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Sulfonylureas: Toxicity and Management

By Nena Bowman, PharmD; Breanna Garcia, PharmD; and Kaitlyn Brown, PharmD

INTRODUCTION

Sulfonylureas are a class of oral diabetic medications recommended as an adjunctive therapy to metformin to improve glycemic control in patients with type 2 diabetes.[1] Sulfonylureas lower HbgA1c by 1-2% and decrease overall blood glucose by 50-60 mg/dL when taken therapeutically. They are a commonly used class of diabetic medication and are found in many American homes. The National Poison Data System (NPDS) reports 3,827 exposures to sulfonylureas reported to poison centers in the US in 2014, with 477 cases having moderate to major effects and two cases resulting in death.[2] This article will briefly describe the mechanism of action, clinical presentation, toxicity, and management of sulfonylurea exposure.

Mechanism of Action and Clinical Effects

Sulfonylureas primarily work by binding to sulfonylurea receptors in the pancreatic β-cell plasma membrane, closing K_{ATP} channels and stimulating insulin secretion.[3]

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Due to this increase in insulin secretion, hypoglycemia (defined as blood glucose (BG) of less than 60 mg/dL) is the adverse effect of greatest concern with this class of medications. Hypoglycemia may occur with therapeutic use, misuse, or overdose. Signs of hypoglycemia include confusion, difficulty speaking, tremors, dizziness, and sweating. If not recognized and treated promptly, symptoms can progress to lethargy, coma, and seizures in severe scenarios. Sulfonylureas have a greater risk of hypoglycemia compared with other oral diabetic agents.[4] Patients at risk for hypoglycemia following small doses of sulfonylureas include non-diabetic patients, treatment naïve patients, children, and patients with reduced renal function.[5]

Toxicity

Sulfonylureas have a narrow therapeutic margin and are listed as one of the "one pill can kill" substances that are deadly to children in small doses.[7] Most accidental pediatric ingestions require management in a healthcare facility. Sulfonylureas typically have a long duration of action and therefore may produce hypoglycemia for an extended period of time.

Pharmacokinetics

	Glipizide	Glipizide XL	Glyburide	Glimepiride
Therapeutic Dose	2.5-40 mg daily	5-20 mg daily	1.25-20 mg daily	1-8 mg daily
Max Adult Dose	40 mg daily*	20 mg daily*	20 mg daily*	8 mg daily*
Half-life	7 hours	7 hours	10 hours	5-9 hours
Duration	16-24 hours	24 hours	18-24 hours	24 hours
Active Metabolites	No	No	Yes	Yes
Renal Excretion	3%	3%	36%	63%

*Adult max doses described above vary by age group and renal function.[6]

(cont. on pg. 2)

IN THIS ISSUE

Cyanobacteria and Algal Blooms

By Sherrie Pace, MS, MCHES

Blue-green harmful algal bloom in Utah Lake
Credit: Utah County Health Department

Blue-green algae, also referred to as cyanobacteria, are organisms that use sunlight to fuel activities. When environmental conditions spur rapid overgrowth of algae or cyanobacteria, algal blooms may occur. These blooms are usually visible on the surface of the water, and cyanobacterial toxins may be present in the algae. If toxins are present, it can pose a risk if it is swallowed or touches the skin. Children and pets are at higher risk of exposure to cyanobacterial toxins because they are more likely to swim in and swallow contaminated water and can ingest a large amount of toxin relative to their body size.

While it is uncommon to experience harmful effects from minimal exposure to cyanobacteria, possible minor effects include headache, fever, nausea, muscle weakness, and itching. Nausea or vomiting may begin within 3-5 hours and can last 1-2 days. Skin may be affected from wading or swimming in contaminated water. Effects that are more serious include liver problems and nerve damage, but are very rare. In most cases, no harmful effects occur, especially if there is limited contact with blue-green algae. Over time, the toxins naturally break down in the body.

To prevent exposure to cyanobacteria, limit recreational activities such as waterskiing and swimming in areas of the water where blooms are present, and avoid drinking contaminated water. Don't let dogs play in the water when visible algae appears, since they are at the highest risk of serious or fatal effects. Do not use contaminated water for washing clothes or dishes. Do not boil the water, as this exacerbates the problem by breaking cell walls and releasing toxins into the water. Fish that are caught in the lake must be cleaned very well before consuming, but they do not pose a health risk if cleaned properly. Water supplies filtered by the city or county are unlikely to contain cyanobacteria and is safe for drinking, showering, and washing clothes. Though it naturally dies out over time, cyanobacteria is most prevalent in late summer and early fall, so it is best to be most cautious during those times.

Contact the Utah Poison Control Center if someone is exposed to blue-green algae or if you have questions about cyanobacterial toxins (1-800-222-1222). Additionally, you may report an algal bloom to the local health department so they can alert the public as needed.

Credit: New York State Department of Environmental Conservation

(cont. from pg. 1) **Sulfonylureas**

Hospital Management

The primary goal of treatment is to correct hypoglycemia. Blood glucose should be monitored at bedside every hour for the first three hours, then every four hours if the patient is stable, as hypoglycemia from sulfonylureas may persist despite glucose administration.

The standard treatment of hypoglycemia (BG < 60 mg/dL) is as follows:

1. Asymptomatic: Give food or drink. If demonstrated hypoglycemia occurs, start an IV of D5W for an adult and D5W with ¼ normal saline in pediatrics. Monitor for 12 to 24 hours; if patient remains asymptomatic, they may be discharged.

2. Symptomatic: Administer a glucose bolus of 0.5-1 g/kg IV of D50W in adults and D25W in pediatrics. Goal is BG 100-150 mg/dL.

3. Recurrent hypoglycemia: Administration of dextrose in a patient with a functioning pancreas results in further insulin secretion and rebound hypoglycemia. Octreotide binds to somatostatin-2 receptors on pancreatic β islet cells to block insulin secretion. It is useful in patients with recurrent hypoglycemia to reduce dextrose requirements and correct hypoglycemia. (See the Poison Pearl, "Octreotide and Drug-Induced Hypoglycemia.") Diazoxide was used in the past as adjunctive therapy since it also blocks insulin secretion. However, due to its propensity to cause hypotension, it has largely been replaced by octreotide.

Caution with Dextrose Administration

Caution is recommended with the administration of dextrose greater than 20% in peripheral vasculature lines both in pediatrics and adults. Due to its concentrated nature, infusing dextrose greater than 20% in a peripheral line can cause vessel irritation, extravasation, and necrosis. Central lines are recommended for infusions of glucose greater than 20%.[6]

Summary

Sulfonylureas cause potentially severe hypoglycemia at both therapeutic and supratherapeutic doses. Sulfonylurea-induced hypoglycemia is best managed in the healthcare setting with food and drink by mouth, IV dextrose as needed, and subcutaneous octreotide to quickly and efficiently correct blood sugar.

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Oral Diabetic Medications

By B. Zane Horowitz, MD

In the last few years, dozens of medications, including combination products, have become available for treating type 2 diabetes. Many of these products can cause hypoglycemia as a side effect when taken in excess. With the overwhelming amount of diabetes medications on the market, it can be difficult to keep track of the ones known to cause adverse side effects.

Here is a brief overview of the various classes of ORAL diabetes medications and some names of medications in each class. (Injectable medications will not be discussed in this article.)

Diabetic agents that cause hypoglycemia:

Sulfonylureas: Increase insulin secretion by direct stimulation of the pancreas. Hypoglycemia may be more profound in patients who do NOT have diabetes and have taken someone else's medication.

Second-generation sulfonylureas: Usually cause hypoglycemia for < 24 hours.

- Glipizide (Glucotrol™)
- Glyburide (DiaBeta™, Micronase™, Glynase™)
- Glimepiride (Amaryl™)

Meglitinides: Non-sulfonylureas causing short-acting insulin secretion. These medications act like sulfonylureas, but hypoglycemic events are shorter in duration.

- Nateglinide (Starlix™)
- Repaglinide (Prandin™)

"Flozins" (SGLT2 inhibitors): Decreases glucose reabsorption in the kidney and increases urinary glucose excretion. Adverse effects include hypoglycemia, volume depletion, acute kidney injury, and, in patients concurrently taking digoxin, may result in digoxin toxicity.

- Canagliflozin (Invokana™)
- Dapagliflozin (Forxiga™)
- Empagliflozin (Jardiance™)

"Gliptins" (dipeptidyl peptidase 4 (DPP-4) inhibitor): Inhibit degradation of incretin hormones, resulting in increased insulin release. Hypoglycemia and pancreatitis are possible side effects of these medications.

- Alogliptin (Nesina™)
- Linagliptin (Tradjenta™)
- Saxagliptin (Onglyza™)
- Sitagliptin (Januvia™)

Diabetic agents less likely to cause hypoglycemia:

Metformin: Increases glucose utilization in muscle and adipose tissue and inhibits gluconeogenesis by blocking pyruvate metabolism, but does not usually cause hypoglycemia. However, there is a risk of lactic acidosis with therapeutic doses in patients with renal or hepatic disease. Following intentional overdose, even in patients with normal renal or hepatic function, severe lactic acidosis may develop and could require hemodialysis if lactate is above 15 mg/dL.

"Glitazones" (Thiazolidinediones™): Do not stimulate the release of insulin, but decrease insulin resistance in liver and muscle, thereby enhancing the body's response to insulin. Usually do not result in hypoglycemia.

- Pioglitazone (Actos™)
- Rosiglitazone (Avandia™)

Alpha-Glucosidase Inhibitors: Decrease glucose absorption by slowing digestion of carbohydrates. Do not cause hypoglycemia.

- Acarbose (Precose™)
- Miglitol (Glyset™)

Making identifying medicines likely to cause hypoglycemia more complicated, these agents are often combined with each other:

- ActoPlus Met™ (pioglitazone/metformin)
- Avandamet™ (rosiglitazone/metformin)
- Avandaryl™ (glimepiride/rosiglitazone)
- Duetact™ (glimepiride/pioglitazone)
- Glucovance™ (glyburide/metformin)
- Glyxambi™ (empagliflozin/linagliptin)
- Invokamet™ (canaglifozin/metformin)
- Janumet™ (sitagliptin/metformin)
- Jentadueto™ (linagliptin/metformin)
- Juvisync™ (sitagliptin/simvastatin)
- Kazano™ (alogliptin/metformin)
- Kombiglyze XR™ (saxagliptin/metformin)
- Metaglip™ (glipizide /metformin)
- Oseni™ (alogliptin/pioglitazone)
- PrandiMet™ (repaglinide/metformin)
- Synjardy™ (empagliflozin/metformin)
- Xigduo XR™ (dapaglifozin/metformin)

Octreotide and Drug-Induced Hypoglycemia

Oral Diabetic Medications
By Nena Bowman, PharmD

Drug-induced hypoglycemia can be life-threatening and difficult for healthcare providers to manage. Drugs that cause hypoglycemia include sulfonylureas, like glipizide and glimepiride; meglitinides, like repaglinide and nateglinide; and through a similar mechanism, quinine. Octreotide is a synthetic somatostatin analog that decreases insulin secretion from the pancreas by blocking the calcium channels located on the beta islet cells. It is given subcutaneously or intravenously in doses of 1-1.5 mcg/kg in pediatrics and 50-100 mcg in adults every 6-12 hours as needed for refractory hypoglycemia after a trial of intravenous dextrose.[1] For intravenous administration, it must be diluted in 50 mL of normal saline and administered over 15-30 minutes to prevent infusion reactions and adverse effects. Subcutaneous administration is preferred. Patients administered octreotide to treat a drug-induced hypoglycemia must have a functioning pancreas for octreotide to be effective. Adverse events are uncommon but acutely can include diarrhea and nausea (5-10%), and in chronic use can cause cardiac conduction abnormalities such as QT prolongation and exacerbation of heart failure. When used for hypoglycemia, octreotide is typically very well tolerated with few, if any, side effects.[1,2]

Unintentional ingestions of sulfonylureas by pediatric patients are common. In a retrospective chart review in Pediatric Emergency Care, 93 patients with a median age of two years were admitted after sulfonylurea exposure; approximately 52% of the admitted patients developed severe hypoglycemia.[3] Octreotide was given to 12 patients with persistent hypoglycemia in this study.

Another retrospective chart review in the Annals of Emergency Medicine demonstrated octreotide's utility in refractory hypoglycemia associated with sulfonylurea ingestion. There were 9 patients in this study with a combined total of 29 hypoglycemic episodes requiring the administration of 27 ampules of 50% dextrose before octreotide was administered.[4] Post-administration of octreotide, the combined total of *(cont. on pg. 4)*

(cont. from pg. 3) **Octreotide**

hypoglycemic episodes was 2, which required the administration of 2 additional ampules of 50% dextrose.[4]

Octreotide has great utility as an adjunct to dextrose in patients with drug-induced hypoglycemia. With its relatively benign adverse effect profile and ease of administration, it should be considered in patients exposed to drugs that cause hypoglycemia, especially sulfonylureas and meglitinides, after their first hypoglycemic event.

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MEET THE UPCC STAFF

Devin Stock, PharmD

began working at the poison control center in December of 2014. He received his pharmacy degree from the University of Utah College of Pharmacy and did his undergraduate studies at the University of Utah. Devin is a native of Salt Lake City and is excited to be working with the Utah Poison Control Center. He loves learning new things and sharing that knowledge through teaching and his interactions with patients and providers. In his free time, Devin enjoys fly fishing, cycling, photography, and writing and recording music. Devin's current toxicology interest is cardiac medications.

Kaitlyn Brown, PharmD

began working at the poison center as a fellow in training in July of 2015. Kait received her doctorate in pharmacy in 2015 from Wilkes University in Wilkes-Barre, Pennsylvania. She grew up in Utica, New York, and first came to the University of Utah during pharmacy school to complete a summer undergraduate research fellowship in the department of pharmacology and toxicology. In her spare time, Kait enjoys hiking, biking, rock climbing, and taking photographs. Her clinical interests include neurotoxins, drugs of abuse, and natural toxins.

UTAH POISON CONTROL CENTER STAFF

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

POISON Help
1-800-222-1222

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