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The Use of Octreotide in the Management of Sulfonylurea-Induced Hypoglycemia

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INTRODUCTION

The sulfonylurea agents are one of the most common causes of drug-induced hypoglycemia. In 2005, the American Association of Poison Control Centers reported a total of 11,521 poisoning cases involving oral hypoglycemic agents, of which 37% (4,285 cases) were sulfonylurea poisonings. More than one-third of the sulfonylurea poisonings occurred in children less than 6 years old, and 77% of cases were unintentional exposures. There were 3,062 patients treated in a health care facility. Moderate or severe clinical effects occurred in 1036 patients and there were 11 fatalities where a sulfonylurea agent was involved¹

CASE REPORT

A 38 year old, 70 kg female with a history of heroin and methadone abuse ingested four 4-mg glimepiride tablets (16 mg total ingestion) about nine hours previously. The glimepiride was not her own, and she did not have a history of diabetes. Her pulse rate was 40-50 beats per minute and glucose testing was 33 mg/dL in the field. She received 50 mL of D50W intravenously en route to the Emergency Department (ED).

In the ED, the patient was alert with BP 140/80 mmHg and pulse 30-40 beats per minute. She changed her story to twelve 4-mg glimepiride tablets (48 mg total) ingested. She received activated charcoal. Administration of octreotide 50-100 ug subcutaneously was recommended if the patient developed hypoglycemia again. Her blood glucose dropped to 49 mg/dL and 50 mL of D50W was administered intravenously.

During the ensuing 18 hours, the patient's blood glucoses were 50, 28, and 42 and 16 mg/dL despite repeated administrations of 50 mL of D50W IV. Therefore, octreotide 100 ug was administered subcutaneously. Octreotide rapidly and effectively stabilized the blood glucoses: 259, 116 and 143 mg/dL. The patient made a complete recovery.

Moderate to severe effects occurred in 24% of sulfonylurea overdoses reported to U.S. poison centers in 2005.

Octreotide rapidly stabilizes blood glucose levels in sulfonylurea overdoses and decreases the need for supplemental dextrose.

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DISCUSSION

The sulfonylurea agents are divided into two classes: the first generation agents such as chlorpropamide, tolazamide, and tolbutamide, and the second generation agents, glyburide, glipizide, and glimepiride. The second generation agents are more potent and have largely replaced the use of the first generation agents due to their once-daily dosing and improved side effect profile. Sulfonylureas exert their hypoglycemic effect by binding to and inhibiting the adenosine triphosphate (ATP)-dependent potassium channel (K^+_{ATP}) on pancreatic beta cells. Normally, glucose is taken up into the pancreatic beta cells and is metabolized to yield ATP which then binds to the K^+_{ATP} channel and inhibits the channel opening. The inhibition of the K^+_{ATP} channel is therefore, under normal physiologic conditions, dependent on the amount of glucose uptake into the pancreas and hence the amount of glucose in the blood stream. Inhibition of the K^+_{ATP} channel prevents the efflux of K^+ ions, and depolarizes the cell. Cell depolarization triggers the opening of voltage-gated calcium (Ca^{2+}) channels and the influx of Ca^{2+} ions. Ca^{2+} ions activate insulin gene expression via the calcium responsive element binding protein (CREB) and results in the subsequent exocytosis of insulin from the pancreatic beta cells.

Sulfonylurea agents are generally well-absorbed orally, and are highly protein-bound, mostly to albumin. They are metabolized via the liver to active metabolites which are then renally excreted. The onset of action of most of the sulfonylurea agents is within 1 to 3 hours, and the duration of action for the majority of the agents is 12 to 24 hours. At therapeutic doses, glimepiride has 100% bioavailability after oral administration and has an onset of action of 2 to 3 hours. It is more than 99.5% protein-bound, and completely metabolized by the CYP450 2C9 enzyme subtype, to both mildly active and inactive metabolites. It has a half-life ($t_{1/2}$) of about 5 to 9 hours and duration of action of 24 hours.

Common adverse effects, with therapeutic use of the sulfonylurea include hypoglycemia, dizziness, headache, nausea, and weakness. The frequency of hypoglycemia varies from 1% to 2% with glimepiride use, to up to 6% with glyburide and chlorpropamide².

Sulfonylurea overdose results in a hyperinsulinemic state and subsequent hypoglycemia. Hypoglycemia is defined as a serum blood glucose concentration of less than 60 mg/dL with signs and symptoms. In non-diabetic persons, the blood glucose is often much lower before signs and symptoms appear, hence many non-diabetic patients may appear asymptomatic initially. The onset of hypoglycemia with acute overdose usually occurs within eight hours. In chronic overdose, the onset of symptomatic hypoglycemia may be more delayed. The duration of action of these agents in overdose is prolonged and hypoglycemia can persist for days.

The clinical manifestations of sulfonylurea overdose reflect the degree of hypoglycemia and are a result of either neuroglycopenia (the shortage of glucose to the brain) or due to increased counter-regulatory hormones. The brain relies almost entirely on glucose as an energy source and so the CNS manifestations of hypoglycemia often predominate. Effects of neuroglycopenia include blurred vision, loss of coordination, fatigue, altered behavior, seizures, coma, and even death. Prolonged neuroglycopenia can cause irreversible CNS damage. The effects of increased catecholamines include tachycardia, hypertension, palpitations, diaphoresis, nausea and anxiety.

Sulfonylurea overdoses are typically managed with the use of activated charcoal to limit drug absorption. Blood glucose measurements should be repeated every one to two hours for the initial 8-12 hours or longer if the product is extended-release. Dextrose supplementation should be initiated to increase blood glucose levels if hypoglycemia ensues (symptoms are present or blood glucose falls below 60 mg/dL). Dextrose solutions are a low cost and effective way of increasing blood glucose levels; however, since the sulfonylureas augment glucose-stimulated insulin release, dextrose supplementation often only increases blood glucose levels transiently, especially in non-diabetic patients. This results in protracted hypoglycemia, and extended dextrose therapy. Other agents that have been used to increase blood glucose levels include glucagon and diazoxide. Glucagon,

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an endogenous hormone, stimulates glucose formation from liver glycogen stores but is of limited value in sulfonylurea overdoses. It has a short duration of action and loses effectiveness as hepatic glycogen stores decrease. In addition, as with dextrose, glucose levels will only be transiently elevated and then decrease following the counter insulin production³. Diazoxide opens the K^+_{ATP} channels to inhibit insulin release. Its primary indication is for the treatment of hypertensive crisis, and its use in managing sulfonylurea-induced hypoglycemia is largely limited by its tendency to cause hypotension, tachycardia, dizziness, nausea and vomiting⁴.

Octreotide (Sandostatin[®]), a synthetic analog of the endogenous hormone somatostatin, has been shown largely through case reports and retrospective studies to be safe and effective in the management of sulfonylurea overdoses. Somatostatin (and octreotide) inhibits insulin release by binding to the somatostatin G-protein coupled receptor (GPCR) on pancreatic beta cells. The receptor is attached to the voltage-gated Ca^{2+} ion channels via the G-protein. Activation of the GPCR inhibits the opening of the Ca^{2+} channels and insulin release⁴. Octreotide is more potent than somatostatin and has a longer duration of action of 6 to 8 hours on average⁵. Some sources recommend the use of octreotide in patients requiring more than one dextrose bolus or a dextrose infusion to maintain euglycemia^{3,6}. Octreotide dosing is 40-100 ug in adults subcutaneously every 6 to 12 hours, and 1 ug/kg in children every 8 hours^{4,5}. Octreotide may be given intravenously; however, the duration of action is shorter than when given subcutaneously. If the intravenous route is preferred, octreotide should be administered as a continuous infusion. With short-term use, octreotide is generally very well tolerated. Possible adverse effects include nausea, vomiting, and injection site pain.

Boyle et al compared the efficacy of octreotide to that of dextrose infusions and diazoxide in sulfonylurea-induced hyperinsulinemia⁷. In the controlled randomized study, eight healthy non-diabetic subjects received three doses of glipizide (1.45 mg/kg/dose). They developed hypoglycemia, defined as a blood glucose concentration less than 50 mg/dL, within three hours, and each subject was treated with 50% dextrose followed by either a continuous dextrose infusion, octreotide (given 30 ng/kg/min, intravenously), or diazoxide (300 mg, intravenously, every 4 hours). The octreotide and diazoxide groups were also given supplemental dextrose to maintain euglycemia. The results of the study showed that the octreotide group had significantly lower insulin concentrations, required significantly less dextrose, and when octreotide treatment was stopped, the subjects remained euglycemic and did not require any further dextrose. Furthermore, no significant side effects were noted with octreotide therapy. The authors concluded that octreotide was a safe and effective treatment for the management of sulfonylurea-induced hypoglycemia.

McLaughlin reported that patients treated with octreotide had fewer hypoglycemic events, required fewer ampules of dextrose, and had a significantly lower risk of recurrent hypoglycemia⁸. All patients treated with octreotide rapidly achieved stable glucose concentrations and no longer had rebound hypoglycemia.

The previously described glimepiride overdose patient exhibited the type of delayed, profound, prolonged and fluctuating hypoglycemia that is described in the literature. This patient had unstable blood glucose levels for at least 22 hours before octreotide was started. After a single octreotide administration the patient remained euglycemic, and did not require any exogenous dextrose supplementation. This case demonstrates the effectiveness of octreotide in rapidly stabilizing blood glucose levels in sulfonylurea overdoses, decreasing the need for exogenous dextrose and possibly decreasing the length and cost of hospital stay.

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TOXNOTES

A 3 year old child swallowed 6 magnets from a toy a few hours ago and is complaining of stomach pain. Are magnets toxic? Is it safe to discharge him home and watch for the magnets to pass?

Magnets are often swallowed by toddlers and are not poisonous; however, there are several cases of ingestions of small magnets that have resulted in severe complications and death. The magnets can attach to each other, or to an ingested metal object, even across intestinal walls, causing perforations, volvulus (intestinal twisting), bowel resection, ulcerations, peritonitis and magnets embedded in stomach lining. Signs and symptoms may be subtle, leading to delayed diagnosis. An x-ray evaluation should be performed on all patients with a history of ingestion of more than one magnet or a magnet and a metal object. To determine whether an unidentified object is a magnet, a compass may be passed by the abdomen. Endoscopy, surgical removal or watchful observation are treatment options to consider, depending on the presence of clinical effects and location of the magnets.

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National Poison Prevention Week

National Poison Prevention Week is March 18-24, 2007. Many communities are planning events and promotions to help raise awareness about the importance of poison prevention. The Maryland Poison Center, however, considers every week Poison Prevention Week! Educational materials such as brochures, magnets, Mr. Yuk stickers and videos are available year-round. Check our website, www.mdpoison.com, for more information, or call Angel Bivens at 410-563-5584.