Sirolimus therapy in a infant with congenital hyperinsulinism

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Introduction

- Congenital hyperinsulinism (CHI) due to mutations in ATP sensitive potassium channel (KATP) in the pancreatic beta cells are the most common and the most severe forms of CHI which was usually unresponsive to diazoxide and octreotide.
- Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, is recently suggested as efficient and safe medication as refractory CHI of infants.
- We present an infant with refractory CHI, who responded to Sirolimus

Case presentation

Patient

- A neonate who presented severe hypoglycemia on the first day of birth.
  (Initial serum glucose level <10 mg/dL)
- Gestational age 34-4 weeks, birth weight 2.94kg (>90 percentile)

Critical sample

Postnatal age  | 3 days | 4 days
---|---|---
Glucose (mg/dL) | 29 | 44
Insulin (mIU/mL) | 23.5 | 100.7
Total ketone | 10 | 19
β-hydroxybutyric acid | <4.0 | <4.0
Acetoacetate | - | -
Cortisol (μg/dL) | 10.5 | 5.6
Growth hormone (mg/mL) | 25.77 | 18.41


Initial management

- Intravenous glucose infusion rate: 18-22 mg/kg/min
- Glucose continuous infusion: maximum 5 μg/kg/hr
- High carbohydrate feeding in every 2 hours
- Diazoxide trial for 4 days: maximum 20 μg/kg/day ➜ Ineffective
- Octreotide (Sandostatin®) subcutaneous injection: 40 μg/kg/day, #4

Laparoscopic near total pancreatectomy at the age of 3 months.

Clinical course after near total pancreatectomy

- He presented hypoglycemia 7 hours after operation.
- IV glucose infusion increased and the dose of octreotide was increased to 35 μg/kg/day.

Sirolimus

- At the age of 4 months (1 month after near total pancreatectomy), he started taking Sirolimus 0.2 mg per day.
- The dosage of Sirolimus was increased with monitoring serum Sirolimus levels.
  - Target blood glucose: >60 mg/dL
  - Target serum Sirolimus level: 5-15 ng/mL

Clinical data after initiating Sirolimus

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>119</th>
<th>120</th>
<th>123</th>
<th>128</th>
<th>131</th>
<th>179</th>
<th>193</th>
<th>234</th>
<th>263</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days *</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>9</td>
<td>12</td>
<td>60</td>
<td>74</td>
<td>115</td>
<td>144</td>
</tr>
<tr>
<td>Dose of Sirolimus (mg)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Octreotide (μg/kg/day)</td>
<td>35</td>
<td>35</td>
<td>25</td>
<td>21</td>
<td>12</td>
<td>4</td>
<td>2</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>IV glucose (mg/kg/min)</td>
<td>4.5</td>
<td>4</td>
<td>3.8</td>
<td>1.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Days starting Sirolimus

Fasting test at 10 months old:
- Serum glucose: 82 mg/dL, plasma insulin: 8.5 μIU/mL

Clinical outcome estimated by 12 months old

- Developmental milestone was normal.
- No other side effect of sirolimus such as serious infection, hyperlipidemia, decrease renal function for 8 months.
- Mild aspartate aminotransferase (AST) elevation

Conclusion

- Sirolimus was effective in maintaining blood glucose level stable in CHI patient with KCNJ11 mutation in genetic test and with both focal adenomatous hyperplasia and diffuse form pathology.
- There were no major side effect of sirolimus except mild elevation of AST for 8 months of follow up.

Reference