The physiology of insulin replacement: DAFNE style!
The contrast......

DCCT

Hypoglycaemia

Retinopathy

Dusseldorf Programme

Haemoglobin A1c

Retinopathy per 100 patient years

Severe hypoglycaemia per 100 patient years
Severe hypoglycemia per 100 pt y
The Goal......

Polonsky et al, J Clin Invest 1988; 81; 442
Periello et al., Diabetologia. 1991;34:21-8
Flexible insulin therapy in which

- QA insulin is taken to cover the carbohydrate to be eaten
- BI controls endogenous glucose production, so that meal timing is flexible
- QA and BI are independent of each other
Periello et al., *Diabetologia* 1991;34:21-8
Diurnal variation in insulin infusion rate

N=322

Range 0 – 3.5 units/hr
14.3 % 0 peak
82.3 % 1 peak
3.4 % 2 peaks
Max 4 – 8 am; min 11am – 8pm

Time of start of rise in insulin infusion rate

Cause of the dawn phenomenon

- Diurnal rhythms in cortisol and catecholamines (rising 4 – 6 am); GH spikes max 1 – 4.30am.
  
  Bolli et al., Diabetes. 1984;33:1150-3

- Nocturnal growth hormone spikes main cause
  (removed and replaced during somatostatin infusion)

  Periello et al., Diabetologia. 1990 Jan;33(1):52-9
**BI replacement: original DAFNE**

**Intermediate**
- 2 hr
- 4 - 8 hr
- 12 - 18 hr

"Typical" requirement = 1 unit/hour = 12 units bd

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Fanelli et al., Ann Intern Med. 2002;136:504-14
Multiple injections of NPH

Patients well controlled on tds soluble and bedtime NPH:

- Lispro and bedtime NPH
  \[ \text{HbA1c} \rightarrow \text{hypo} \]

- Lispro at meals with NPH and NPH bedtime
  \[ -0.35\% \rightarrow \]

- HS 10-40 min pre-meal with NPH bedtime
  \[ \rightarrow \rightarrow \]

- HS at meals
  \[ + 0.18 \uparrow \]

Humulin S + bedtime NPH vs Humalog and qid NPH

With Lispro + qid NPH:
HbA1c 6.3±0.1 vs 6.7±0.1%, p < 0.002
Less hypoglycaemia

30% less QA
30% more BI with Humalog

Insulin Time Action Curves

- **Relative Insulin Effect**
  - **Time (Hours):** 0, 2, 4, 6, 8, 10, 12, 14, 16

- **Insulin Time Action Curves**
  - **Intermediate (NPH)**
  - **Long (Glargine)**
Glargine once a day vs NPH qid

NPH 0.2 units/kg

Rosetti et al, Diabetes Care, 2003; 26: 1490
Figure 2. Glucose infusion rate profiles for participants with type 1 diabetes who each received four single subcutaneous NPH insulin, insulin glargine or insulin detemir injections in a glucose-clamp study.
There isn’t a good evidence base for..........

• the number of people in whom analogues last 24 hours?
• the number of people who have different day and night basal requirements?
• how to adjust once daily background for exercise and alcohol?
• when to give analogues in a bd regimen
There is an evidence base for:

- Efficacy of bd NPH in the Dusseldorf programmes
- Reduced rates of nocturnal hypoglycaemia with analogue BI
- Better fasting glucose with analogue BI

Lower HbA1c with bd insulin

Lawrence et al., Diabetologia 2010
QA Insulin replacement

Soluble
Onset 30 min
Peak 2 - 4 hr
Duration 4 - 8

Analogue
Onset 15 min
Peak 50 min
Duration 3 - 5 hrs

CHO matching
The timing of the meal injection
Post meal injection

Schernthaner et al, Diabetes Care 1998; 21, 570
BI

• The background insulin requirement for the “average” man is 1 unit per hour
• It is affected by
  – Insulin sensitivity
    • Diurnal rhythm
    • Exercise
    • Alcohol
    • Stress
• The current evidence supports bd dosing
QA

• With adequate BI, analogue has advantages
• Optimal timing of analogue is 10 min pre meal
• Post meal injection should not be used routinely
BUT....

There is still a lot we need to learn!
Background Insulin Replacement:
Implementing the most clinically effective Background Insulin regimen in DAFNE

DAFNE collaborative 2010 Workshop
- Reflect on the audit data presented earlier
- Discuss current practice: reasons & influences
- Discuss barriers to change from once daily to twice daily
  BI: patient / professional
- Review Michael Berger’s regimen and discuss advantages
- Practise using the DAFNE Isophane/Levemir course dose adjustment examples
- Discuss scenarios around changing patients to twice daily
  BI pre- or post-DAFNE