Oral Hypoglycemic Agents

Oral hypoglycemic agents have been used for the treatment of Type 2 Diabetes (noninsulin-dependent diabetes mellitus) for decades. Although these drugs have proven very effective in combating the hyperglycemia associated with diabetes, they also have potentially serious side effects; predictably, the most common and crucial of these is hypoglycemia, which essentially amounts to an extreme form of "over-treatment." Hypoglycemia is characterized by a variety of symptoms, such as lethargy, confusion, dizziness, nausea, sweating and hunger. By definition, the glycemic threshold is the serum glucose value below which symptoms of hypoglycemia occur.  

Diabetic individuals may have symptoms of hypoglycemia at a mean of 78 mg/dl, as compared to 53 mg/dl in nondiabetic patients according to one study.

In 2002, oral hypoglycemics were responsible for 9,047 toxic exposures resulting in 4,919 hospital admissions, 222 "major outcomes" and twenty deaths. As with any prescription drug, related exposures included both unintentional cases (primarily in children) and both unintentional and intentional overdoses in adults. Oral hypoglycemics comprise many sub-classes of drugs that have varied mechanisms of action, pharmacokinetics and toxicologic concerns. Each will be discussed below, followed by a brief review of potential treatment modalities.

SULFONYLUREAS

Hypoglycemic effects of sulfonylurides were discovered in the 1940s and lead to the development of sulfonylureas. As insulin secretagogues, these drugs act by binding to ATP-sensitive K+ channels on pancreatic β-cells, which also leads to depolarization. Two different generations of sulfonylureas have been developed, differing slightly from each other in their structures at the R1 and R2 substitutions. However slight the structural differences, the two generations differ dramatically in their potencies: second generation drugs are up to 100 times more potent than their predecessors. The tables below summarize the contrasts between the drugs' key pharmacological factors.

First Generation

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Time to Peak (hr)</th>
<th>Duration of Effect (hr)</th>
<th>T1/2 (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetohexamide</td>
<td>Dymelor</td>
<td>3</td>
<td>12-18</td>
<td>4-6</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>Diabinese</td>
<td>2-7</td>
<td>24-72</td>
<td>36</td>
</tr>
<tr>
<td>Tolazamide</td>
<td>Tolnase</td>
<td>4-6</td>
<td>12-24</td>
<td>4-6</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Omnase</td>
<td>3-4</td>
<td>6-12</td>
<td>3-28</td>
</tr>
</tbody>
</table>

Second Generation

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Time to Peak (hr)</th>
<th>Duration of Effect (hr)</th>
<th>T1/2 (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimpiride</td>
<td>Amaryl</td>
<td>2-3</td>
<td>16-24</td>
<td>5-9</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>Glucotrol (XL)</td>
<td>1-3 (6-12)</td>
<td>12-24 (24+)</td>
<td>7</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Micronase, Glynase, DiaBeta, Glucovance w/Metformin</td>
<td>2-6</td>
<td>12-24</td>
<td>10</td>
</tr>
</tbody>
</table>

Adverse effects of this class predominantly include hypoglycemia, which may progress to coma or death. In one prospective, multicenter study, approximately 30% of all unintentional exposures in children resulted in a blood glucose level of < 60 mg/dL. Notably, 95% (53/56) of these cases manifested hypoglycemic symptoms within the first eight hours.
after exposure. One of the remaining three patients, who had a recorded blood glucose level of 62 mg/dL at three hours, became significantly hypoglycemic at sixteen hours, despite being treated with glucose. The remaining two patients were already hypoglycemic when they presented twelve hours post-ingestion.

With any sulfonylurea ingestion, it is important that the treating physician consider the potential for severe and prolonged hypoglycemia. Knowledge of the ingestant's pharmacokinetics is a key factor in treatment, as it will help the provider judge the potential duration of its effects post-exposure. For example, as all of the second-generation sulfonylureas may have durations of effect up to one whole day, any ingestion of one of these drugs mandates admission for serial glucose monitoring for a full twenty-four hour period. When making treatment decisions, it is important to note that hypoglycemia can result even after ingestion of a single oral hypoglycemic pill. Other adverse effects of sulfonylureas include disulfiram-like EtOH effects in 10-15% of patients, and hyponatremia in approximately 5% of patients. Both are predominantly associated with chlorpropamide.

BIGUANIDES

Although guanidine was discovered in the 1920's, it proved to be too toxic for use and was overshadowed by the development of insulin for the treatment of diabetes mellitus. It wasn't until the 1950's that its metabolites, the biguanides, were discovered as a treatment alternative. The two main drugs in this class, metformin and phenformin, act by increasing insulin sensitivity in patients rather than by acting as direct secretagogues. Although phenformin is no longer available in the United States due to its toxic side effect profile, it is still available in Canada and Europe. Therefore, related ingestions may be seen here in immigrant populations, or in patients who buy their medications internationally.

Notably, hypoglycemia is not a major concern with biguanide-only ingestions. However metformin is also used in combination with glyburide (Glucovance®), and in those cases has been known to cause hypoglycemia. The major adverse effect of this class of drugs is lactic acidosis, at the level of 0.03/1000 pt-yrs for metformin, and 0.64/1000 pt-yrs for phenformin. In keeping with the drug's more toxic profile, phenformin induced lactic acidosis occurs at approximately twenty times the rate of incidence than occurs with metformin ingestions. Such acidosis usually occurs in the setting of renal failure. However, dialysis is not an option to treat biguanide toxicity as these drugs have large volumes of distribution and are eliminated by tubular secretion, not glomerular filtration.

α-GLUCOSIDASE INHIBITORS

The drugs in this class, including acarbose and miglitol, act by decreasing glucose absorption and delaying digestion. Their chief adverse effects include dose-related abdominal pain, cramping and flatulence. Hypoglycemia, however, is not seen when an α-glucosidase inhibitor is the only ingestant.

THIAZOLIDINEDIONES

Similar to the biguanides, the thiazolidinediones act by increasing insulin sensitivity. Pioglitazone (Actos®) and rosiglitazone (Avandia®) are the two available preparations in the United States. As with the biguanides, hypoglycemia is not generally a concern, since counter-regulatory mechanisms can still maintain glucose homeostasis. However, there have been reports of hepatotoxicity and myopathy in patients treated with thiazolidinediones. In fact, the drug troglitazone (Rezulin®) was withdrawn in 2000, after being introduced in 1997, due to the incidence of severe liver failure in those individuals on troglitazone therapy.

MEGLITINIDES

Repaglinide (Prandin) and Nateglinide (Starlix) are the two available drugs in this class. Although both have similar mechanisms of action, they are not structurally related. Repaglinide is a benzoic acid derivative that acts by increasing insulin production. The first associated case report of hypoglycemia was published in Feb 2001. Nateglinide is a phenylalanine derivative that also acts as an insulin secretagogue. Although theoretically there should be a related risk, no case reports of hypoglycemia in patients treated with this drug have been published to date. Presumably, since its elimination half-life is 1.4 hours, any such hypoglycemia would be relatively short-lived and may therefore go undetected. Still, it is important to consider that the duration of effect is dose-dependent and may be significantly longer in cases of overdose.

TREATMENT

Any suspected ingestion of a hypoglycemic agent should be taken seriously. Although Spiller's study demonstrated that most cases of hypoglycemia are revealed within eight hours
after ingestion, one must exercise caution as patients often get food or intravenous glucose during that time which may mask the drugs’ effects. Therefore, conservative but careful management includes observing such patients for twenty-four hours, and longer for cases of chlorpropamide ingestion. Treatment of oral hypoglycemic-induced hypoglycemia should be supportive, including the standard ABCs and prompt administration of glucose (PO or IV depending on the patient’s level of consciousness and the presence of IV access). Gut decontamination is helpful, especially in the first hour after ingestion, and activated charcoal is the agent of choice. Treatment with whole bowel irrigation may offer some additional benefit for exposures to extended release preparations, but this has yet to be directly studied.

For severe or refractory hypoglycemia, several adjunctive therapies are available, including: octreotide, diazoxide and glucagon. Octreotide, a somatostatin analogue that antagonizes the release of pancreatic insulin, appeared to be the most advantageous of the three in one study comparing their efficacy in treatment, but no subsequent follow-up research has been performed. However, a known drawback of the drug diazoxide is that as a potent vasodilator it can cause significant hypotension. In contrast, the administration of either octreotide or glucagon is relatively safe, and therefore octreotide, is the antidote of choice. Dosing recommendations for octreotide are as follows: For adults, 50-100 mcg/dose sc/iv q 6-12 hrs pm or 100-125 mcg/hr continuous iv infusion in rare cases where hypoglycemia persisted > 24 hours. In pediatrics, 4-5 mcg/kg/day sc/iv divided q 6 hrs pm. Following blood sugars for at least 12 hours is recommended after octreotide use is discontinued.

CONCLUSIONS
Ingestions of oral hypoglycemics occur regularly as they are a common treatment for Type 2 diabetes. A range of serious sequelae may be seen post-exposure dependent on the class of the ingestant. Lactic acidosis occurs with exposures to the biguanide class, usually in conjunction with underlying renal dysfunction. In addition, one member of the thiazolidinedione class has been withdrawn from the market due to its hepatic toxicity. Most significantly, hypoglycemia may be seen with the sulfonylureas and, rarely in cases of meglitinide class ingestions. Management of exposures will depend on the class of drug ingested, its known pharmokinetics and the patient’s presentation. Octreotide is the antidote of choice for the acutely hypoglycemic patient.

Chad Connor, MD
Written as an MS-4
Harvard Medical School

REFERENCES
3. 2002 AAPCC Annual Report