

# SULFONYLUREA INTOXICATION AT A TERTIARY CARE PAEDIATRIC HOSPITAL

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## ABSTRACT

### Background

Unintentional poisoning with sulfonylurea hypoglycaemic drugs is a serious danger to infants and children, as the ingestion of relatively small amounts can be fatal. Although the administration of octreotide is considered effective in patients that remain hypoglycaemic despite glucose administration, experience in children is limited.

### Methods

A retrospective chart review of the clinical features of all children following sulfonylurea ingestion presenting between April 2001 and November 2008 at the Hospital for Sick Children in Toronto.

### Results

Ten children were identified with sulfonylurea exposure; six were classified as suspected ingestion and four had confirmed signs of sulfonylurea overdoses (mean age: 8.2 years; range 1.5 – 15). All four patients with confirmed ingestion were exposed to glyburide and developed severe hypoglycaemia; two were toddlers and two teenagers. Ingestion was accidental in the case of the toddlers, and suicidal attempts in the case of the adolescents. All patients were initially treated with glucose infusions. Both toddlers also received octreotide with favourable response and no rebound hypoglycaemia. The two teenagers were treated only with prolonged glucose infusions; in both cases rebound hypoglycaemia and increased glucose requirements were observed.

### Discussion

Glyburide-induced hypoglycaemia was pronounced in all patients identified. Treatment with octreotide proved effective in the 2 infants treated, agreeing with the limited experience reported to date in the literature, and suggesting that octreotide should be considered the treatment of choice in children.

**Key Words:** *Sulfonylurea, glyburide, chlorpropamide, poisoning, toxicity, children*

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Sulfonylureas are oral hypoglycaemic drugs, commonly prescribed for type II diabetes mellitus in adults and adolescents.<sup>1</sup> Their main mechanism of action is stimulating the release of insulin from the pancreas.<sup>2</sup> They act by reducing potassium conductance of ATP-dependent potassium channels and stimulating the depolarization of pancreatic beta-cells, leading to insulin secretion through exocytosis.<sup>3</sup>

Sulfonylureas also inhibit hepatic clearance of insulin.<sup>4</sup>

Gastrointestinal absorption of sulfonylureas is rapid. Appearing in blood within 15 minutes of ingestion and exhibiting a prolonged duration of action, especially with the extended-release preparations.<sup>5</sup> Sulfonylureas are mostly metabolized in the liver to metabolites that are renally excreted.<sup>6</sup> Peak plasma concentration of

the second generation sulfonylureas occurs within 2 to 4 hours after therapeutic doses<sup>7</sup>, which coincides with the onset of hypoglycaemia. Yet, paediatric case reports have described later onset of hypoglycaemia, up to 11 hours after ingestion.<sup>8</sup> The duration of hypoglycaemia may be significantly prolonged in overdoses, and can last up to 72 hours.<sup>9</sup> This may be life-threatening if overlooked in children, such as when the patient is discharged prematurely.<sup>10</sup>

Persistent hypoglycaemia after sulfonylurea overdose despite repeated or continuous glucose administration was typically treated with glucagon or diazoxide; however, these drugs are associated with several shortcomings including further stimulation of insulin release and rebound hypoglycaemia<sup>11</sup>, as well as electrolyte imbalances and hypotension (diazoxide)<sup>12</sup>, and gastrointestinal adverse effects (glucagon).<sup>13</sup>

A useful alternative to these drugs is the long-acting somatostatin receptor agonist octreotide, now considered the treatment of choice for dextrose-refractory hypoglycaemia in sulfonylurea poisoning in adults.<sup>14</sup> Treatment with octreotide results in marked decrease of insulin secretion<sup>14</sup>, reducing the requirement for intravenous dextrose. Its safety profile is excellent and no major adverse effects have been described to date.<sup>15</sup>

Little information is available in the literature regarding octreotide use in children exposed to sulfonylureas. We present a review of the clinical and laboratory features of children presenting with sulfonylurea intoxication at our institution, describe the treatments given and compare our experience with the published literature.

## MATERIAL AND METHODS

A retrospective chart review was performed of all patients aged less than 17 years with confirmed or suspected sulfonylurea intoxication seen from April 2001 to November 2008 at the Hospital for Sick Children, Toronto, Ontario, Canada. Charts were retrospectively identified using specific ICD 10 codes T38.3 (“Poisoning by insulin and oral hypoglycaemic drugs -antidiabetic- drugs”) and Y42.3 (“Insulin and oral hypoglycaemic drugs causing adverse effect in therapeutic use”).

Inclusion criteria for the study were the presentation to the emergency department or admission to an inpatient unit or intensive care unit of a paediatric patient with suspected sulfonylurea intoxication. No exclusion criteria, other than age limit, were used.

Data were extracted by two independent investigators from charts using a structured form. Clinical outcomes such as the extent and duration of hypoglycaemia, treatments received, clinical response and outcomes were collected and analyzed. Concomitant medications and other toxic exposures were recorded, as well as specific treatments and antidotes administered. The study was approved by the institutional Research Ethics Board.

## RESULTS

The medical records of 10 patients meeting inclusion criteria were reviewed. The group included five females and five males with ages ranging from 2 to 17 years (Mean 8.6 years). Based on the clinical course, children were classified into one of two categories: Group 1: Patients without clinical symptoms of hypoglycaemia; Group 2: Patients with clinical manifestations of hypoglycaemia.

### Group 1 (suspected sulfonylurea ingestion)

Six patients, with suspected sulfonylurea intoxication, were included in this group. Four had a history of being found by a family member with a bottle of sulfonylurea tablets but ingestion could not be confirmed; the remaining two patients were adolescents who admitted to have ingested a sulfonylurea, together with others drugs, but who developed no clinical manifestations and no hypoglycaemia. Four patients in this group received activated charcoal, and there was no mention in their charts regarding other decontamination procedures such as gastric lavage (Table 1). The most common suspected drug was glyburide (N=4), followed by chlorpropamide (N=2). All patients remained asymptomatic during the observation period, with blood glucose within normal levels and were all discharged home approximately 24 hours after admission.

**TABLE 1** Patients with Suspected Sulfonylurea Ingestion

Patient	Age (year)	Sulfonylurea	Clinical Manifestation	Cause of Ingestion	Charcoal Treatment
1	3	Chlorpropamide	Asymptomatic	Accidental	Yes
2	14	Glyburide	Asymptomatic	Suicidal	No
3	13	Glyburide	Asymptomatic	Suicidal	Yes
4	2	Glyburide	Asymptomatic	Accidental	Yes
5	3	Glyburide	Asymptomatic	Accidental	Yes
6	17	Chlorpropamide	Asymptomatic	Accidental	No

**Group 2 (symptomatic sulfonylurea ingestion)**

Four patients (range 2 – 15 years) were included in this group (Table 2); all were exposed to glyburide, all had clinical manifestations of sulfonylurea intoxication, including severe hypoglycaemia, and all were initially treated with a glucose bolus followed by glucose infusion. Ingestion was accidental in the two toddlers, and

part of a suicidal attempt in the two teenagers. The teenagers were treated with prolonged glucose infusions, but received no octreotide, and in both cases rebound hypoglycaemia and increased glucose requirements were observed. The reasons why octreotide was not administered in these cases could not be located in the charts.

**TABLE 2** Group 2 Patients: Proven Sulfonylurea Ingestion

Patient	Age (year)	Sulfonylurea	Glucose 50%	Octreotide Treatment	Rebound hypoglycaemia
1	2	Glyburide	Yes	Yes	No
2	15	Glyburide	Yes	No	Yes
3	14	Glyburide	Yes	No	Yes
4	1.5	Glyburide	Yes	Yes	No

**Octreotide use in symptomatic patients**

Both toddlers in the symptomatic group received subcutaneous octreotide with favourable response and no rebound hypoglycaemia. The first patient was a two year old boy presenting to the emergency department because of accidental ingestion of glyburide 5 mg (10 tablets). He was drowsy but responded to voice. His glucometer blood glucose was 2.2 mmol/l (40 mg/dl). A 1 ml/kg intravenous bolus of 10 % dextrose was given and infusion of 5 % dextrose at 50ml/h was commenced. He was noted to be irritable with blood glucose of 3.6mmol/l (65 mg/dl). Other vital signs were within normal limits with no abnormal findings on examination. After the patient required two additional glucose boluses, it was decided to administer octreotide (2 microgram/kg) subcutaneously. The blood glucose was 5.7 mmol/l (103 mg/dl) two hours

after administration of the antidote and remained stable for the rest of the observation period with no further symptoms of hypoglycaemia.

The second patient was an 18 month old previously healthy boy found with his grandmother's glyburide pills in his mouth. He rapidly became irritable and thirsty and had a seizure. The emergency medical services team responding to the parents emergency services call administered intravenous 50% dextrose at the patient's home after finding a blood glucose of 1.3mmol/l (24 mg/dl), and transferred the child to a peripheral hospital. The patient had an additional seizure on arrival at the peripheral emergency department and was transferred to our institution. On arrival to our institution he was given 10 % dextrose and two doses of intravenous octreotide 1microgr/kg, six hours apart. Blood glucose level remained over 5 mmol/l after the

first octreotide dose. The patient was discharged home 48 hours later without further complications.

## DISCUSSION

Ingestion of a single 5 mg tablet of glipizide or a 10 mg tablet of glyburide can be potentially lethal for a 10 kg child<sup>16</sup>. We describe 10 patients admitted to our institution for suspected sulfonylurea exposure. Six patients (60%) did not develop any of the signs or symptoms commonly associated to exposure to these drugs, and were considered suspected, but unconfirmed, exposures. We believe that it is unlikely that these patients were exposed to clinically significant amounts of sulfonylurea given the profound hypoglycaemic effects commonly associated with even relatively small doses of these drugs in children. This is the likely explanation for the absence of symptoms in this group, especially the infants, as other cases of infant exposures described in the literature presented with profound hypoglycaemia and sulfonylureas are considered one of the group of drugs where “one pill can kill”<sup>16-17</sup>. Unfortunately, no blood screening for sulfonylureas was available at our institution at the time that these patients presented, so presence of small amounts of the drug in blood cannot be completely ruled out.

Ingestion of oral hypoglycaemic agents places children at greater risk than adults because they are less capable of meeting obligatory glucose demands, and may rapidly become hypoglycaemic.<sup>18</sup> For this reason some studies suggest that the absence of hypoglycaemia within 8 hours of the estimated time of ingestion signals a benign outcome in children.<sup>19-20</sup> However a letter by Szlatenyi described delayed onset of hypoglycaemia in a child after ingestion of one tablet of glypizide<sup>8</sup>, which has prompted recommendations to extend the period of observation to at least 12 hours for a child suspected of ingesting a sulfonylurea, coupled with frequent glucose monitoring.<sup>21</sup>

In the symptomatic patients (Group 2) the adverse effects of oral hypoglycaemic medications were clear, including protracted hypoglycaemia (blood glucose level of < 60 mg/dl = 3.3 mmol/l). Clinical findings included behavioural changes, irritability, and loss of appetite, weakness, seizures

and coma. Although the use of activated charcoal did not appear to prevent or influence hypoglycaemia this may have been due to delayed administration, considering that oral hypoglycaemics are rapidly absorbed from the gastrointestinal tract.<sup>4</sup> Use of oral activated charcoal should still be considered, as it has been shown to be effective in reducing absorption of glipizide and to be effective in patients who present early after sulfonylurea ingestion.<sup>22</sup>

All symptomatic patients in our study ingested glyburide and required multiple doses of hypertonic IV glucose. Two of these patients received octreotide and, as shown in Table 2, their levels of glucose normalized without any further complications and without the need to repeat glucose boluses. Dextrose is a potent stimulus for additional insulin release which is potentiated by sulfonylureas with resultant rebound hypoglycaemia. The prolonged use of hypertonic dextrose infusions may also cause phlebitis necessitating central vascular access, which may cause treatment delays and further morbidity.<sup>23</sup> A particularly useful alternative to these drugs is the long acting somatostatin receptor agonist octreotide, which is now considered the treatment of choice for dextrose-refractory hypoglycaemia in sulfonylurea poisoning.<sup>24</sup> Octreotide, a synthetic peptide analog of somatostatin, binds to somatostatin receptors and inhibits cellular cyclic AMP production and calcium influx through a voltage-gated calcium channel, resulting in pancreatic cell hyper polarization and marked decrease of insulin secretion.<sup>25</sup> Octreotide also decreases hormone secretion in other endocrine glands such as the thyroid, and reduces gastrointestinal motility and splanchnic blood flow which may reduce the absorption of ingested sulfonylureas.

Octreotide-induced decrease in insulin secretion reduces the requirement for intravenous dextrose compared to controls<sup>26</sup>. Its safety profile is excellent<sup>25</sup> with abdominal pain and diarrhoea as common but mild adverse reaction<sup>27</sup>. Paediatric octreotide doses have not been well defined but a subcutaneous or intravenous dose of 1 – 1.25 microgram/kg is usually extrapolated from adults for use in children.<sup>23</sup> We were able to locate only 4 citations describing a total of 5 cases of octreotide use in children with sulfonylurea intoxication and, like our patients, episodes of

hypoglycaemia and the need for bolus doses of dextrose 50% were markedly reduced (see Table 3).<sup>28</sup> The advantages of octreotide use in sulfonylurea intoxication include the prevention of hypoglycaemic relapses despite continuous glucose infusion, reduction in glucose and fluid

requirements, reduction in the need for central venous access for the administration of more concentrated hypertonic glucose solutions and reduction in the need for admission to an intensive care unit. All these advantages are especially important in children.<sup>23</sup>

**TABLE 3** Published Cases of Octreotide Use in Children with Sulfonylurea Poisoning

Investigators	Age (year)	Sulfonylurea	Glucose 50%	Octreotide Treatment	Rebound of hypoglycaemia
Mordel (28)	5	Glypizide	Yes	Yes	No
Kent (27)	1.3	Glyburide	Yes	Yes	No
Rath (23)	2	Glibenclamide	Yes	Yes	No
Rath(23)	1	Glibenclamide	Yes	Yes	No

### CONCLUSIONS

The use of octreotide appears to reduce hypoglycaemia and glucose requirements in sulfonylurea overdose, with no significant toxicities described to date. Clinical experience suggests that octreotide is effective in treating sulfonylurea-induced prolonged or refractory hypoglycaemia in children. These findings require confirmation by larger paediatric studies; but, given the sporadic nature of paediatric sulfonylureas intoxication, it is unlikely that such a study will be performed in the near future. In light of the safety and effectiveness of octreotide in adults and the limited paediatric cases reported to date, we believe that this drug should be considered the treatment of choice for paediatric sulfonylurea intoxication. At the same time, we would urge physicians who apply this treatment in children to report their experiences, in particular adverse reactions potentially associated to octreotide, to help accumulate evidence on this drugs' safety in the paediatric population.

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