OctreoTIDE and Sulfonylurea Toxicity: The wave of the Future

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Octreotide: All the Cool Toxicologists Are Using It

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Case Study

- Elderly patient started to stagger while walking in the St. Patty's Day Parade. When EMS arrives and lifts his "I'm Irish what's your excuse" T-shirt, they discover a Diabetic Med-alert necklace.

Key Questions?
- What type of diabetic is he?
- When was the last time he took his meds?
- When was the last time he ate?
- Does he know all the words to the "Wild Rover?"

Sulfonylurea

- **Mechanism of action:**
  - By stimulating endogenous pancreatic insulin secretion
    - $K_{ATP}$ channels
    - High affinity sulfonylurea receptors
  - By enhancing peripheral insulin receptor sensitivity and reducing glycogenolysis
Sulfonylurea: Adverse effects

- Hypoglycemia enhanced by:
  - ↓ Food intake
  - ↑ Age
- Hypothermia
- Disulfiram reactions
- Hyponatremia
  - More common with chlorpropamide

<table>
<thead>
<tr>
<th>Generation</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Time to Peak (hr)</th>
<th>Duration of Action (hr)</th>
</tr>
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<tbody>
<tr>
<td>First</td>
<td>Chlorpropamide</td>
<td>Diabinase</td>
<td>2-7</td>
<td>60</td>
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<tr>
<td>First</td>
<td>Tolbutamide</td>
<td>Orinase</td>
<td>3-4</td>
<td>6-12</td>
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<tr>
<td>Second</td>
<td>Glipizide</td>
<td>Glucatrol XL</td>
<td>6-12</td>
<td>24</td>
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<tr>
<td>Second</td>
<td>Glyburide</td>
<td>Micronase</td>
<td>2-6</td>
<td>12-24</td>
</tr>
<tr>
<td>Third</td>
<td>Glimepiride</td>
<td>Amaryl</td>
<td>2-3</td>
<td>16-24</td>
</tr>
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</table>
Sulfonylurea Toxicity

- Other hypoglycemics
- Sulfonamides
- Propranolol
- Salicylates
- Clofibrate
- Probenecid
- Pentamidine
- Valproic Acid
- Dicumarol
- Cimetidine
- MOA Inhibitors
- Alcohol

Sulfonylurea Toxicity

- Hepatic Insufficiency
- Renal Insufficiency
- Pediatric ingestion of single pill

www.healthsquare.com
Sulfonylurea Toxicity

- **U.S. 2000**
  - 6910 poisonings (2.3:100,000)
  - 36% patients were < 6 yrs old
  - 19% were intentional

**Initial Management**

- **Dextrose**
  - Result in recurrent rebound hypoglycemia
  - Frequent Accu Checks
  - Skin necrosis with IV extravasation
  - Must dilute with saline 3-4:1 for children
Caloric Content 1 Amp D50?

- 50 % = 50 gms in 100 cc
- 50 cc contains 25 gms of dextrose
- Dextrose: 4 calories per gram
- 4 calories x 25 grams = 100 calories in 1 amp of D50

1 Amp D50 Caloric Equivalency

www.snickers.com
www.celacorner.com
Vicious Cycle

Other Potential Treatments?
Glucagon?

- Stimulates glycogenolysis
- Effective only if sufficient stores
- Stimulates insulin secretion
- **NO!**

Diazoxide?

- Used in some case reports
- Open $K_{ATP}$ channels
- Direct inhibitor of insulin release
- Increases hepatic glucose output
- Dose: 300 mg q 4 hrs (over 30 minutes)
- May cause hypotension, hypernatremia
- **POSSIBLE**
Octreotide

- 1982, Synthesized at Sandoz Labs
- Long acting analog of somatostatin
- Treatment for:
  - acromegaly,
  - pituitary adenomas
  - pancreatic islet cell tumors,
  - carcinoid tumors,
  - portal hypertension,
  - esophageal varices,
  - secretory diarrhea

Octreotide

**Mechanism of Action**

[Diagram of Octreotide mechanism of action]
Volunteers received O.D. of glipizide on 3 occasions
- D50 + dextrose infusion
- D50 + octrotide (30 ng/kg/min)
- D50 + diazoxide (300 mg q 4 hr)

# pt’s with hypoglycemic episodes

Frequency of rebound hypoglycemia

Dextrose requirement significantly lower in octreotide group (p<0.0001)

Rebound hypoglycemia occurred in all patients receiving dextrose or diazoxide.

Only 25% in the octreotide group.
McLaughlin SA, et al

- Retrospective study
- 9 pts. Treated with octreotide for sulfonylurea induced hypoglycemia
- Before octreotide treatment
  - # of rebound hypoglycemic events - range 1-6
  - # of amps of D50 given - range 1-7
- Following octreotide treatment (SQ)
  - # of rebound hypoglycemic events -2
  - # of amps of D50 given - 2

McLaughlin SA, et al

- The hypoglycemic episode 14-36 hours post last octreotide dose
- Risk of recurrent hypoglycemia before octreotide was 27 times the risk after octreotide.
- No significant consequences
- No side effects of intervention
Retrospective double blind placebo controlled study

40 pts. received 1 amp D50, oral carbohydrates then randomized to placebo or 75 mcg octreotide SQ (1 dose)

Duration of action around 8 hours, then hypoglycemia can recur

No pt who received octreotide had more than 1 episode of hypoglycemia

Octreotide

Still not FDA approved for treatment of sulfonylurea hypoglycemia

Side effects: N/V/D

Can be given IV or SQ
  - Initial dose: 50 mcg every 6 hours
  - Infusion doses: 100 mcg/hr

Pediatric Dose: 1 mcg/kg

Pregnancy Category B

Onset of effect may be up to 1 hour

End point: 24-48 hours

No effect on metformin or insulin induced hypoglycemia
Summary

- Accu check all patients with mental status change
- 1 amp D50 IV
- Eat large caloric meal. (Ensure via NGT)
- Octreotide 50 mcg SQ every 6 hours
- Continue accu checks
- When in doubt - Admit

Questions?

Happy St. Patrick’s Day!!