In the hospital, two to three subsequent doses should be routine by the admitting team. Once the patient is octreotide-free and hypoglycemia-free for 12 hours, one is likely out of the woods.

**Calculating the Caloric Content of a Single 50 ml Ampule of 50% Dextrose**

- 50% means 50 grams of dextrose in 100 ml.
- 50 ml contains 25 grams of dextrose.
- Dextrose provides four calories per gram.
- Four calories x 25 grams means the caloric content of 50 ml of 50% dextrose is 100 calories.
- A two-ounce Snickers has 34.5 grams of carbohydrate and 271 calories.
- A 12-ounce can of Coke has 155 calories.
- Bottom line: Give a hypoglycemic patient a high-calorie hospital meal in the ED.

**Comparison of Octreotide and Standard Therapy versus Standard Therapy Alone for the Treatment of Sulfonylurea-Induced Hypoglycemia**

Fasano CJ, et al

_Ann Emerg Med_ 2008;51(4):400

This is the only prospective, double-blind, placebo-controlled trial in the literature addressing this subject. It included 40 patients treated with either placebo or octreotide following initially reversed hypoglycemia secondary to sulfonylurea use. Patients received one ampule of 50% dextrose and oral carbohydrates, and were then randomized to either placebo or 75 mcg SC octreotide (1 dose).

This study demonstrated that recurrent hypoglycemic episodes were much less frequent in patients who received octreotide compared with placebo, but one ampule dose was not always successful. Although octreotide worked for about eight hours, the effect was subsequently lost after that, and hypoglycemia recurred unless additional octreotide was administered. This is an extremely important point, and emphasizes the fact that patients given a single dose of octreotide cannot readily be discharged nor can they be forgotten on the floor.

**InFocus**

**Induced Hypoglycemia**

**Standard Therapy versus Standard Therapy Alone**

**Comparison of Octreotide and Standard Therapy versus Standard Therapy Alone for the Treatment of Sulfonylurea-Induced Hypoglycemia**

Fasano CJ, et al

_Ann Emerg Med_ 2008;51(4):400

**InFocus**

**Induced Hypoglycemia**

**Standard Therapy versus Standard Therapy Alone**

**Comparison of Octreotide and Standard Therapy versus Standard Therapy Alone for the Treatment of Sulfonylurea-Induced Hypoglycemia**

_Fasano CJ, et al_ 2008;51(4):400

This is the only prospective, double-blind, placebo-controlled trial in the literature addressing this subject. It included 40 patients treated with either placebo or octreotide following initially reversed hypoglycemia secondary to sulfonylurea use. Patients received one ampule of 50% dextrose and oral carbohydrates, and were then randomized to either placebo or 75 mcg SC octreotide (1 dose).

This study demonstrated that recurrent hypoglycemic episodes were much less frequent in patients who received octreotide compared with placebo, but one ampule dose was not always successful. Although octreotide worked for about eight hours, the effect was subsequently lost after that, and hypoglycemia recurred unless additional octreotide was administered. This is an extremely important point, and emphasizes the fact that patients given a single dose of octreotide cannot readily be discharged nor can they be forgotten on the floor.

**Continued on next page**

**Reader Feedback:**

Readers are invited to ask specific questions and offer personal experiences, comments, or observations on InFocu topics. Literature references are appreciated. Pertinent responses will be published in a future issue. Please send comments to emn@lww.com.

**Dr. Roberts:** I enjoyed your article “Now That You’re a Real Doctor,” and we’ll use it for our new hires also. (EMN 2009;31[11]:12.) The only thing I would add for your letter next year would be a word of caution about social boundaries between work and play. Dating the staff is not much different from taking your date to the workplace. Behavior that looks bad elsewhere becomes bad behavior at work. Thanks for sharing your experiences.

— John Mueller, MD, Virginia
No patient who received octreotide had more than one hypoglycemic episode, but these were not overdose cases.

Comment: Octreotide is not FDA-approved for treating sulfonylurea-induced hypoglycemia, although it is a common recommendation and sound clinical practice. Minimal nausea, abdominal cramps, and diarrhea may occur, but they have not been problematic in this scenario. Whether octreotide should be given after the first hypoglycemic episode or reserved for recurrent episodes is controversial. This study suggests that it be routinely used after the first hypoglycemic event is reversed with IV glucose. It is known, however, that all octreotide effects wane after eight to 10 hours. The authors of this study chose only the first hypoglycemic episode as the stimulus for initiating octreotide. This makes the most sense to me, so I have been ordering octreotide routinely after the first bout of hypoglycemia is reversed. Why wait for another drop in blood sugar or risk a tardy repeat Accu-Chek? No downside, lots of upside with this approach.

This article answers some previously unknown questions. First, a single dose of octreotide may take an hour to be effective, and the antidote activity only lasts for about eight hours. One may see hypoglycemia prior to the peak action of octreotide. Such was observed in a few patients in this study. Check the glucose again within 20 to 30 minutes of dextrose reversal. Subsequent doses of octreotide are often required. One cannot simply give a dose of octreotide and consider the problem solved nor can one wait for a routine lab draw to check the glucose on the floor for morning rounds; it must be measured frequently in the post-ED setting.

Most patients who experience hypoglycemia from the use of regular insulin (not longer-acting insulin preparations) can be treated with glucose and sent home after four to six hours of observation because the effects of insulin are gone. Octreotide will have no effect on metformin or insulin-induced hypoglycemia. This article and the previous literature support a change in practice. Simply giving glucose for hypoglycemia secondary to an oral agent is not always permanently curative, and actually can be counterproductive in the absence of the octreotide-mediated blockade of continued insulin release.

Cocktail party trivia: Quinine, used for treating malaria, also can cause prolonged hypoglycemia, a little known side effect that is also blocked by octreotide.

---

**Commentaries**

Continued from previous page

**Antidotes**

For treating malaria, quinine, also can cause secondary hypoglycemia. This article and the previous literature support a change in practice. Simply giving glucose for hypoglycemia secondary to an oral agent is not always permanently curative, and actually can be counterproductive in the absence of the octreotide-mediated blockade of continued insulin release.

**Cocktail party trivia:** Quinine, used for treating malaria, also can cause prolonged hypoglycemia, a little known side effect that is also blocked by octreotide.

---

**CME Participation Instructions**

To earn CME credit, you must read the article in *Emergency Medicine News*, and complete the evaluation questions and quiz, answering at least 80 percent of the questions correctly. Mail the completed quiz with your check for $12 payable to Lippincott Continuing Medical Education Institute, 530 Walnut Street, 8th Floor East, Philadelphia, PA 19106. Only the first entry will be considered for credit, and must be received by Lippincott Continuing Medical Education Institute by February 28, 2011. Acknowledgment will be sent to you within six to eight weeks of participation.

Lippincott Continuing Medical Education Institute is accredited by the Accreditation Council for Continuing Medical Education to provide medical education to physicians. Lippincott Continuing Medical Education Institute designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activities.

**February 2010 Questions:**

1. How does a sulfonylurea cause hypoglycemia?
   - A. Inhibition of circulating growth hormone.
   - B. Decrease in gluconeogenesis.
   - C. Increase of insulin release from the pancreas.
   - D. Inhibition of peripheral effects from epinephrine and glucocorticoids.

2. What is the primary mechanism by which octreotide reverses recurrent hypoglycemia?
   - A. Blocks calcium entry into pancreatic cells.
   - B. Facilitates calcium entry into pancreatic cells.
   - C. Blocks release of epinephrine from adrenal medulla.
   - D. Increases epinephrine release from the medulla.

3. Which best describes the clinical use of octreotide for sulfonylurea-induced hypoglycemia?
   - A. Use after first or recurrent hypoglycemia is identified.
   - B. Use is based on sulfonylurea blood levels.
   - C. Use if insulin is combined with sulfonylurea ingestion.
   - D. Used only for intentional overdose of sulfonylurea.

4. What route of administration is unacceptable for octreotide?
   - A. Subcutaneous.
   - B. IV.
   - C. Continuous IV infusion.
   - D. Oral.

5. Which best describes the clinical use of octreotide?
   - A. 50 mcg IV every two hours, continuous 10% dextrose infusion.
   - B. 50 mcg SC or IV every eight hours, glucose checks every two to three hours.
   - C. 500 mcg IM, discharge to be checked in 24 hours.
   - D. Only after continuous infusion of 50% dextrose via central line is unsuccessful.

**Directions**

Your successful completion of this activity includes evaluating it. Please indicate your responses below filling in the blanks or by darkening the circles with a pencil or pen.

**Please rate your confidence in your ability to achieve the following objectives, both before this activity and after it: (1-minimally) to 5 (completely)**

1. How does a sulfonylurea cause hypoglycemia?
   
2. What is the primary mechanism by which octreotide reverses recurrent hypoglycemia?
   
3. Which best describes the clinical use of octreotide for sulfonylurea-induced hypoglycemia?
   
**Please indicate how well the activity met your expectations: (1-Needs serious improvement, 5-A model of its kind)**

Your successful completion of this activity includes evaluating it. Please indicate your responses below filling in the blanks or by darkening the circles with a pencil or pen.

**Please rate your confidence in your ability to achieve the following objectives, both before this activity and after it: (1-minimally) to 5 (completely)**

**Use antidotes to reverse hypoglycemia secondary to sulfonylurea drugs.**

**Please indicate how well the activity met your expectations: (1-minimally) to 5 (completely)**

**Was effective in meeting the educational objectives**

**Content was useful and relevant to my practice**

**Please rate your confidence in your ability to achieve the following objectives, both before this activity and after it: (1-minimally) to 5 (completely)**

**Please address the practical application of this activity below**

**How many of your patients may be affected by what you learned from this activity? _____________**

**Please indicate how well the activity met your expectations: (1-Definitely will not change, 5-Definitely will change)**

**How will you apply what you learned from this activity? (Mark all that apply.)**

- In diagnosing patients
- In monitoring patients
- In educating students and colleagues
- To confirm current practice
- For maintaining board certification

**Please complete these overall activity assessment questions.**

**Did you perceive any bias for or against any commercial products or devices?**

**If yes, please explain:**

**Compared with other educational activities in which you have participated over the past year, how would you rate this activity? (1-Needs serious improvement, 5-A model of its kind)**

**Future activities concerning this subject are necessary.**

(1-Strongly disagree, 5-Strongly agree)

**My biggest clinical challenges related to this topic are:**

**Please use the space below to provide any additional information that will help the activity planners and faculty evaluate this activity.**

**Yes, I am interested in receiving more information on this topic and future CME activities from Lippincott CME Institute. I am willing to help evaluate the outcomes of this activity.**

(Place a check mark in the box.)

**Name __________________________**

**Street Address __________________________**

**City ___________________ State ___________ ZIP Code __________**

**Telephone ___________________ E-mail ___________________**