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Extended-release glipizide overdose presenting with delayed hypoglycemia and treated with subcutaneous octreotide

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Abstract

The onset of symptomatic hypoglycemia in children with ingestions of second-generation sulfonylureas has never been documented to be later than 21 hours post-ingestion. We report a case with the longest known interval, 45 hours, between ingestion of a sulfonylurea and the onset of hypoglycemia requiring medical intervention. The hypoglycemia was severe and required multiple dextrose boluses in addition to continuous dextrose infusion for 36 hours. This patient was also treated with multiple doses of subcutaneous octreotide because of persistent hypoglycemia despite the above management. This case represents the first report of subcutaneous octreotide used as a treatment for pediatric hypoglycemia secondary to sulfonylurea exposure.

Keywords

Sulfonylurea; hypoglycemia; octreotide

Introduction

The prevalence of Type 2 diabetes mellitus is increasing in both children and adults (1, 2), and there has been a commensurate increase in pediatric exposures to oral hypoglycemic agents. The Toxic Exposure Surveillance System of the American Association of Poison Control Centers reported nearly a tripling in unintended oral hypoglycemic exposures in children less than 6 years from 1990 to 2001 (3, 4). The sulfonylureas accounted for 56% of these exposures in 2001 (4), and there is a debate as to the duration of time required to monitor such exposures in the hospital.

We report here a case of a 6 year-old girl with confirmed ingestion of an extended-release formulation of glipizide, who presented with hypoglycemia approximately 45 hours post-exposure. The case is also remarkable because of the severity and persistence of hypoglycemia, which lasted 30 hours after the child was brought to medical attention. This patient was treated with subcutaneous octreotide, which has been shown in a number of adult studies to be efficacious for treating hypoglycemia induced by sulfonylureas, but has not been previously used in children for this indication.

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Patient Report

A previously healthy 28.4 kg 6 year-old girl was thought to be sleeping in class, but she could not be roused when her teacher tried to wake her. The emergency medical service (EMS) documented a blood glucose concentration of 20mg/dl. The child was given glucagon and taken to the emergency department (ED), where she was noted to be “sleepy” but otherwise asymptomatic. Her vital signs were: BP, 136/75 mmHg; pulse, 120 beats/min; respiratory rate, 22 breaths/min; and temperature, 36.6°C. Her finger-stick blood glucose (FSBG) upon arrival to the ED was 42mg/dl.

Her parents stated that approximately 45 hours earlier she had ingested one of her grandmother’s 10 mg extended-release glipizide pills, which the patient was told were ‘sugar pills’. On the following day, she was slightly more fatigued than usual with a headache, but was not symptomatic enough to require medical attention. On the day of her presentation to the hospital, she had skipped breakfast.

While in the ED, she required three doses of 25% dextrose despite eating and the continuous intravenous administration of 12.5% dextrose providing a glucose infusion rate (GIR) of 9.8 mg/kg/min. Despite her recurrent hypoglycemia, she remained asymptomatic other than being “sleepy.” She was transferred to our institution, where she continued to receive 12.5% dextrose at a GIR of 9.8 mg/kg/min. Octreotide 25 mcg (0.9 mcg/kg) subcutaneously every 6 hours was started within 3 hours after her transfer in an effort to decrease her intravenous glucose requirements and stabilize the blood glucose concentrations. Indeed, her GIR was weaned to 4.8 mg/kg/min after the first dose. However, her FSBGs continued to fluctuate despite repeat doses of octreotide, and she required two additional 0.5 g/kg boluses of 50% dextrose approximately 68 and 71 hours after ingestion. With the above combined octreotide and intravenous glucose therapy, hypoglycemia resolved approximately 22 hours after admission to our hospital. Her intravenous fluids were discontinued 9 hours later. Overall, she received four 25-mcg doses of octreotide over 24 hours, with the first 3 doses spaced six hours apart and the fourth dose given twelve hours after the third dose. The last dose was given to facilitate weaning off dextrose administration. She had no adverse affects to the octreotide. A graphical depiction of her hospital course can be seen in Figure 1, which is remarkable for hypoglycemia persisting up to 70 hours after her ingestion of glipizide.

Her laboratory evaluation that was obtained on admission to our institution confirmed sulfonylurea poisoning (Table 1). These results are remarkable for elevated concentrations of endogenous insulin, c-peptide, and proinsulin in the presence of hypoglycemia and an elevated glipizide level of 1000 ng/mL. Mean plasma glipizide concentrations 24 h after ingestion of 10 mg of Glucotrol XL are 158 ± 20 ng/mL in adults with type 2 diabetes mellitus (10).

Discussion

This case demonstrates that ingestion of an extended-release formulation of glipizide can cause hypoglycemia presenting almost 48 hours after ingestion. This patient had particularly severe hypoglycemia, as demonstrated by her initial presentation, the number of dextrose boluses she required, and by the duration of her hypoglycemia. This case is also notable in that a glipizide level was performed, which demonstrates that glipizide in an extended-release formulation can persist in a child at elevated levels for up to 56 hours after an ingestion.

A prospective multi-center study of 185 children 12 years old exposed to sulfonylureas between September 1994 and August 1995 concluded that the absence of a blood glucose <60 mg/dL in the first 8 hours after ingestion is predictive of a benign outcome (5). Another

study of 93 children 16 years old whose sulfonylurea ingestions were reported to a single regional poison control center revealed that the time of onset of hypoglycemia from ingestion ranged from 0.5 to 16 hours (6). This study, in contrast, concluded that children ingesting sulfonylureas should be observed for 24 hours in an inpatient setting. Additional case reports supporting observation beyond 8 hours include a report of a 3 year-old with symptoms 24 hours after ingestion of an unknown dose of chlorpropamide (7) and a report of a 1 year-old with the onset of hypoglycemia 21 hours after the ingestion of 30 mg of glyburide (8). In the only previously documented case of a pediatric exposure to an extended-release formulation of glipizide, the onset of symptoms was four hours post-exposure, and the hypoglycemia was controlled with intravenous and oral dextrose within five hours of exposure (9). All of the aforementioned studies, of note, do not report serum sulfonylurea levels to confirm the ingestions.

The recommended initial management of patients with sulfonylurea ingestion includes administration of activated charcoal and/or whole-bowel irrigation (11), but neither was utilized for this patient. Neither charcoal nor whole-bowel irrigation was indicated in this patient due to the long time interval since the suspected ingestion. Her initial treatment with glucagon by the EMS was appropriate for her initial presentation with hypoglycemia of unknown etiology. However, glucagon is not the ideal antidote for a known sulfonylurea ingestion, as glucagon further stimulates endogenous insulin secretion (12). Glucose administration, either oral or intravenous, is the recommended treatment for sulfonylurea-induced hypoglycemia, but this was insufficient to treat this patient's hypoglycemia. Specifically, a higher GIR could not be achieved for this patient without either obtaining central access to allow for higher glucose concentrations than 12.5% or increasing her fluid administration to more than twice maintenance. Therefore, this patient received subcutaneous octreotide, which allowed for a reduction in her GIR (see Fig. 1).

One notable aspect of this case in this patient's extraordinarily high serum glipizide level. Although the parents reported only one pill was ingested, it is reasonable to speculate that the child may have taken more than one pill. This is potentially substantiated by her serum glipizide level of 1,000 ng/ml; a study in adults with type 2 diabetes mellitus found a plasma glipizide concentration 24 hours after ingestion of 10 mg of extended-release glipizide to be 158 ± 20 ng/ml (10).

Nevertheless, this case represents the first pediatric report of *subcutaneous* octreotide, a drug that inhibits insulin secretion, as a treatment for hypoglycemia due to unintentional exposure to a sulfonylurea. In a single previous report, a persistently hypoglycemic 20 kg 5 year-old who accidentally received glipizide 7.5 mg twice daily for 3 days instead of his prescribed medicine for attention deficit disorder was successfully treated with a single *intravenous* 25 mcg (1.25 mcg/kg) dose of octreotide (13). In children, subcutaneous octreotide is primarily used in the treatment of congenital hyperinsulinemic hypoglycemia, with doses ranging from 2 to 10 μ g/kg/day divided into three to four doses (14). Therefore, the dose used in our case, 3.5 μ g/kg/day, is within the range used for other pediatric patients with hypoglycemia.

Subcutaneous octreotide has been reported as a treatment for sulfonylurea overdose in adults. In a retrospective study of nine adults (15), patients received between 40 to 100 μ g subcutaneously for their initial dose, and all patients had improvement of their hypoglycemia. Although two of the nine patients experienced one episode of hypoglycemia after completing courses of octreotide ranging from one to four doses, all of the patients were discharged from the hospital without apparent neurological sequelae. None of the patients experienced side effects or adverse events resulting from octreotide administration. In addition, in 6 case reports involving a total of 7 adults (16–21), 50 or 100 μ g doses of subcutaneous octreotide were successful in treating hypoglycemia. Three of these patients

required one dose, three required three doses, and one required four doses of octreotide to prevent recurrence of their hypoglycemia. Six of the seven patients recovered completely without adverse events; the one patient who died had resolution of his hypoglycemia after one dose of octreotide but had irreversible post-hypoglycemic encephalopathy.

As the number of adults with type 2 diabetes mellitus is expected to increase (2), and the number of pediatric sulfonylurea exposures has tripled from 1990 to 2001 (3, 4), it is reasonable to assume that the number of pediatric exposures to sulfonylureas will continue to rise. This case highlights the variability in presentation, severity and duration of hypoglycemia after sulfonurea ingestion. Given the potential for such a severe presentation, we recommend careful observation of all children who ingest an extended-release formulation of a sulfonylurea. Furthermore, this case demonstrates that subcutaneous octreotide can be a useful adjunct in the management of sulfonylurea-induced hypoglycemia in children.

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Figure 1.

This represents the fingerstick blood glucoses (FSBG, black line) and the glucose infusion rate (GIR, red line) plotted against the hours post-ingestion. The GIR only reflects the continuous intravenous fluids administered. Dextrose boluses are presented separately; arrows below the graph denote when the glucagon and intravenous dextrose boluses were administered. The blue arrows above the graph indicate when octreotide (0.9 mcg/kg) was given.

Table 1

Laboratory values upon presentation and admission to our institution

Test	Outside Institution (estimated 51 hours post-ingestion)	Our Institution (estimated 57 hours post-ingestion)
C-peptide	10.1 ng/mL (0.8 – 3.1 ng/mL)	8.8 ng/mL (1.1 – 4.6 ng/mL)
Glipizide *	Not performed	1000 ng/mL (elevated)
Insulin	121 uIU/mL (<17)	112 uIU/mL (0 – 15.6 uIU/mL)
Proinsulin	Sample hemolyzed	366 pmol/L (2.1–26.8 pmol/L)
Serum Glucose	44 mg/dL (60–100)	33 mg/dL

* Mean plasma glipizide concentrations 24 h after 10 mg of Glucotrol XL are 158 ± 20 ng/mL in adults with Type 2 diabetes (Simonson et al).