The next five years in diabetes technology: closed-loop systems

J. H. (Hans) DeVries
Academic Medical Center at the University of Amsterdam, the Netherlands
Keystone, CO, 19 July 2013
Disclosure

AP@home, the FP7 consortium of which I am the scientific coordinator, receives research support from Dexcom, Roche Diagnostics and Insulet

I am on an advisory board for Johnson & Johnson and Roche Diagnostics
At the conclusion of this presentation, the participant should be able to:

- Identify at least two access routes into the body for closed loop treatment
- Summarize at least two hurdles to be taken in the coming five years for closed loop treatment
Approaches

• Sc-sc (ip delivery, implanted sensor)

What is needed?

• Better CGM
• Faster insulin?
• Better pumps?
• Better algorithms?
• A product
Roche prototype CGM sensor

- MARD: 9.2%

JDST 2013
Cambridge Experience n=52; Error more than 1 hour

Leelarathna L, ADA Philadelphia 2012, OR-3
Pharmacokinetics: Insulin Lispro Profile after a Test Meal in Type 1 Diabetes

Heinemann et al. Diabetic Medicine, 13:625-629, 1996
Injection 15 minutes before the meal lowers postprandial glucose excursion.

Luijf, van Bon, Hoekstra, DeVries, Diabetes Care 2010;33:2152-5
Dose response study with MedTone® Inhaler:

- Healthy volunteers, n = 12
- Relative bioavailability 30-50%

### Table 1. Time to Occlusion Alert in Different Commercial Devices with a Length of the Infusion Set of 60 or 2.5 cm

<table>
<thead>
<tr>
<th>Device (manufacturer), stepsize</th>
<th>Manufacturer alert</th>
<th>Basal rate, catheter length</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.0 IU/h 60 cm</td>
</tr>
<tr>
<td>Paradigm Veo (Medtronic Minimed), step size 0.05</td>
<td>Basal rate 1.0 IU/h: 2 h 25 min–3 h 9 min, Basal rate 0.025 IU/h: 66–189 h</td>
<td>1 h 55 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 h 56 min</td>
</tr>
<tr>
<td>D-Tron plus (Roche Diagnostics), step size 0.1</td>
<td>Basal rate 1.0 IU/h: 2–4 h</td>
<td>3 h 17 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 h 45 min</td>
</tr>
<tr>
<td>Accu-Chek Spirit Combo (Roche Diagnostics), step size 0.05</td>
<td>Basal rate 1.0 IU/h: ≤5 h, Basal rate 0.1 IU/h: ≤50 h</td>
<td>1 h 51 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 h 6 min</td>
</tr>
<tr>
<td>Dana Diabecare R (Sool), step size 0.1</td>
<td>No information about occlusion time</td>
<td>Sensitivity: Medium: 4 h 32 min, 2 h 20 min, 1 h 53 min</td>
</tr>
<tr>
<td>OmniPod (Insulet Corp.), step size 0.05</td>
<td>No information about occlusion time</td>
<td>7 h 20 min</td>
</tr>
</tbody>
</table>

Van Bon DT&T 2012; 14: 447-8
Algorithms; AP@home CAT trial

- 46 subjects completed full day CL
- Hypo 6% in open loop, 2% in CL (for both CAM and iAP algorithms)

Diabetes Care, in press
Moving out of the CRC

- iAP (hotel and short walk, November 2011)
- DeVries (48 hrs at home, March 2012)
- Phillip (overnight, June 2012)
- Buckingham (diabetes camp, August 2012)
- Cambridge, UK (2013)
Feasibility of a portable bihormonal closed-loop system to control glucose excursions at home under free conditions for 48 hours

Manuscript Submitted

1A.C. van Bon, 1Y.M. Luijf, 2R. Koebrugge, 2R. Koops, 1J.B.L. Hoekstra, 1J.H. DeVries

1Academic Medical Centre, Department of Internal Medicine, Amsterdam, The Netherlands.
2Inreda Diabetic B.V., Goor, The Netherlands
APPEL 3

Methods

N = 16
DM Type 1
CSII > 6 months

Open Loop

Sensor insertion | Home | Breakfast day 1 | Breakfast day 2 | End day 3
16:00 | 8:00 | 8:00 | 8:00

Closed Loop

Sensor insertion | Dinner | Breakfast day 1 | Home | Breakfast day 2 | End day 3
16:00 | 18:30 | 8:00 | 8:00 | 8:00
APPEL 3
Closed loop

- 2 D-Tron+ pumps, Disetronic Medical Systems
- 2 Sof-Sensor/Enlite sensors, Medtronic
- Portable PC
- Telemonitoring
- Safety alerts
<table>
<thead>
<tr>
<th>Demographic characteristics</th>
</tr>
</thead>
</table>
| Male / Female              | 7 / 4  
| Age (year)                 | 52.1 (25-66)  
| HbA1c (%)                  | 7.6 (6.2-9.1)  
| DM duration (year)         | 35.3 (12-46)  
| Pump duration (year)       | 11.2 (4-17)  

Mean (range)
APPEL 3

Results

Mean Glucose During Entire Experiment

- Open Loop day 1
- Open Loop day 2
- Closed Loop day 1
- Closed Loop day 2

Time (min)

MMOL/L
# APPEL 3

## Results Glycemic Ranges

<table>
<thead>
<tr>
<th>Time (% ) spent in:</th>
<th>OL day 1</th>
<th>CL day 1</th>
<th>$p$ value</th>
<th>OL day 1</th>
<th>CL day 2</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Euglycemia</strong></td>
<td>67.2 (38.5)</td>
<td>79.2 (16.9)</td>
<td>0.19</td>
<td>66.0 (29.8)</td>
<td>76.5 (23.9)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>0.7 (8.7)</td>
<td>2.1 (7.6)</td>
<td>0.59</td>
<td>0.0 (11.1)</td>
<td>2.8 (9.8)</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>Hyperglycemia</strong></td>
<td>32.4 (44.8)</td>
<td>13.2 (16.1)</td>
<td>0.17</td>
<td>31.0 (29.8)</td>
<td>18.3 (20.0)</td>
<td>0.089</td>
</tr>
</tbody>
</table>

Median (IQR)
## APPEL 3

Results median glucose values

<table>
<thead>
<tr>
<th>Glucose levels (mmol/l):</th>
<th>OL day 1</th>
<th>CL day 1</th>
<th>p value</th>
<th>OL day 2</th>
<th>CL day 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire Experiment</td>
<td>8.3 (0.83)</td>
<td>7.4 (2.2)</td>
<td>0.21</td>
<td>8.8 (0.87)</td>
<td>7.7 (2.3)</td>
<td>0.027</td>
</tr>
<tr>
<td>Night only</td>
<td>7.7 (0.44)</td>
<td>6.6 (0.20)</td>
<td>0.28</td>
<td>8.8 (0.71)</td>
<td>6.2 (0.38)</td>
<td>0.0039</td>
</tr>
<tr>
<td>Breakfast</td>
<td>8.9 (2.0)</td>
<td>8.9 (2.6)</td>
<td>1.0</td>
<td>10.3 (1.4)</td>
<td>9.8 (3.2)</td>
<td>0.65</td>
</tr>
<tr>
<td>Lunch</td>
<td>9.5 (1.7)</td>
<td>9.1 (2.0)</td>
<td>0.56</td>
<td>8.8 (0.44)</td>
<td>10.5 (3.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Dinner</td>
<td>9.0 (1.0)</td>
<td>8.5 (1.4)</td>
<td>0.77</td>
<td>9.8 (0.86)</td>
<td>8.6 (0.88)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Median (IQR)
APPEL 3
Conclusion

Full day closed loop achievable at the patient’s home under free living conditions

- Technical issues
- Closed loop really challenged
A Portable bihormonal Closed loop for Diabetes

AMC
Medical University Graz
Inreda Diabetic BV
Novo Nordisk A/S
Profil Institute for Metabolic Research GmbH
Full Group
University of Twente
APPEL 4

Miniaturized prototype

Incorporated:
• Controller
• 2 pumps
• Accelerometer
APPEL 4
Study design similar to APPEL 3; n=12

Open loop
• Prototype with inactive control algorithm
• 2 Medtronic glucose sensors
• Heart rate belt

Closed loop
• Prototype
• 2 Medtronic glucose sensors
• Heart rate belt
• Telemonitoring
THE LONGER WE GO HOME, THE LESS TELEMEDICINE WE CAN DO

• 24/7 monitoring has its limits

What we can do:
• Automated technical failure detection
• Optimization of algorithm settings
Hardware

3G connection for remote monitoring

Bluetooth®

Communication Device

UCSB/Sansum APS® Artificial Pancreas System
Market access

• Medtronic
• Johnson & Johnson
• Roche
• BD
• Dexcom
• Tandem
• Insulet
• Abbott
Legal

- Severe hypo and liability

- Is 1 severe hypo too much, or will less than current practice suffice?
- Back to open loop in high risk situation?
Which patient groups

• Moving from the tech-savvy to the ones in need
• Reimbursement
The next five years

Ready to GO HOME with E.T. A.P.