CSII from its beginning

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Why was CSII invented?

Back to the 1970s
Mysteries of the 1970s

Why do people like John Travolta?

What causes diabetic Complications?
Views on diabetic complications in the 1970s

? Diabetes ? hyperglycaemia ? complications

? Diabetes

hyperglycaemia

complications
Testing the hypothesis:
allocate diabetic patients to near-normoglycaemia for a prolonged period,
observe effect on complications

The problem

No way of maintaining strict glycaemic control with insulin injections – need new ways of improving control
Can we mimic non-diabetic insulin delivery by infusing insulin?

Non-diabetic subjects: meal-time boosts and slow basal insulin throughout 24 hours

Insulin pump: infuses insulin at basal rate, with patient-activated boosts at meals
Slama, Hautecouverture, Assan, Tschobroutsky 1974

- 7 type 1 diabetic patients
- Regular insulin IV for 1-5 days from peristaltic pump in shoulder bag
- Basal rate and 15 fold higher prandial rate
- Prolonged insulin infusions feasible
- Very good glycaemic control possible without closing the loop but IV route has problems
Continuous subcutaneous insulin infusion (CSII)

- Developed as a research procedure to test effect of improved control on complications
- Basal and augmented preprandial insulin infusion given subcutaneously

The first insulin pump for CSII (Pickup et al., 1976/77)
What we asked 30 years ago

• Can technology for insulin infusion be improved?

(Pumps were relatively unreliable and not programmable)
What we asked 30 years ago

- Can technology for insulin infusion be improved?
- Is CSII any better than best injection therapy, e.g. with pens?
- Is long term insulin infusion safe – what are the complications?
- Is CSII an experimental or routine treatment?
- If routine, what are the clinical indications?
- If experimental, does improved control influence diabetic complications?
- Is there a better pump insulin than regular insulin?
- Can closed-loop insulin delivery be a routine treatment?
- Are there advantages for alternative delivery routes – im, ip, intranasal, inhaled, oral?
The evolution pump technology
What we asked 30 years ago

- Is glycaemic control on CSII any better than best injection therapy?
- 30 years of controversy and confusion
Best evidence for effectiveness of CSII

CSII reduces the frequency of hypoglycaemia compared to insulin injection therapy

Known in mid 1980s but had to be rediscovered 10 years later
Severe hypoglycaemia CSII vs. insulin injection therapy (n=40, >6 mo treatment)
Bending, Pickup, Keen 1985

![Bar chart showing the number of severe hypoglycaemic events for CSII and injections for all patients, those without proteinuria, and those with proteinuria.](chart)

- **All patients**: p<0.03
- **No proteinuria**: p = 0.005
- **Proteinuria**: ns
Reduction in severe hypoglycaemia in the Oslo Study (1986): RCT of MDI (and CIT) vs. CSII

- **MDI:** 2 episodes
- **CSII:** 14 episodes

\( p < 0.001 \)
Reduction in severe hypoglycaemia in 55 type 1 diabetic subjects: multiple insulin injections vs pumps  Bode et al. 1996
Meta-Analysis of Severe Hypoglycaemia MDI vs CSII

- 21 trials

- Rate of severe hypoglycemia on MDI reduced by CSII from median 46 (23 - 81) to 12 (9 - 20) episodes / 100 patient-years

Pickup JC, et al. Unpublished Data
Severe hypoglycaemia is not improved by MDI with glargine or detemir vs. NPH regimens

**Glargine**
- Raskin et al Diabetes Care 2000; 23: 1666
- Warren et al Hlth Tech Assess 2004; 8: 1 (systematic review)

**Detemir**
- Russell-Jones et al Clin Ther 2004; 26: 724
- Hermansen et al Diabetologia 2004; 47: 622
- Home et al Diabetes Care 2004; 27: 1081
What we asked 30 years ago

- Is HbA1c any better on CSII vs. best injection therapy?

- Many people still confused about pump effectiveness in 2006

- Had to discover that pumps are most effective for worst controlled patients (last year or so)
Meta-analysis in general diabetic patients
HbA1c in RCTs of MDI vs. CSII, Pickup et al., 2002

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Standardised mean difference in glycated haemoglobin

<table>
<thead>
<tr>
<th>Study</th>
<th>Standardised Mean diff. (95% CI)</th>
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<tbody>
<tr>
<td>Schiffrin et al 1982</td>
<td>0.40 (-0.30, 1.10)</td>
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<tr>
<td>Home et al 1982</td>
<td>0.83 (-0.09, 1.74)</td>
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<tr>
<td>Nathan et al 1982</td>
<td>2.47 (0.74, 4.20)</td>
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<tr>
<td>Schiffrin et al 1984</td>
<td>0.94 (0.34, 1.54)</td>
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<tr>
<td>Dahl-Jørgensen et al 1986</td>
<td>0.29 (-0.43, 1.01)</td>
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<tr>
<td>Helve et al 1987</td>
<td>0.14 (-0.21, 0.48)</td>
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<tr>
<td>Marshall et al 1987</td>
<td>-0.13 (-0.93, 0.67)</td>
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<tr>
<td>Saurbrey et al 1988</td>
<td>0.00 (-0.60, 0.60)</td>
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<tr>
<td>Schmitz et al 1989</td>
<td>0.70 (-0.21, 1.61)</td>
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<tr>
<td>Dusseldorf 1990</td>
<td>0.68 (0.27, 1.09)</td>
</tr>
<tr>
<td>Hannaire-Broutin et al 2000</td>
<td>0.37 (-0.06, 0.81)</td>
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<tr>
<td>Overall (95% CI)</td>
<td>0.44 (0.20, 0.69)</td>
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NB: small difference in HbA1c

[HbA1c 0.5%]
BUT

Reduction of HbA1c not well studied in (clinically-recommended) group of hypoglycaemia-prone type 1 diabetic patients
Reduction in HbA1c on switching to CSII is greater than expected in hypoglycaemia-prone type 1 diabetes
Switching to CSII in hypoglycaemia-prone type 1 diabetes (n=27), Pickup et al Pract Diab Int 2005; 22: 10-14

Mean fall in HbA1c ~1.5%
Improvement in HbA1c on switching to CSII depends on HbA1c on MDI


\[ r = 0.79, p < 0.0001 \]
HbA1c achievable on MDI is related to blood glucose variability on MDI


Subjects with high blood glucose variability on MDI resist improvement to avoid hypoglycaemia, thereby maintaining a high HbA1c
CSII reduces hypoglycaemia, and within- and between-day blood glucose variability (Pickup et al 2005)
HbA1c during glargine MDI is further improved by CSII (Pickup et al 2005)

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<th>Treatment</th>
<th>HbA1c (%)</th>
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<tr>
<td>Glargine MDI</td>
<td>8.7 ± 1.2%</td>
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<tr>
<td>CSII</td>
<td>7.2 ± 1.0%</td>
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p <0.001
What we asked 30 years ago

How many diabetic patients should receive CSII?
Who should receive CSII? Our changing views

- 1978: Research patients only
- 1980s: Those with the dawn phenomenon
- 1990s: Those with severe hypoglycaemia on MDI
- 2006: Those with elevated HbA1c and unpredictable glycaemic oscillations on MDI
How many type 1 diabetic patients have severe hypoglycaemia?
Distribution of Severe Hypoglycaemia on MDI

- 1076 adults with Type 1 DM in Denmark and UK
- 21% had 2 or more episodes in previous year
- Distribution very skewed: 5% of patients have >50% of episodes

How many type 1 diabetic patients have severely elevated HbA1c on best injection therapy?
30 type 1 diabetic subjects after an intensive MDI programme including glargine (median 5 mo) (Pickup et al Diab Metab Res Rev 2006; 22: 232-7)

20% have an HBA1c >9.5%
Efficacy of MDI regimens

- **DAFNE (2002)**  HbA1c 8.4 ± 1.2% (no reduction in severe hypo vs. standard therapy)
  (17% HbA1c >9.5%)

- **Hermansen et al. (2004)** detemir/aspart  HbA1c 7.9 ± 0.9% (no reduction in severe hypo vs. NPH regimen)
  (15% HbA1c >9%)
Estimating the appropriate use of CSII

- Frequent severe hypoglycaemia on MDI 5%
- Severe hypoglycaemia lesser frequency on MDI 5%
- HbA1c >9 or 9.5% on MDI 15%
- Dawn phenomenon on MDI <5%

- Even if one quarter not suitable for CSII (decline CSII/prefer MDI, psychologically unsuitable)

At least 15-20% of type 1 diabetic subjects should be offered a trial of CSII on clinical grounds alone
Clinical indications and treatment strategy for insulin pump therapy

- Low insulin requirements
- Dawn phenomenon
- Hypoglycaemia unawareness
- Erratic lifestyle
- Pregnancy
- Unpredictable insulin absorption/action
- Attempts to correct BG swings
- Attempts to lower HbA1c

Frequent, unpredictable hypoglycaemia or high HbA1c/BG variability

MDI including glargine/detemir

Continued hypoglycaemia

- Not suitable for CSII
- Suitable for CSII

Trial of CSII
Strategy for treating patients by CSII

1. Poor diabetic control
   - GP or hospital consultant
     - 25/75%
     - Pump Clinic in Hospital, assessed by Consultant
     - Not suitable for pump treatment
     - Pump nurse and dietitian, optimize control on injections, including glargine/detemir, assess suitability for pump
     - Control improved
     - Control not improved
     - Trial of pump treatment

~75% of referred
The future of CSII

- Should choice of insulin delivery also be based on patient preference: the issue of quality of life?
- Technical improvements in pumps - smaller and cheaper
- Sensor-augmented pumps and closing-the-loop
CSII from the past to the future