The In-Clinic Close Loop Experience in the US

Keystone Symposium, Practical Ways to Achieve Targets in Diabetes Care
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Disclosure

I am an employee of Medtronic Diabetes

I am also a Pediatric Endocrinologist – so there will be arrows, tables, p-values and little humor
Learning Objectives:

- To understand the LGS feature
- To be familiar with the results of the study inducing hypoglycemia with LGS
- To understand the findings with regards to reduction in duration of hypoglycemia
- To be aware that there was an order effect as the result of hypoglycemia begetting hypoglycemia
Investigators of the ASPIRE Trial:

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The Role of the Artificial Pancreas

- Diabetes outcomes remain suboptimal despite a myriad advances and innovations

- Less than optimal outcomes driven by multiple factors
  - Patient centered factors
  - Disease related factors
  - Health care system related factors

- The next 10-20 years will be the “Time of Technology”
  - Waiting for eventual beta-cell replacement
30 Years of Technology

1985
Al Mann starts first commercial pump company

2003
Continuous Glucose Monitoring, Retrospective

2005
CGM RealTime

2006
Sensor Pump Integration

2009
Low Glucose Suspend System
Background: Protection From Hypoglycemia

Cessation of Insulin Secretion

Release of Counterregulatory Hormones

Symptoms
- Neuroglycopenia
- Seizures
- Coma
- Dead in Bed

Hypoglycemia is the Rate Limiting Step in Diabetes Management
The LGS System
The ASPIRE Study: Background
The Low Glucose Suspend (LGS) Feature of the Veo Pump

• Optional; can be turned on or off
• Works only in the context of receiving CGM data
• Default: pump shutoff for maximal 2 hours at pre-set CGM hypoglycemic threshold
  • Can resume insulin delivery and cancel LGS at any time
  • Cannot deliver a bolus when suspended
  • Alarm associated with LGS: can be shut off and continue suspend
• After 2 hours, pump resumes basal insulin delivery
• Available outside the US since 2009
The ASPIRE Study: Background
The Low Glucose Suspend (LGS) Feature of the Veo Pump

Graph showing the glucose levels over time with the insulin infusion stopped and resumed, indicating a maximum duration of 2 hours.
Low Glucose Suspend Does What It Is Meant To Do!

Four Studies Published To Date… What Have We Found?

1. **CareLink Data Mining**
   Agrawal P, J Diabetes Sci Technol 2011;5(5)

2. **UK User Evaluation**
   Choudhary, P, Diabetes Care 34:1–3, 2011

3. **German Pediatric Study**
   Danne, T, Diabetes Technology & Therapeutics Volume 13, Number 11, 2011

4. **The Australian Hypoglycemia Prevention Study**
   Ly TT, Jones TW, Diabetes Care, 2012
   DOI:10.2337/dc12-0052

Veo is not available in the US
Common findings across studies
- LGS set between 50-60 mg/dL
- LGS event everyday or every other
- >50% turn on insulin in <5 minutes
- 2/3 of LGS events during the day
- LGS events lasting 2 hours
  - Mainly at night
  - 10% of all LGS events

Decrease in hypoglycemia
- Fewer sensor glucose values in hypo range
- Increase ~20 mg/dL per hour with suspend and 2 hours post

No increase in hyperglycemia

Veo is not available in the US
Objectives

- Assess Low Glucose Suspend feature in the MiniMed Paradigm® Veo System to lower duration and severity of hypoglycemia induced from exercise in 50 subjects

Primary Endpoints

- Duration <70 mg/dl (max of 4hrs)
  - If YSI glucose reached <50 mg/dl, experiment was aborted
- Severity: Nadir <70 mg/dl and ≥50 mg/dl

Secondary Endpoint

- YSI glucose at end of observation period (3.5 – 4.5hrs after <70 mg/dl)

Veo is not available in the US
- Washout period lasted 3-10 days
- Unsuccessful experiments could be repeated up to 3 times
The ASPIRE Study: Exercise Session Details

- Sessions done after overnight fast
- 15-30 min exercise cycles repeated (up to 6x) until YSI* \( \leq 85 \) mg/dL
- Observation period started when YSI <70 mg/dL, then YSI sampling q 5-15 min for 3-4 h
- LGS ON experiments: Pump stopped insulin for 2 h once SG \( \leq 70 \) mg/dL
- LGS OFF experiments: Continued basal insulin
- Stopped experiments if YSI <50 mg/dL, >300 mg/dL, or safety concern

*plasma glucose concentration as measured by a YSI reference instrument
The ASPIRE Study: Frequent Sample Testing Examples

**LGS ON**
- Hypo Duration = 154 minutes
- Nadir = 55.5 mg/dL
- AUC<70 = 1163 mg/dL*min

**Same Subject**

**LGS OFF**
- Hypo Duration = 248 minutes
- Nadir = 50.3 mg/dL
- AUC<70 = 3493 mg/dL*min
### Baseline Characteristics of Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LGS On → Off</th>
<th>LGS Off → On</th>
<th>Both Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>34.5 ± 12.2</td>
<td>34.1 ± 12.7</td>
<td>34.3 ± 12.4</td>
</tr>
<tr>
<td>BMI (kg/m², mean ± SD)</td>
<td>27.7 ± 3.8</td>
<td>26.2 ± 4.6</td>
<td>26.9 ± 4.3</td>
</tr>
<tr>
<td>A1C (% mean ± SD)</td>
<td>8.0 ± 0.6</td>
<td>7.8 ± 0.5</td>
<td>7.9 ± 0.6</td>
</tr>
</tbody>
</table>

56% male
Age range 17-58 years
## LGS Experiments

<table>
<thead>
<tr>
<th></th>
<th>LGS ON</th>
<th>LGS OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sessons (n)</strong></td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td><strong>Subjects (n)</strong></td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>Attempts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Successful attempts</strong></td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td><strong>Failed attempts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YSI remained ≥70 mg/dL</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>YSI fell to &lt;50 mg/dL</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Did not follow protocol for session procedure</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

*2 subjects completed LGS OFF but not LGS ON experiments.

• 1 subject did not reach YSI of 70 mg/dL after 3 attempts and withdrew.
• 1 subject reached YSI <50 mg/dL on each of 3 attempts and withdrew.

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Garg et al., DT&T 14:205, 2012
The ASPIRE Study

<table>
<thead>
<tr>
<th></th>
<th>Duration of hypo, min</th>
<th>Nadir, mg/dL</th>
<th>End-observation YSI, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGS ON</td>
<td>138.5 ± 76.68</td>
<td>59.6 ± 5.72</td>
<td>91.4 ± 41.84</td>
</tr>
<tr>
<td>LGS OFF</td>
<td>170.7 ± 75.92</td>
<td>57.6 ± 5.69</td>
<td>66.2 ± 13.48</td>
</tr>
<tr>
<td>p value</td>
<td>0.006</td>
<td>0.015</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>95% CI</td>
<td>{-57.7, -7.8}</td>
<td>{0.3, 3.8}</td>
<td>{12.3, 38.1}</td>
</tr>
</tbody>
</table>
Mean YSI Glucose Values by Time for LGS ON and LGS OFF Sessions

The ASPIRE Study: Results

Garg et al., DT&T 14:205, 2012
The ASPIRE Study: *Safety Results*

- No serious adverse events
  - No DKA, severe hypoglycemia, or death

- 4 moderate adverse events
  - 1 study procedure-related (ie, pain at IV site)

- 25 mild adverse events
  - 1 study device/procedure-related (ie, bleeding at sensor site)
  - 2 device-related
    - Ecchymosis at sensor site
    - Urine ketones due to infusion set connection problem
  - 5 study procedure-related (ie, headache, muscle strain)
The a priori statistical plan called for analysis by order ("carry-over effect") of experiments to ensure the validity of the cross-over design.

The effect of the order of LGS ON and LGS OFF was to be deemed significant if $p \leq 0.1$.

If the order effect criterion was met, subjects’ first successful experiments were analyzed separately to assess treatment effect.
The ASPIRE Study: *Results*
Analysis Shows Presence of an Order Effect for Duration Only

<table>
<thead>
<tr>
<th></th>
<th>All Periods</th>
<th></th>
<th>First Period Only</th>
<th></th>
<th></th>
<th>Order Effect (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LGS ON</td>
<td>LGS OFF</td>
<td>LGS ON</td>
<td>LGS OFF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (subjects)</td>
<td>50</td>
<td>50</td>
<td>25</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (min)</td>
<td>138.5</td>
<td>170.7</td>
<td>107.8</td>
<td>173.6</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td>Nadir (mg/dL)</td>
<td>59.5</td>
<td>57.6</td>
<td>61.1</td>
<td>57.1</td>
<td>0.134</td>
<td></td>
</tr>
</tbody>
</table>

*95% Confidence Intervals for the difference between LGS ON and LGS OFF*

- Duration (all periods, min): {-57.7, -7.8}
- Duration (first period only, min): {-106.5, -25.5}
- Nadir (all periods, mg/dL): {0.3, 3.8}
The ASPIRE Study:
Comparison of Mean YSI Glucose Values at 30-min Time Intervals
Present for duration only, not nadir

LGS OFF was unaffected by order

LGS ON was affected by order

- The LGS ON experiment after the cross-over had a significantly longer duration of hypoglycemia than the LGS ON experiment prior to the cross-over
- Even though duration of hypoglycemia with LGS ON is longer after the cross-over, there is still benefit compared to LGS OFF
- Post-hoc analysis plan to determine etiology of order effect
The ASPIRE Study:  
Post-hoc Analysis for Etiology of Order Effect

<table>
<thead>
<tr>
<th>Period</th>
<th>1</th>
<th>2</th>
<th>p value</th>
<th>1</th>
<th>2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGS Setting</td>
<td>ON</td>
<td>ON</td>
<td></td>
<td>OFF</td>
<td>OFF</td>
<td></td>
</tr>
<tr>
<td>Preceding cumulative induced hypoglycemia (min)</td>
<td>16.6 ± 57.3</td>
<td>204.6 ± 123.7</td>
<td>&lt;0.001</td>
<td>29.3 ± 82.6</td>
<td>115.9 ± 111.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Number of experiments (N)</td>
<td>0.36 ± 0.64</td>
<td>1.57 ± 0.84</td>
<td>&lt;0.001</td>
<td>0.32 ± 0.63</td>
<td>1.64 ± 0.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal YSI ROC(^1) (mg/dL/min)</td>
<td>-1.34 ± 0.46</td>
<td>-1.35 ± 0.60</td>
<td>0.935</td>
<td>-1.02 ± 0.48</td>
<td>-1.09 ± 0.36</td>
<td>0.545</td>
</tr>
<tr>
<td>Duration of exercise(^2) (min)</td>
<td>101.0 ± 58.03</td>
<td>99.7 ± 59.66</td>
<td>0.941</td>
<td>80.2 ± 53.09</td>
<td>80.4 ± 46.10</td>
<td>0.987</td>
</tr>
<tr>
<td>AUC&lt;70 (mg/dL • min) for the prior 2 days</td>
<td>1687.8 ± 1883.3</td>
<td>1716.5 ± 2919.5</td>
<td>0.968</td>
<td>1224.2 ± 1827.3</td>
<td>1500.0 ± 2581.0</td>
<td>0.665</td>
</tr>
</tbody>
</table>

Values given as mean ± SD. p values refer to Period 1 versus Period 2 comparisons.

1. “Maximal YSI ROC” defined as the largest negative rate of change of YSI glucose readings on the day of the experiment
Order effect prolongs hypoglycemic exposure, suggesting that Hypoglycemia Begets Hypoglycemia
  • Depletion of glycogen
  • Failure of counter-regulation

Lessons learned for future studies requiring hypoglycemic inductions
  • Lengthen washout period beyond 10 days
  • Consider alternatives to cross-over design

Order effect was not due to duration of exercise, ROC of glucose, or spontaneous exposure to hypoglycemia during the preceding two days
The LGS feature reduces the duration and severity of hypoglycemia

Although the order effect lengthened the duration of hypoglycemia with the second experiment, there was still a benefit to LGS

- With cessation of insulin delivery, there is a chance to recover from exercise-induced hypoglycemia as opposed to when there is continued insulin delivery

Long term use of LGS should help to further reduce hypoglycemia by disrupting the vicious cycle of “hypoglycemia begetting hypoglycemia”

The in-home ASPIRE study is currently underway