How Close are we to Auto-Stop and Closed-Loop

Roman Hovorka, PhD
Institute of Metabolic Science and Department of Paediatrics
University of Cambridge, UK
Presenter Disclosure Information

Roman Hovorka

Advisory Panel: Animas, Medtronic

Research Support: Minimed Medtronic, Abbott Diabetes Care, Smiths Medical

Speaker’s Bureau: LifeScan, Minimed Medtronic, BBraun, Novo Nordisk, Eli Lilly

License fees: Becton Dickinson

Other: Patent applications
The artificial pancreas

- Sensor
- Control algorithm
- Insulin pump
Content

- Low glucose suspend (auto-stop)
- Fully vs. semi-closed loop
- Semi-closed loop
  - Overnight studies: Young and adults
  - Day-and-night studies: Young
  - Type 1 pregnancy
Some terminology …

- **Open loop**
  - “A control system that does not have a feedback loop and thus is not self-correcting”
  - Conventional therapy in type 1 diabetes

- **Closed-loop**
  - “A control system with a feedback loop”
  - Artificial Pancreas
Closed-loop generations

Low glucose suspend
Pump suspension to prevent hypoglycaemia
Treat-to-range
Overnight closed-loop

Minimed Paradigm Veo

Dual hormone
Meal & exercise control with automated dosing
Meal control with manual boluses
Low glucose suspend (auto-stop)
Insulin pump with low glucose suspend (VEO)

- At low glucose threshold
  - Alert sounded
  - Pump basal rate suspended
- Option
  - Either continue suspend for up to 2 hours
  - Or until user cancels
- Four hours in between of 2 hour suspensions

- Aimed to reduce severity of hypoglycaemia

(not available in the US)
Example: two LGS events
LGS evaluation

- Children to adults (N = 25; 2320 LGS events; ~ 1700 days)

Nocturnal 2-hour LGS events (N = 190)

Ly et al, ADA 2011
Status

- Conclusions from clinical evaluations
  - LGS safe and well tolerated
  - LGS may reduce risk of prolonged hypoglycaemia
- US
  - FDA draft guidelines (Jun 2011)
  - Endpoints: at least 10% reduction in
    - severe hypoglycaemia
    - or CGM-based event rate (prevention)
    - or hypo AUC reduction (mitigation)
    - non-inferiority for HbA1c

Pickup, DTT, 2011
Ly et al, ADA 2011
Danne et al, ADA 2011
Kaufman et al, ADA 2011
Closed-loop insulin delivery
Fully vs. semi closed loop

Fully closed loop

Semi-closed loop
Case study – type 1 pregnancy
28 wks, 5.4% HbA1c, 54U TDD, 72 kg

60 g CHO breakfast
18 U actrapid

- plasma glucose
- insulin infusion

- total Ra
- Rd
- plasma insulin
Randomised crossover trials of overnight closed-loop

Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial

Hovorka et al, Lancet 375: 2010

BMJ

Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies

Hovorka et al, BMJ 342: 2011
Rationale for overnight closed-loop

Postprandial control is challenging

Severe hypoglycaemia 55-75% during night

Gradual introduction of closed-loop

Overnight closed-loop

Davis et al, Diabetes Care 20: 1997
Screening visit
Inclusion criteria:
• 5-18 yrs (young)
• 18-65 yrs (adults)
• T1D ≥ 6 mths
• CSII ≥ 3 mths
• No significant comorbidities

Randomisation

Control (CSII) night

Closed Loop night

Closed Loop night

Control (CSII) night

0 wks

1 – 2 wks

2 – 3 wks

[CSII=continuous subcutaneous insulin infusion]
Feasibility study in children and adolescents

Hovorka et al, Lancet 375: 2010

N = 12
Population: Randomised crossover studies

<table>
<thead>
<tr>
<th></th>
<th>Young N = 17</th>
<th>Adults N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>8/9</td>
<td>10/14</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>13.4 ± 3.6</td>
<td>37.5 ± 9.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.0 ± 4.0</td>
<td>25.7 ± 4.2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.5 ± 1.8</td>
<td>7.8 ± 0.6</td>
</tr>
<tr>
<td>Duration of diabetes (yrs)</td>
<td>6.2 ± 4.0</td>
<td>20.6 ± 9.7</td>
</tr>
<tr>
<td>Duration on pump (yrs)</td>
<td>1.7 ± 1.0</td>
<td>2.4 ± 3.0</td>
</tr>
<tr>
<td>Total daily insulin (U/kg)</td>
<td>0.92 ± 0.24</td>
<td>0.73 ± 0.17</td>
</tr>
</tbody>
</table>

N=Number of participants

### Overnight closed-loop in young and adults

Plasma glucose from the start of closed-loop control

<table>
<thead>
<tr>
<th></th>
<th>Closed-loop</th>
<th>CSII</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*aN = 45</td>
<td>*aN = 45</td>
<td></td>
</tr>
<tr>
<td>Mean overnight glucose (mg/dl)</td>
<td>124 27</td>
<td>133 50</td>
<td>NS</td>
</tr>
<tr>
<td>SD of overnight glucose (mg/dl)</td>
<td>27 (20 – 38)</td>
<td>38 (29 – 52)</td>
<td>0.007</td>
</tr>
<tr>
<td>Time in target 70 – 145mg/dl (%)</td>
<td>71 (53 – 88)</td>
<td>43 (27 – 63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time ≤ 70mg/dl (%)</td>
<td>2.1 (0 – 10)</td>
<td>4.1 (0 – 28)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time &gt; 145mg/dl (%)</td>
<td>20 (2 – 42)</td>
<td>33 (13 – 58)</td>
<td>0.03</td>
</tr>
<tr>
<td>LBGI (unitless)</td>
<td>1.1 (0.3 – 2.2)</td>
<td>1.6 (0.4 – 4.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Insulin infusion (U/h)</td>
<td>0.8 (0.6 – 1.2)</td>
<td>0.9 (0.6 – 1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin concentration (pmol/l)</td>
<td>148 (103 – 215)</td>
<td>146 (102 – 242)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*a Number of nights per treatment

Closed loop (after midnight)

plasma glucose (mg/dl)

proportion of values

Closed loop young (33 nights)
Closed loop adults (24 nights)
Conventional pump therapy (after midnight)

<table>
<thead>
<tr>
<th>Plasma Glucose (mg/dl)</th>
<th>Proportion of Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>0.00</td>
</tr>
<tr>
<td>80</td>
<td>0.05</td>
</tr>
<tr>
<td>120</td>
<td>0.10</td>
</tr>
<tr>
<td>160</td>
<td>0.15</td>
</tr>
<tr>
<td>200</td>
<td>0.20</td>
</tr>
<tr>
<td>240</td>
<td>0.25</td>
</tr>
<tr>
<td>280</td>
<td>0.30</td>
</tr>
</tbody>
</table>

- **CSII young (21 nights)**
  - 6% at 40 mg/dl
  - 20% at 80 mg/dl
  - 41% at 120 mg/dl
  - 33% at 160 mg/dl

- **CSII adults (24 nights)**
  - 2% at 40 mg/dl
  - 9% at 80 mg/dl
  - 53% at 120 mg/dl
  - 36% at 160 mg/dl

Legend:
- Yellow: CSII young (21 nights)
- Orange: CSII adults (24 nights)
Day and night randomised crossover study

Elleri et al, ADA 2011
Study design

- 36 hour study in adolescents (N = 12)
- Announced to algorithm
  - Main meals 50-80g CHO
  - Insulin boluses
- Not announced
  - Snacks 15 and 30g CHO
  - Walks (2x20min)
  - Bicycle @140bpm (40min, 20min)

Elleri et al, ADA 2011
Insulin infusion

Start of Closed-loop

Insulin pump therapy

Closed-loop delivery
Results over 32 hours

- Reduced plasma glucose levels
  - $128 \pm 20$ vs. $166 \pm 54$ mg/dl $p = 0.04$

- Time in target 70 – 180mg/dl increased
  - $84\% (78, 88)$ vs. $49\% (26, 79)$ $p = 0.02$

- Hypoglycaemia could not be prevented
  - During/after exercise
  - After prandial insulin overdosing
Type 1 pregnancy
Closed-loop early and late gestation (N = 10)

- Comparable plasma glucose levels
  - 117 mg/dl (100.8-154.8) early vs. 126 mg/dl (109.8-140.4) late
- Comparable overnight plasma glucose time in target
  - 84% (50-100) early vs. 100% (94-100) late (p=0.09)

Murphy et al, Diabetes Care 34: 2011
Glucose turnover early and late gestation

- Late gestation
  - Delayed postprandial glucose disposal $R_d$
  - Reduced peripheral insulin sensitivity
  - Delayed insulin absorption
Devices and algorithm

**Sensor**
- Single sensor
- Guardian RT
  - 1 study
- FreeStyle Navigator
  - 7 studies
  - 1 ongoing study
- DexCom
  - 1 study
  - 1 ongoing study
- Calibrated according to manufacturer instructions

**Insulin pump**
- Cozmo
  - 6 studies
- Animas
  - 2 studies
  - 1 ongoing study
- Insulet
  - 1 ongoing study
- Aviator
  - 1 study
- Aspart insulin

**Algorithm**
- Model predictive control
- Adaptive
- Easily initialised
Conclusions

• Low glucose suspend
  • First generation closed-loop system
  • Readily available outside US
  • US: Regulatory pathway outlined by FDA

• Overnight closed-loop
  • Feasible treatment option
  • Home studies justified

• Day and night closed-loop
  • Benefits occur primarily during night period
  • Prandial insulin overdosing and unannounced exercise may lead to hypoglycaemia

• Limiting factors
  • Delay insulin absorption
  • Sensor accuracy
Artificial Pancreas: Large momentum

**Pump suspension**

**Overnight**

**Day-and-night**

**Day-and-night intraperitoneal delivery**

**Dual hormone (insulin and glucagon)**
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- Smiths Medical
- Minimed Medtronic
- Wellcome Trust CRF
- Volunteers and parents
... what next
Florence System: Home prototype

Navigator CGM

Aviator insulin pump

Laptop running MPC algorithm

Combined controller
Florence status

- Evaluated in CRC
  N = 8 on two occasions

- Randomised home study over 3 weeks
  - Approved by Ethics Committee
  - Approved by UK regulatory agency
Closed loop (after midnight)

- Plasma glucose (mmol/l)
  - Closed loop adults (24 nights)
  - Closed loop young (33 nights)

Estimated density
- 0.00
- 0.05
- 0.10
- 0.15
- 0.20
- 0.25
- 0.30

Portion of values

Plasma glucose (mmol/l)
Conventional pump therapy (after midnight)

- Conventional pump therapy (after midnight)
  - Plasma glucose (mmol/l)
    - 2% 6% 20% 41% 33%
    - 2 4 6 8 10 12 14 16

- CSII (45 nights)
  - Plasma glucose (mmol/l)
  - Estimated density
    - 0.00 0.05 0.10 0.15 0.20 0.25 0.30

- CSII adults (24 nights)
  - CSII young (21 nights)
  - Portion of values

- Graph showing plasma glucose levels with percentages of values distribution.