Old Drug, New Tricks: Diazoxide Use with Continuous Glucose Monitoring in the Management of Glut1 Deficiency Syndrome

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Background

• Standard of care for Glut1 deficiency syndrome (Glut1DS): ketogenic diet (KD), alternative fuel for brain but not preferred energy source
• Treatment options limited if patients fail KD
• Diazoxide: ↓ insulin ➔ ↑ blood glucose ➔ ↑ cerebral glucose ➔ restoration of brain energy metabolism ➔ ↓ seizure activity
• Previous use of diazoxide complicated by hyperglycemia
• Continuous glucose monitoring (CGM): demonstrated benefit in diabetes, congenital hyperinsulinism
• Can CGM enable diazoxide use in KD-resistant Glut1DS?
• CGM: small sensor inserted under skin, measures interstitial glucose every 5 minutes
• Interstitial glucose correlates well w/ blood glucose, can lag if blood glucose changing rapidly

Clinical Case

• 14 yo F w/ Glut1DS (c.398_399delGCinsTT:p.Lys133Phe)
• Failed KD and modified Atkins diet due to severe nausea, vomiting, abdominal pain and hypertriglyceridemia
• Before diazoxide: CSF glucose 36 when blood glucose 93 (ratio 0.39)
• After diazoxide: CSF glucose 55 when blood glucose 118 (ratio 0.47)
• Course complicated by fluid retention and weight gain
  • Fluid retention management: hydrochlorothiazide (thiazide diuretic), amiloride (potassium-sparing diuretic), sodium-restricted diet
• Weight management: ↓ caloric intake, ↓ cornstarch, pairing complex carbohydrates w/ protein, goal interstitial glucose 90-110 mg/dL, treatment threshold <90 mg/dL sustained for 3-4 hours

Learning Points

1. CGM: safe initiation and precise titration of diazoxide
2. Diazoxide addresses neuroglycopenia unlike KD ➔ a new standard of care for Glut1DS?
3. Management of diazoxide-induced fluid retention requires frequent laboratory monitoring for hypokalemia, alkalosis, and renal dysfunction

Timeline: CGM data is reported with average glucose ± SD and diazoxide dose is presented as total daily dose.

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Glucose Levels</th>
<th>Diazoxide Dose</th>
<th>EEG Seizure Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2 months</td>
<td>-</td>
<td>-</td>
<td>84 per 24 h</td>
</tr>
<tr>
<td>3 weeks</td>
<td>92-145 mg/dL (blood)</td>
<td>9.0 mg/kg/day</td>
<td>6 per 24 h (2 day study)</td>
</tr>
<tr>
<td>2 months</td>
<td>124-190 mg/dL (interstitial)</td>
<td>7.3 mg/kg/day</td>
<td>4 per 24 h (3 day study)</td>
</tr>
<tr>
<td>6 months</td>
<td>140-284 mg/dL (interstitial)</td>
<td>7.9 mg/kg/day</td>
<td>0 per 24 h (2 day study)</td>
</tr>
<tr>
<td>8 months</td>
<td>80-201 mg/dL (interstitial)</td>
<td>8.4 mg/kg/day</td>
<td>0 per 24 h (1 day study)</td>
</tr>
</tbody>
</table>

Diazoxide initiation data.

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