Current Medical Treatment Options for Hyperinsulinism

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Goals of Therapy

- **Immediate:**
  - To promptly restore blood glucose to normal range [>70 mg/dL(>3.9 mmol/L]

- **Mid-term:**
  - To identify optimal treatment regimens according to type of hyperinsulinism
  - To maintain normal blood glucose concentrations 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
Neurodevelopmental Outcomes in Hyperinsulinism

- A significant number of children with hyperinsulinism continue to suffer brain damage
  - Children with focal and transient disease equally affected
- Early identification is important to establish appropriate therapy
- How to improve developmental outcomes:
  - Identification and screening of infants at risk
  - Early diagnosis and treatment with close monitoring of glycemic control
  - Better treatment options

Avatapalle, *Front Endocrinol*, 2013
Current Medical Therapies

Diazoxide: mainstay therapy for HI

Mechanism of action:
- Activates the potassium channel via the SUR1 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
- UCP2 hyperinsulinism
Current Medical Therapies

Diazoxide:

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

- **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

- **Mechanism of action:**
  - Activates potassium channel, affects intracellular translocation of Ca, direct inhibition of insulin secretion
  - Tachyphylaxis is common

- **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
  - Long-acting octreotide available for dosing once monthly

- **Side effects:**
  - Suppression of GH, TSH, ACTH
  - GI side effects
  - Gall bladder pathology (32%*)
  - Transient elevation of LFTs (46.4%*)
  - Thrombosis (2%**)
  - Necrotizing enterocolitis (1%**)  
  
**McMahon, et al. ESPE, 2013 (n=103)
Laje, et al. Ped Diabetes, 2010
**Current Medical Therapies**

**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>
</tr>
</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>
Current Medical Therapies

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

**Glucagon:**

- **Mechanism of action:**
  - 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
  - Necrolytic Migratory Erythema
  - Available preparation crystallizes in pump tubing

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Lado, Givler, De León. PAS, 2015
Current Medical Therapies

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/problems**
  - Vomiting/reflux
  - Suppression of appetite
  - Limits mobility
Treatment of Hyperinsulinism

Surgery:

- Usually required for $K_{\text{ATP}}$-HI
- May be curative for focal $K_{\text{ATP}}$-HI
- Goal is to distinguish between diffuse and focal HI and to localize the focal lesion
Focal vs. Diffuse

Clinical presentation
- Subtle differences: focal vs. diffuse: lower birth weight, later presentation, lower GIR requirement*

Mutation analysis
- Monoallelic recessive $K_{ATP}$ mutation – 97% sensitivity and 90% specificity
- If mutation is paternal – 94% PPV for focal HI**

Imaging
- US, CT, MRI – not useful
- ASVS, THVS: invasive, poor accuracy
- $^{18}$F-DOPA PET: not FDA approved, good sensitivity (85%) and specificity (96%)**. Almost 100% accurate for localization

Surgical Treatment: Outcomes at time of discharge

Focal Hyperinsulinism
- Cured: 94%
- Not Cured: 6%

Diffuse Hyperinsulinism
- Controlled: 36%
- Hypoglycemia: 41%
- Insulin: 23%

Surgical Treatment: Long-Term Outcomes

- Neurodevelopmental deficits
  - 48% reported problems
  - 28% abnormal on formal testing

- Diabetes:
  - Prevalence: 36.4% (42% by age 8, 91% by age 14*)
  - Median age at diagnosis of diabetes: 7.7 years (0.7-43)
  - Current A1c: 7.4 % (6-12.6)

- Exocrine insufficiency:
  - Tested: 20.2%
  - Enzyme replacement: 9.7%

* Beltrand, Diabetes Care, 2012
* Lord, De León, JCEM, 2015
To operate or not to operate

➢ Surgery indicated:
  - Focal HI after lesion has been localized by $^{18}$FDOPA PET
  - Diffuse diazoxide-unresponsive HI if unable to manage medically

➢ Surgery not indicated:
  - “Blind” pancreatectomy for focal HI
  - Diffuse HI that can be managed medically
  - Cases that are likely to be transient: BWS
Diagnosis of HI

5 day trial of Diazoxide

Send genetic testing

Suggests K\textsubscript{ATP} HI

Refer to center with \textsuperscript{18}F-Dopa PET Scan

Diazoxide Responsive

Safety Fast with BS > 70 mg/dL

Diazoxide Unresponsive

Stop Diazoxide. Initiate glucagon infusion 1mg/day if unable to maintain BS > 70 with dextrose IV

Focal

\textsuperscript{18}F-DOPA PET Scan

Diffuse

Limited Resection

Aggressive Medical Therapy with Octreotide + G-tube Dextrose
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

- Experience and multidisciplinary team are essential for success
CHOP Hyperinsulinism Center

- [http://www.chop.edu/service/congenital_hyperinsulinism-center/home.html](http://www.chop.edu/service/congenital_hyperinsulinism-center/home.html)
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