METABOLIC SUPPORT AS TREATMENT FOR INTRACTABLE NEONATAL SEIZURES

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Neonatal seizures

- Neonatal seizures occur in 1 to 3 of 1000 term infants\textsuperscript{1,2}
- Differ to later-life seizures in clinical manifestations, aetiologies, treatment, management and outcomes\textsuperscript{2,3}
- Most common cause is hypoxic-ischaemic brain injury\textsuperscript{3,4}
  - Diagnosed in 1 to 2 of 1000 live births
- Diagnosis and prediction can be challenging
- Main risk factor\textsuperscript{2}:
  - Low birth weight
  - Male sex
  - Low gestational age
Neonatal seizures

Pharmacological treatment

• Prompt treatment is considered necessary
  • Untreated seizures may lead to secondary brain injury and are associated with poor neurodevelopmental outcomes\(^4-7\)
• Phenobarbitone remains first-line for most neonatal seizures\(^8-10\)

Phenobarbitone
20 mg/kg IV bolus, repeat if seizures persist after 30 minutes

Midazolam
150 micrograms/kg/dose IV bolus, followed by 1-4 micrograms/kg/min infusion

Levetiracetam
20 mg/kg IV bolus

Figure 1. Local protocol for management of neonatal seizures
Neonatal seizures

Metabolic support drugs

- Infants failing third-line antiepileptics may be trialled on metabolic support medicines in case of congenital vitamin-responsive seizures\(^{11,12}\)
  - Pyridoxine
  - Biotin
  - Folinic acid
  - Pyridoxal-5-phosphate
- 2-4 day lead time for metabolic urine screening
- Currently no specific guidelines and limited data describing treatment of intractable neonatal seizures using metabolic support drugs
Objective

- **Aim:** to describe our experience of the use, administration, tolerance and outcomes of these therapies as a case series.

- Medical records were reviewed for infants admitted to NICU who received metabolic support drugs
  - Between January 2014 to January 2019

- Data collected included demographics, details of pharmacological seizure management, seizure activity, metabolic screening test results, and documentation of suspected adverse effects.
## Clinical Features

<table>
<thead>
<tr>
<th>Case no.</th>
<th>GA</th>
<th>Gender</th>
<th>BW (g)</th>
<th>Mode of delivery</th>
<th>Major co-morbidities</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>Female</td>
<td>2670</td>
<td>V</td>
<td>Hypoxic-ischaemic encephalopathy, multi-organ dysfunction with coagulopathy and hypotension</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>39+1</td>
<td>Male</td>
<td>3200</td>
<td>NVB</td>
<td>Hyperinsulinaemia, hypoglycaemia, secondary brain injury, hyperkalaemia, hyponatraemia, hypocalcaemia</td>
<td>Improved</td>
</tr>
<tr>
<td>3</td>
<td>36+3</td>
<td>Female</td>
<td>2057</td>
<td>CS</td>
<td>Respiratory distress, hypoglycaemia, drug withdrawal secondary to maternal tramadol use</td>
<td>Improved</td>
</tr>
<tr>
<td>4</td>
<td>36+4</td>
<td>Male</td>
<td>2500</td>
<td>CS</td>
<td>Hypoxic-ischaemic encephalopathy, metabolic acidosis, electrolyte disturbances</td>
<td>Death</td>
</tr>
<tr>
<td>5</td>
<td>40+3</td>
<td>Male</td>
<td>3190</td>
<td>CS</td>
<td>Hypoglycaemia, sepsis</td>
<td>Improved</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>Male</td>
<td>3544</td>
<td>F</td>
<td>Respiratory distress, stridor, encephalopathy, metabolic acidosis</td>
<td>Life-long pyroxidine</td>
</tr>
<tr>
<td>7</td>
<td>41+4</td>
<td>Male</td>
<td>3583</td>
<td>V</td>
<td>Hypoxic-ischaemic encephalopathy, respiratory distress, cardiac dysrhythmia, metabolic acidosis, oedema, sepsis</td>
<td>Improved</td>
</tr>
</tbody>
</table>
Case Progress and Outcomes

• All infants received first-line phenobarbitone and second-line midazolam
• Six infants received third-line levetiracetam
• Clonazepam and phenytoin were trialled for one and three infants, respectively
## Case Progress and Outcomes

<table>
<thead>
<tr>
<th>Metabolic support drugs</th>
<th>n</th>
<th>Typical dosing</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyroxidine</td>
<td>7</td>
<td>100mg IV stat</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>50mg orally, twice daily</td>
<td>Oral</td>
</tr>
<tr>
<td>Biotin</td>
<td>3</td>
<td>10mg daily</td>
<td>Oral</td>
</tr>
<tr>
<td>Folinic acid</td>
<td>2</td>
<td>2.5 to 7.5mg daily</td>
<td>Oral</td>
</tr>
<tr>
<td>Pyridoxal-5-phosphate</td>
<td>3</td>
<td>30mg/kg 8-hourly</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Typical dosing of metabolic support drugs administered in neonates (n=7)
Case Progress and Outcomes

- Adverse effects were observed in two infants, with vomiting associated with pyridoxine and pyridoxal-5-phosphate.
- Five infants became seizure-free.
- Two infants died from complications unrelated to seizure activity.
Discussion

• Metabolic support medicines were prescribed in these babies after a trial of conventional treatments as per protocol.

• All babies were started on intravenous pyridoxine.
  • It was not always clear what factors guided choice of subsequent medicines.

• As paediatric formulations are not available commercially, challenges for the pharmacy department included sourcing dosing and formulation information, and administration strategies for nil-by-mouth infants.
  • **Biotin** can be dispersed in water to draw the required dose
  • **Pyridoxal-5-phosphate** can be suspended using Ora-Blend®
  • Generally well tolerated
Conclusion(s)

• In this case series, **biotin, pyridoxine, folinic acid and pyridoxal-5-phosphate** were used safely in neonates for intractable seizures.

• There is variation in practice that can occur with limited published guidance.

• Larger studies are required to further explore treatment choice, dosing, duration, and prophylactic use of these medicines in this patient population.
References

QUESTIONS?

For more information:
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