Hypoglycemic Agent Overdose

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PATHOPHYSIOLOGY

The primary metabolic substrate for the central nervous system (CNS) is glucose. Usual sources of glucose are diet, endogenous production (through gluconeogenesis), and storage (through glycogenolysis). Serum glucose concentrations are relatively tightly controlled by physiologic mechanisms. After dietary sources of glucose are completely used, glycogenolysis is the major physiologic mechanism for maintaining euglycemia. Typically, an adult has enough glycogen to last approximately 6 to 8 hours. When glycogen stores are depleted, gluconeogenesis, which is fueled by amino acids from muscle, takes over. The CNS cannot make or store glucose, and it relies on the previously mentioned mechanisms to maintain normal metabolic activity during fasting periods. As glucose use exceeds glucose production and serum glucose concentrations decrease, various counterregulatory pathways are activated. Counterregulatory pathways triggered at the glycemic threshold are increases in glucagon, epinephrine, growth hormone, and cortisol. Glycemic thresholds are fairly reproducible in research studies on healthy subjects, but these thresholds can vary significantly among patients with both type 1 and type 2 DM. These thresholds also depend on other factors, such as tightness of glucose regulation, the presence of chronic hyperglycemia, and recent episodes of hypoglycemia.

Hypoglycemic agents induce hypoglycemia by various mechanisms. Insulins cause rapid transport of amino acids and glucose intracellularly. Sulfonylureas stimulate insulin secretion by binding to specific membrane receptors on the pancreatic beta-islet cell. These drugs also benefit glucose homeostasis by decreasing hepatic glucose production and improving insulin sensitivity at the receptor and postreceptor levels. Other drugs may induce hypoglycemia by inhibition of gluconeogenesis, glycogenolysis, counterregulatory hormones, or other unknown mechanisms. Ethanol, a toxin commonly encountered in the ED, inhibits gluconeogenesis by depleting nicotinamide adenine dinucleotide and also inhibits the effects of cortisol, growth hormone, and epinephrine.

PRESENTING SIGNS AND SYMPTOMS

The symptoms of hypoglycemia can be divided into two basic groups: hyperadrenergic symptoms and neuroglycopenic...
Symptoms of Hypoglycemia

Hyperadrenergic Symptoms
- Anxiety
- Nervousness
- Tremulousness
- Irritability
- Nausea and vomiting
- Palpitations and tachycardia
- Sweating
- Pallor
- Hypersalivation
- Pupillary changes

Neuroglycopenic Symptoms
- Decreased cognitive ability
- Agitation and emotional lability
- Sensations of warmth (despite cool, clammy skin)
- Blurred vision
- Slurred speech
- Lethargy
- Confusion
- Unresponsiveness
- Focal neurologic deficits
- Psychotic behavior
- Seizures

Three Categories of Hypoglycemia

<table>
<thead>
<tr>
<th>TYPE OF HYPOGLYCEMIA</th>
<th>CAUSES</th>
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<tbody>
<tr>
<td>Postprandial</td>
<td>Early diabetes, Alcohol intake, Postgastrectomy status, Renal failure, Drugs (e.g., salicylates, beta-blockers, pentamidine)</td>
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<tr>
<td>Fasting</td>
<td>Conditions of excess insulin, including insulinoma and self-administration of insulin or oral hypoglycemic agents (diabetic insulin overdose), Alcohol abuse and liver disease (decreased gluconeogenesis), Pituitary or adrenal insufficiency</td>
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<tr>
<td>Drug- or toxin-induced</td>
<td>Ethanol, Quinidine, Beta-blockers, Pentamidine, Monoamine oxidase inhibitors, Angiotensin-converting enzyme inhibitors, Salicylates, Haloperidol, Disopyramide, Ackee fruit, Trimethoprim-sulfamethoxazole</td>
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Hypoglycemia has numerous causes and may be classified into the following three categories: (1) postprandial, (2) fasting, and (3) drug- or toxin-induced (Table 156.1). In healthy patients, fasting hypoglycemia is usually the result of unintentional or intentional drug ingestion and insulinoma. In patients who are severely ill or hospitalized, hypoglycemia may be a complication of the illness, drug interactions, or other iatrogenic factors.

Hypoglycemic agents can be divided according to their route of administration (i.e., parenteral or oral). Insulins and the newer agents, incretins (e.g., exenatide [Byetta], liraglutide [Victoza]), are the only medications for the treatment of DM that are given parenterally. Many antidiabetic medications are given orally, including the sulfonylureas (e.g., glyburide [Diabeta], glipizide [Glucotrol]), meglitinides (e.g., nateglinide [Starlix], repaglinide [Prandin]), biguanides (e.g., metformin), thiazolidinediones (e.g., rosiglitazone [Avandia], pioglitazone [Actos]), and α-glucosidase inhibitors (e.g., acarbose [Precose]). Of all these antidiabetic drugs, only a few classes are commonly associated with hypoglycemia—the insulins, sulfonylureas, and meglitinides.

For adults with DM, insulin treatment is the most common cause of hypoglycemia. Factors associated with higher frequency of hypoglycemia in patients with type 1 DM include lower hemoglobin A1c, higher daily insulin requirements, longer duration of DM, and a previous history of hypoglycemia. Approximately 25% of patients with DM are unable to recognize impending hypoglycemia because of a lack of autonomic warning symptoms; this characteristic is also an important predictor of hypoglycemia. Patients with insulin-dependent type 2 DM are also susceptible to hypoglycemia, especially if their disease has been treated with insulin for a long time and if their DM is tightly controlled.

For patients who are taking oral agents rather than insulin, sulfonylureas are a common cause of hypoglycemia. According to the 2010 annual report of the American Association of...
Poison Control Centers’ Toxic Surveillance System, 4109 reported sulfonylurea exposures, with 38 major outcomes and 1 death, occurred in 2009. The incidence of hypoglycemia secondary to these agents rises in older patients and with long-acting agents (e.g., chloropropamide). Consequently, independent risk factors for hypoglycemia include recent hospitalization, advanced age, and polypharmacy. Other risk factors for sulfonylurea-induced hypoglycemia are hepatic and renal dysfunction because of decreased metabolism (e.g., glyburide, glibenclamide, glipizide) and decreased elimination (e.g., chloropropamide, glyburide). The most commonly used sulfonylureas have a duration of effect of at least 24 hours, and hypoglycemia in a patient taking such an agent can be prolonged, especially in the setting of overdose. In one case report, sulfonylurea-induced hypoglycemia was reported to last up to 27 days. Most other oral agents (e.g., thiazolidinediones, biguanides) used for the treatment of DM do not usually cause significant hypoglycemia.

Hypoglycemia is a simple diagnosis to make, provided it is considered early in a patient’s presentation. In most cases, hypoglycemia is considered in a patient with altered sensorium or depressed mental status. Bedside blood glucose testing using a glucose meter in the patient with neuroglycopenic symptoms is generally the fastest technique, as well as a fairly reliable method, to determine hypoglycemia. In general, the correlation of capillary blood glucose levels (which are measured by a glucose meter) with venous or arterial glucose measurements seems to be good. At extreme values (either high or low) and in cases of systemic hypoperfusion, however, a clinically significant discrepancy may be apparent. In the setting of suspected hypoglycemia, confirmatory laboratory testing of a serum specimen is therefore necessary. Furthermore, because symptoms of hypoglycemia vary among individuals, hypoglycemia is still a possible diagnosis even in a patient with a glucose level categorized as euglycemic.

Additional diagnostic testing may be necessary, depending on the clinical situation. For most patients with DM who present with hypoglycemia, routine testing of liver and renal function is indicated. Ethanol (or other alcohol) ingestion may also result in hypoglycemia, and measurement of serum ethanol concentration may be useful in the setting of alcohol intoxication. Other tests that may be helpful are thyroid function tests and measurements of serum cortisol, insulin, and C peptide concentrations. Insulin and C peptide measurements are particularly useful in the setting of surreptitious exposure to insulin or sulfonylureas. Unlike endogenous insulin synthesized by the pancreas, exogenous insulin has no concomitant C peptide. In cases of intentional insulin poisoning, insulin concentrations are high, but C peptide concentrations are normal. On the contrary, sulfonylurea ingestions cause elevations in both insulin and C peptide, the same findings as in patients with insulinoma. Finally, in patients with intentional self-harm, testing of serum acetaminophen concentration is potentially useful.

### Treatment

The emergency physician must institute basic supportive measures, with particular attention to airway, breathing, and circulation, along with cardiorespiratory monitoring on encountering the obtunded patient with hypoglycemia. Supplemental oxygen, intravenous (IV) thiamine, and naloxone are generally benign therapies that may be judiciously administered in a patient with depressed mental status of unknown origin.

After the primary survey has been performed and any needed measures taken, gastrointestinal decontamination should be considered for patients who have taken an intentional oral overdose of a hypoglycemic agent. The particular modality of decontamination implemented depends on the usual factors, such as time of ingestion, quantity of tablets, mental status of the patient, and potential harm to the patient. Activated charcoal has been shown to be very effective in binding to multiple sulfonylurea agents in vitro. A single dose of activated charcoal may be beneficial in these ingestions. In theory, multiple-dose activated charcoal may enhance elimination of the sulfonylurea glipizide because glipizide undergoes enterohepatic circulation. IV sodium bicarbonate administered to alkalize the urine has been shown to reduce the half-life of the sulfonylurea agent chlorpropamide. These and other forms of decontamination and enhanced elimination should be used on a case-by-case basis.

Patients who are documented to have hypoglycemia by rapid bedside glucose testing should be given glucose as soon as possible. If a patient is awake and is believed to have intact airway reflexes, oral carbohydrates in the form of flavored glucose tablets, juice, and soda may be given. The patient should show response within 10 to 15 minutes as he or she returns to a euglycemic state. After this initial therapy, the
patient should be given additional nutrition in the form of a snack or meal for a sustained source of calories. If the patient does not show response to oral carbohydrates, parenteral therapy is required.

IV dextrose is the preferred treatment for severe hypoglycemia with obtundation and a patient’s inability to take oral carbohydrates. The administration of 0.5 to 1 g/kg of IV dextrose rapidly reverses the clinical effects of hypoglycemia. Hypertonic dextrose solutions are commonly found in syringes containing 50 mL of 50% dextrose in water (D50W), which is equivalent to 25 g of dextrose (4 calories/g of glucose or 100 calories). An average man weighing 70 kg would therefore require 35 to 70 g of dextrose. Administration of hypertonic dextrose is fairly safe, and only a few cases of significant adverse effects such as seizures, hyperosmolar coma, and death have been reported. A much more common effect is phlebitis, which can be mitigated by injection of the dextrose into a large vein, followed by a saline flush.

After initial euglycemia is achieved, patients should be given continuous IV infusions of dextrose. Dextrose-water solutions of 5% (D5W) and 10% (D10W) are usually used in this setting, and the dose is titrated along with other therapies to maintain euglycemia. For patients with repeated episodes of hypoglycemia, higher concentrations of dextrose and repeated boluses of D10W may be required. In this setting, hypertonic dextrose solutions should be administered by central line access because of the irritant venous effects of these solutions.

Treatment of overdose with a specific hypoglycemic agent depends on the agent. Some hypoglycemic agents, such as the meglitinides, are very short-acting drugs, and the resulting hypoglycemia is unlikely to be prolonged. For longer-acting insulins and the sulfonylureas, intensive therapy may be necessary for 1 or 2 days or even longer. The previously described approach to management is a general guideline to patients with hypoglycemia. Regardless of the cause of the hypoglycemia, patients should be frequently observed for signs of neuroglycopenia, bedside glucose checks should be performed every 1 to 2 hours at a minimum, and serum electrolyte levels should be monitored every 4 hours. Some patients may also require specific antidotal therapy, as described later. Glucagon may also be administered by the subcutaneous, intramuscular, or IV route to stimulate hepatic glycogenolysis. Glucagon is most beneficial if it is given soon after the onset of hypoglycemic coma and to treat hypoglycemia in type 1 DM. Glucagon is less effective in patients with type 2 DM because it causes the release of insulin. These patients are also likely to already have depleted glycogen stores, thus limiting the efficacy of glucagon. Furthermore, glucagon administration may cause nausea and vomiting, which impair the ability to give oral carbohydrate therapy. Hypertonic IV dextrose is therefore the preferred initial therapy in the setting of acute hypoglycemia.

In patients with sulfonylurea-induced hypoglycemia, the same supportive measures as previously described are initially implemented. Occasionally, prolonged hypoglycemia may occur after a sulfonylurea overdose, especially with the long-acting agents. Antidotal therapy with octreotide should be considered in such refractory cases. A synthetic somatostatin analogue, octreotide inhibits the secretion of several neuropeptides, including insulin, and it is used clinically to suppress excessive growth hormone secretion, inhibit thyrotropin-secreting pituitary adenomas, and treat certain gastrointestinal and pancreatic neuroendocrine tumors (e.g., carcinoid insulomas).

Previously, the antihypertensive diazoxide was the recommended agent of choice for refractory hypoglycemia resulting from a sulfonylurea because of its ability to inhibit insulin secretion by opening adenosine triphosphate (ATP)–sensitive potassium (KATP) channels in pancreatic beta-islet cells. Although the use of octreotide for sulfonylurea-induced hypoglycemia is “off label” (i.e., the agent has not been approved by the U.S. Food and Drug Administration for this purpose), multiple case reports and research document its efficacy and safety. On the contrary, diazoxide has been shown to be less effective and has several undesirable properties. Diazoxide is usually administered by IV infusion, and its efficacy is limited in these situations because of associated hypotension, tachycardia, nausea, and vomiting. Adverse effects associated with octreotide are minimally significant; they include pain at the injection site, nausea, bloating, flatulence, diarrhea, and constipation. For these reasons, octreotide has supplanted diazoxide as the treatment of choice for sulfonylurea-induced hypoglycemia.

Octreotide has an IV half-life of 72 minutes, but when administered subcutaneously, it appears to be effective for approximately 6 hours. Consequently, a reasonable dosing scheme for most sulfonylurea agents would be 50 mcg subcutaneously every 8 to 12 hours (one noted textbook recommends every 6 hours) for at least 24 hours. After the octreotide is discontinued, an observation period for repetition of hypoglycemia is warranted for a minimum of 12 to 24 hours.

### TIPS AND TRICKS

- Ill-appearing patients may have sepsis, chronic liver or renal failure, endocrinopathy resulting in deficiencies of cortisol or thyroid hormone, or acute-on-chronic alcohol abuse superimposed on chronic liver disease, with or without a state of chronic malnutrition.
- Hypoglycemia should be presumed to be present in all patients presenting to the emergency department with altered mental or psychiatric status, and hypoglycemia should be expeditiously excluded by rapid bedside glucose testing.
- For overdose with longer-acting insulins and the sulfonylureas, intensive therapy may be necessary for 1 or 2 days or even longer.
- Although the use of octreotide for sulfonylurea-induced hypoglycemia is “off label,” multiple case reports and research document its efficacy and safety. On the contrary, diazoxide has been shown to be less effective and has several undesirable properties.

### FOLLOW-UP, NEXT STEPS IN CARE, AND PATIENT EDUCATION

The decision to admit patients after an episode of hypoglycemia is multifactorial and in all cases depends on the cause.
Patients with systemic conditions, such as sepsis, hepatic or renal failure, drug-induced hypoglycemia, hypoglycemia of unknown origin, and persistent neurologic signs and symptoms, usually require admission. Patients who present with overdoses (unintentional or intentional) of insulin, sulfonylureas, and meglitinides need inpatient observation because of the unpredictable kinetics of these agents in this setting. For patients with DM in whom hypoglycemia develops despite therapeutic dosing and without a history of an overdose, admission depends on the expected duration of effect of the drugs, the severity and recurrence of hypoglycemia, and other possible toxic effects. Because most commonly used sulfonylureas have a duration of effect of at least 24 hours, admission is warranted even for a single episode of hypoglycemia, even though in theory it may be possible to observe these patients closely at home. Discharge is possible for patients with hypoglycemia if the likelihood of recurrence is minimal or the patient has a simple explanation for the episode of hypoglycemia (e.g., a missed meal). In patients who do not require any treatment with glucose, observation for 8 hours may be considered. In all patients with hypoglycemia, the emergency physician should err on the side of caution and exercise good clinical judgment when deciding on disposition.

Patients who are discharged home from the ED must be educated on frequent home glucose monitoring, and they should be instructed to obtain rapid follow-up with their primary care physician. Educating patients on warning signs and symptoms of hypoglycemia is crucial to prevent severe episodes from recurring.

Complications associated with hypoglycemia may be severe and include death. Myocardial infarction, cardiac dysrhythmias (e.g., QT prolongation, increased QT dispersion, ectopy, sudden bradycardia) and seizures may all occur. In the long term, neuroglycopenia may cause neurologic dysfunction and subsequent irreversible brain injury in patients with profound and prolonged hypoglycemia. Even in mild cases of hypoglycemia, long-term neurologic dysfunction may occur.

The prognosis of most patients with drug-induced hypoglycemia should be good, provided the diagnosis is promptly made and immediate therapy is instituted. The major pitfall in the treatment of hypoglycemia is usually the failure to make the diagnosis, by attributing the patient’s symptoms to some other condition (e.g., stroke, acute psychosis). Other pitfalls include failure to perform frequent glucose checks and underestimation of the pharmacokinetics or toxicokinetics of the specific agent involved. Consultation with the regional poison control center or with a local medical toxicologist may be of assistance in the management of these cases.

**SUGGESTED READINGS**


**REFERENCES**

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES