Current Treatment Options and New Treatment Investigations

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Goals of Therapy

- **Immediate:**
  - To promptly restore blood glucose to normal range (> 70 mg/dL)

- **Mid-term:**
  - To identify optimal treatment regimens according to type of hyperinsulinism
  - To maintain normal blood glucose levels while encouraging normal feeding/diet
  - Anticipation and prevention are key elements of intervention and management

- **Long-term:**
  - To prevent neurologic damage
  - To promote normal life and development
Treatment of Hypoglycemia: why is it important?

- Inadequate cerebral glucose supply during neonatal period leads to serious long-term neurological impairments:
  - Repeated low glucose in infants is associated with delayed neurological complications [Lucas, BMJ 1988]
  - Range of complications learning disabilities to cerebral palsy and persistent or recurrent seizure disorders, as well as intellectual disabilities of varying degrees
Current Medical Therapies

Diazoxide: *mainstay therapy for HI*

- **How does it work:**
  - Activates the potassium channel via the SUR subunit
  - Not effective in most potassium channel mutations

- **What types of hyperinsulinism can be treated with it:**
  - Hyperinsulinism/hyperammonemia - GDH-HI
  - HNFs hyperinsulinism
  - Glucokinase hyperinsulinism (some cases)
  - SCHAD hyperinsulinism
  - Some dominant $K_{ATP}$ channel mutations
Current Medical Therapies

Diazoxide:

- **Dose:**
  - 5-15 mg/kg/day by mouth
  - Only suspension available in US - capsules

- **Side effects:**
  - Fluid retention (worse in neonates) – use of diuretics
  - Excessive body hair
  - Suppression of appetite
  - Suppression of blood count (less common)
Current Medical Therapies

Octreotide: *second line therapy for HI*

- **How does it work:**
  - Activates potassium channel, affects intracellular translocation of Ca, direct inhibition of insulin secretion
  - Response is good for a couple of days and then wears off

- **What types of hyperinsulinism can be treated with it:**
  - Diazoxide-unresponsive hyperinsulinism
Current Medical Therapies

Octreotide:

- **Dose:**
  - 5-20 mcg/kg/day by subcutaneous injection 2-4 times daily or as continuous intravenous or subcutaneous infusion (pump)

- **Side effects:**
  - Suppression of growth hormone, thyroid hormone or/and cortisol
  - GI side effects: nausea, anorexia, abdominal pain, loose stools, diarrhea
  - Gall stones
  - Necrotizing enterocolitis (1% in a series of 103 children with HI)
Current Medical Therapies

Glucagon:

- **How does it work:**
  - Increases glucose release from the liver

- **Dose:**
  - 1 mg/day continuous intravenous infusion or through subcutaneous pump
  - 1 mg intramuscularly for emergencies

- **Side effects/problems:**
  - Nausea/vomiting
  - Available preparation crystallizes in pump tubing
Enteral Dextrose:

- **How does it work:**
  - Provides continuous supply of glucose

- **Dose:**
  - Dextrose 10-20% up to 10 mg/kg/min continuously through gastrostomy tube

- **Side effects**
  - Vomiting/reflux
  - Suppression of appetite
Diet in the Management of Hyperinsulinism

Diet:

- Frequent high-carbohydrate feedings: formula supplemented with glucose polymer
- Continuous feedings through nasogastric or gastric tube
- Cornstarch: slow-release carbohydrate
- Avoidance of protein-rich meals

Side effects:

- Reflux
- Feeding aversion
Treatment Paradigm

Diagnosis of Hyperinsulinism

Diazoxide Trial: 15 mg/kg/day for 5 days

Mutation Analysis

Diazoxide Responsive

- Blood glucose monitoring at home
- Safety fast once a year

Diazoxide Unresponsive

Octreotide +/- Continuous Enteral Dextrose

18FDOPA PET

Surgery

Cured

Fasting Test

Not Cured
New Therapeutic Options

Long acting Somatostatin Analogs:

- **Octreotide LAR**: long half-life given IM every 4 weeks

  - 10 children (age 1.3-8.5 years) transitioned from 3 SQ injections a day (or continuous) to 1 IM injection every 4 weeks for 6 months (Eur J Ped Endocrinol, 2012)

  - Well tolerated

  - Parent’s questionnaires of general satisfaction were highly positive while children’s QoL evaluation remained unchanged

<table>
<thead>
<tr>
<th></th>
<th>Octreotide</th>
<th>Octreotide + Octreotide LAR</th>
<th>Octreotide LAR</th>
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</thead>
<tbody>
<tr>
<td>Blood glucose &lt; 54 mg/dL</td>
<td>0</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Total measurements of glucose</td>
<td>56</td>
<td>314</td>
<td>812</td>
</tr>
</tbody>
</table>
New Therapeutic Options

Long acting Somatostatin Analogs:

- **Lanreotide (Somatuline Autogel):** long half-life given by deep SQ injection every 4 weeks
  - 2 children age 4 yrs transitioned from short-acting octreotide to once monthly Lanreotide (J Clin Endocrinol Metab, 2011)
  - GOSH series: 8 children (age 3.5-16 yrs) transitioned from octreotide (6) and diazoxide (2) to Lanreotide every 28 days
  - Germany series: 6 children (7 months-4 yrs) mean duration 40.8 months in 3/6 lanreotide raised mean BG and reduced episodes of hypoglycemia
Sirolimus

- mTOR inhibitor
- Constitutive activation of mTOR pathway in hyperinsulinism
- 4 children with diazoxide-unresponsive hyperinsulinism treated with sirolimus
  - 1 with typical diffuse $K_{\text{ATP}}$HI weaned off fluids but required octreotide
  - 3 weaned off all other therapies
- Mechanism unknown
  - $\downarrow$ ß-cell replication vs. $\downarrow$ insulin signaling
- Non-controlled study
- Safety profile in young children unknown: immunosuppression, effect on growth?

Exendin-(9-39)

- Specific antagonist of the GLP-1 receptor
- Impairs glucose tolerance in humans and a variety of animal models \(^{\text{Goke JBC, 1993; Thorens Diabetes, 1993}}\)
- N-terminus truncation of exendin-4 - - Exenatide (Byetta®) approved for type 2DM
- Inhibits insulin secretion and corrects fasting hypoglycemia in mouse model of \(K_{\text{ATP}}\) hyperinsulinism \(^{\text{De León, et al. J Biol Chem, 2008}}\)
Mouse model, subcutaneous infusion exendin-(9-39) for 2 weeks
Suppresses insulin secretion
Corrects fasting hypoglycemia
Exendin-(9-39) inhibits insulin Secretion in $K_{ATP}$ HI Islets

Calabria, Li, Gallagher, Stanley, De León. *Diabetes*, 2012
Pilot Proof-of-Concept

- Pilot study to examine the effect of exendin-(9-39) on fasting blood glucose of subjects with $K_{ATP}$ Hyperinsulinism

**Methods:**

- 9 subjects
- Randomized, open-label, two-period complete crossover
- Fasted subjects received an intravenous infusion of exendin-(9-39) (100, 300 and 500 pmol/kg/min) or vehicle for 6 hours in 2 consecutive days (in random order)
- Primary outcome: Blood glucose levels

www.Clinicaltrials.gov: NCT00571324
## Subject Characteristics

<table>
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<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
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<td>M</td>
<td>S408P*</td>
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<td>F</td>
<td>3992-9 G&gt;A</td>
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*Dominant
Exendin-(9-39) elevates fasting blood glucose

Calabria and De León. Diabetes, 2012
Exendin-(9-39) suppresses plasma insulin

Calabria and De León. *Diabetes*, 2012
Summary/Conclusions

- Medical treatment easy if the hyperinsulinism is diazoxide responsive, more challenging if not responsive

- Treatment decisions should be individualized and well informed
  - Genetics
  - 18-FDOPA PET scan
  - Severity of hyperinsulinism

- Great promise for new therapies in the near future
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