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Evaluating Use of Higher Dose Oxybutynin in Combination with Desmopressin for Refractory Nocturnal Enuresis

Aaron Berkenwald MS4, Jacqueline Pires MS3, Pamela Ellsworth MD

Background

Nocturnal Enuresis (NE) is a common pediatric condition with an overall prevalence of 15-20% at 5 years of age, with a spontaneous resolution of about 15% per year. 2% of children age 15 still suffer from the condition and limited treatment options exist. Behavioral therapy achieves success in nearly 3/4 of children, but many families prefer medical intervention, especially in older children. Pharmacologic therapies including Desmopressin (DDAVP) or Imipramine are effective in 40-50% of children. However Imipramine has serious safety concerns. DDAVP in combination with a fixed dose anticholinergic has been shown to be useful in individuals who fail DDAVP alone, but still fails to achieve success rates greater than 60%. We hypothesize that by titrating up the dose of Oxybutynin in combination with DDAVP in patients who fail initial monotherapy, we will achieve higher rates of success with limited additional adverse events. We will also record patient demographics, associated symptoms and co-morbidities to determine if we can predict treatment success in patient subgroups.

Methods

IRB approved retrospective analysis of NE patients, ages 7-18 seen at the UMMS Pediatric Urology Clinic from Nov, 2013 – Dec, 2014.

Inclusion Criteria

✓ Diagnosis of Primary Nocturnal Enuresis or Nocturnal Enuresis with Controlled* or resolved Daytime Voiding Symptoms (CDVS)
✓ Treatment with at least 1 dose DDAVP
✓ At least one follow-up visit in clinic *controlled with daytime use anticholinergic

Exclusion Criteria

○ Active daytime incontinence
○ Dysfunctional voiding requiring PT
○ Neurogenic bladder
○ Noncompliance with therapy
○ Failure to attend follow-up

Treatment Overview

- Standard Bladder Education
- Associated Factors and Demographics Documented
- Initial Monotherapy with DDAVP
- Starting Dose 0.2 or 0.4mg DDAVP with 0.2mg increase at 2 week intervals (0.6mg max dose)
- Follow-up prior to beginning combination therapy
- Low Dose Combination Therapy (LDCT) 0.6mg DDAVP + 5mg Oxybutynin IR
- Advanced Dose Combination Therapy (ADCT) Starting Dose 0.6mg DDAVP + 7.5mg Oxybutynin IR with 2.5mg increase in Oxybutynin after 2 weeks without success (10mg max dose)

Primary Objective

To investigate the efficacy of combination therapy (DDAVP + escalating dose Oxybutynin) in children with nocturnal enuresis refractory to maximal dose DDAVP

Secondary Objectives

- Identify risk factors for monotherapy refractory NE
- Identify factors that predict success with combination therapy

Objectives

- BEDDING Alert (Behavioral Therapy) ~75%
- DDAVP ~50%
- Imipramine ~40%
- DDAVP + Fixed Dose Anticholinergic 44-57%

End Points

- Success on any medication was defined as 14 consecutive nights without bed-wetting event
- Telephone contact occurred during the dose titration interval until:
  1. Effective dose had been achieved
  2. Maximal doses of DDAVP and oxybutynin had been tried
- Adverse events were solicited verbally during the phone conversation or in the clinic

Results

Combination Therapy Subgroup Analysis

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>N</th>
<th>LDCT</th>
<th>ADCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All responders</td>
<td>23</td>
<td>17 (73.9%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>6 (75%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Daytime Voiding Sx</td>
<td>10</td>
<td>7 (70%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Low PVR</td>
<td>6</td>
<td>5 (83.3%)</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>High PVR</td>
<td>1</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>ADH/ADD</td>
<td>10</td>
<td>7 (70%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Family History</td>
<td>4</td>
<td>4 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Psych Medication</td>
<td>2</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>BMI ≥ 24.9</td>
<td>20</td>
<td>14 (70%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>5</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Obese</td>
<td>8</td>
<td>6 (75%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Male</td>
<td>37</td>
<td>22 (59.5%)</td>
<td>15 (40.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>14 (58.3%)</td>
<td>10 (41.7%)</td>
</tr>
</tbody>
</table>

Monotherapy Subgroup Analysis

<table>
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<th>Patient Subgroup</th>
<th>N</th>
<th>Response</th>
<th>No Response</th>
</tr>
</thead>
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<tr>
<td>Total</td>
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<td>36 (59.0%)</td>
<td>25 (41.0%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>21</td>
<td>13 (61.9%)</td>
<td>8 (38.1%)</td>
</tr>
<tr>
<td>Daytime Voiding Sx</td>
<td>18</td>
<td>7 (38.9%)</td>
<td>11 (61.1%)</td>
</tr>
<tr>
<td>Low PVR</td>
<td>20</td>
<td>14 (70.0%)</td>
<td>6 (30.0%)</td>
</tr>
<tr>
<td>High PVR</td>
<td>4</td>
<td>2 (50.0%)</td>
<td>2 (50.0%)</td>
</tr>
<tr>
<td>ADH/ADD</td>
<td>16</td>
<td>6 (37.5%)</td>
<td>10 (62.5%)</td>
</tr>
<tr>
<td>Family History</td>
<td>16</td>
<td>11 (68.8%)</td>
<td>5 (31.2%)</td>
</tr>
<tr>
<td>Psych Med</td>
<td>8</td>
<td>6 (75%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>BMI ≥ 24.9</td>
<td>48</td>
<td>27 (56.3%)</td>
<td>21 (43.8%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>5</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
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<td>Female</td>
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<td>10 (41.7%)</td>
</tr>
</tbody>
</table>

Conclusions

- 97% Overall success rate using dose titration
- No reported adverse events
- ADD/ADHD and CDVS’ subgroups had statistically significant decreased response to monotherapy
- High monotherapy response rate in low PVR, family History, Psych Medication and Obese subgroups
- Age was not a predictive factor
- High dose combination therapy is safe and effective

Acknowledgements

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- UMMS Department of Pediatric Urology
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