Designer Insulins

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www.endocrinology-specialist.com

History – case 1

- 33 yr old male bank manager
- Type I diabetes since age 6
- Actrapid 8U tds and Ultratard 38 units noote'

- Wt 78.7kg, BMI 30
- No evident microvascular complications
- BP 158/92
- HbA1c 7.8%

- Commenced on Humalog 6U tds and Ultratard 36U to improve control

Follow up - case 1

- 1999
  - Weight 83.0kg
  - Fall in HbA1c .... To ....

- 2003
  - Nocturnal hypos
  - Weight 80.2kg
  - HbA1C 8.4%??? Check results on

24 hr glucose profile - case 1

History - case 2

- 61 yr old woman with Type II diabetes (1997)
- Maculopathy
- Hypothyroidism
- Mixtard 30/70 24U bd
- Weight 71.3kg, BP 170/80
- HbA1C 10.5%

- Plan
  - Humalog mix 25 20U bd to improve control

Follow up - case 1

- Ultratard substituted with Glargine 32U

- At follow up
  - HbA1C 8.1%
  - BP 130/61
  - Wt 82.4kg
  - No further hypoglycaemic episodes
Follow up - case 2

- 2004
  - Weight 70kg BMI 30Kg/m²
  - HbA1c 11.5%
  - For poor control switched to
    - Basal bolus
    - Novorapid 10U lds and Glargine 10U nocte
- 2005
  - HbA1c 9.5%
  - Weight 73.0kg

Summary

- Case 1
  - Type I diabetes with poor control and hyps
  - Short acting analogues failed to improve HbA1c
  - Nocturnal hyps improved with long acting analogue
- Case 2
  - Type II with poor control
  - Twice daily insulin analogue failed to improve HbA1c
  - Basal bolus regime was more successful

Objectives

- The structure and functions of insulin
- History of insulin preparations
- Current preparations
- Insulin analogues
- Future preparations
- Final recommendations

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Structure of insulin

Serum insulin in normal individuals

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History of insulin preparations

- Frederick Grant Banting
  - Born in Nov 1891
  - Surgeon in Ontario
  - “Fond” of dogs
  - Searched for the “anti-diabetic” component of the pancreas
  - Isolated insulin in 1921 with Charles Best
  - Died 1941

1930s  Protamine zinc insulin
1950s  Neutral protamine Hagedorn and insulin zinc
1970s  “Split-mix” insulins
1980s  Purified pork insulins
1980s  Recombinant human insulins
1990s  Insulin analogues

Insulin preparations available in UK

<table>
<thead>
<tr>
<th>SHORT-ACTING (n&gt;8)</th>
<th>RAPID-ACTING ANALOGUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actrapid</td>
<td>NovoRapid (Aspart)</td>
</tr>
<tr>
<td>Humulin S</td>
<td>Humalog (Lispro)</td>
</tr>
<tr>
<td></td>
<td>Apidra (Glulisine)</td>
</tr>
<tr>
<td>MEDIUM AND LONG-ACTING INSULINS (n&gt;13)</td>
<td></td>
</tr>
<tr>
<td>Insulatard</td>
<td>Lantus (Glargine)</td>
</tr>
<tr>
<td>Ultratard</td>
<td>Levemir (Detemir)</td>
</tr>
<tr>
<td>Humulin I</td>
<td></td>
</tr>
<tr>
<td>MIXED INSULINS (n&gt;16)</td>
<td></td>
</tr>
<tr>
<td>Mixard 30/70</td>
<td>Humalog Mix 25, Mix 50</td>
</tr>
<tr>
<td>Humulin M3</td>
<td>NovoMix 30</td>
</tr>
</tbody>
</table>

Principle of bd mixed-insulins

- **Breakfast**
- **Tea**
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• Future preparations
• Final recommendations

Why develop new insulin preparations?

Insulin uptake

Adapted from: The DCCT Study Group, NEJM, 1993; Vol. 329, No. 14: 977-986
Insulin analogues

Short acting analogues

Clinical effectiveness of Lispro and Aspart

• In type I diabetes
  – Better postprandial glucose
  – Reduced severe hypoglycaemic episodes
  – Improved HbA1c versus regular insulin when used in pumps
  – No or little improvement in HbA1c

• In type II diabetes
  – 25% reduction in severe hypos
  – No improvement in HbA1c

Long acting analogues

Glargine

N. Younis, H. Soran and D. Bowen-Jones.
Glargine

Glaraline Lantus NPH insulin

Time of Day (hr)

20 22 24 2 4 6 8 10 12 14 16 18 20

B               L                       D

Basal insulin

M. Riddle, J. Rosenstock, and J. Gerich. The Treat-to-Target Trial: Randomized Addition of Lantus or Human NPH Insulin to Oral Therapy of Type 2 Diabetes Patients for the Insulin Glargine. Diabetes Care 2005;28:11

The Thomas Addison Unit

Type I

Type II

100 90 80 70 60 50 40 30 20 10 0

Regular insulin Insulin analogues

n=52

n=52, Type I =17% and type II=83% of all patients

Short acting analogues HbA1c in type I diabetes

Anderson (1997)

Bode (2002)

Bode (2002)

Ciofetta (1999)

Home (2000)

Iwamoto (2001)

Rossin (2000)

Recasens (2000)

Anderson (1997)

Annunci (2001)

Favours regular

Favours analogues

5.5-6.7

5.5-6.7

Anderson (1997)

Anderson (1997)

Ross (2001)

Vignati (1997)


Short acting analogues hypoglycaemic episodes in type I diabetes

Anderson (1997)

Anderson (1997)

Bode (2002)

Bode (2002)

Ciofetta (1999)

Dal Sindaco (1998)

Dal Sindaco (1998)

Gale (2000)

Home (2000)

Renner (1999)


Short acting analogues HbA1c in type II diabetes

Anderson (1997)

Anderson (1997)

Ross (2001)

Vignati (1997)

Anderson (1997)

Ross (2001)

Vignati (1997)

Favours analogues

Favours regular

Anderson (1997)

Anderson (1997)

Herz (2002)

Ross (2001)

Vignati (1997)


**Insulin analogues in type I (summary)**

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Severe hypos</th>
<th>Noct hypos</th>
<th>Minor hypos</th>
<th>Overall hypos</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>→</td>
</tr>
<tr>
<td>Glargine</td>
<td>↑↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>→↓</td>
</tr>
<tr>
<td>Detemir</td>
<td>→</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

**Why develop new insulin preparations?**


**Insulin analogues in type II (summary)**

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Severe hypos</th>
<th>Noct hypos</th>
<th>Minor hypos</th>
<th>Overall hypos</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro</td>
<td>→</td>
<td>↓↓</td>
<td>↑</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td>→</td>
<td>↓↓</td>
<td>↓↓</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>→↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>→↓</td>
</tr>
<tr>
<td>Detemir</td>
<td>→</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

**Cost**

<table>
<thead>
<tr>
<th>Approximate annual costs*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short acting insulins</strong></td>
</tr>
<tr>
<td>Aspart (NovoRapid)</td>
</tr>
<tr>
<td>Lispro (Humalog)</td>
</tr>
<tr>
<td>Aschpid</td>
</tr>
<tr>
<td>Humulin S</td>
</tr>
<tr>
<td><strong>Long acting insulins</strong></td>
</tr>
<tr>
<td>Levemir (Detemir)</td>
</tr>
<tr>
<td>Lantus (Glargine)</td>
</tr>
<tr>
<td>Longer-acting Humulin I</td>
</tr>
<tr>
<td>Insulatard</td>
</tr>
<tr>
<td><strong>Biphasic insulins</strong></td>
</tr>
<tr>
<td>NovoMix 30</td>
</tr>
<tr>
<td>Humalog Mix25</td>
</tr>
<tr>
<td>Humulin M10</td>
</tr>
<tr>
<td>Miotard 30</td>
</tr>
</tbody>
</table>

* Based on information in Chemist & Druggist. Calculated using cartridge costs, and assuming the patient is using 50 units daily of a short-acting insulin, 20 units daily of a long-acting insulin or 50 units daily of a biphasic insulin.

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**Future preparations**

- New insulin analogues
- Inhaled insulin
- Oral Modified insulin
- Sublingual insulins
- Buccal insulins
- Rectal insulins
Inhaled insulins

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Inhaled insulin profile

Insulin analogue recommendations

- Type I diabetes mellitus
  - with frequent severe hypoglycaemia¹

- Type II diabetes mellitus
  - Not first line¹
  - If significant recurrent hypos¹
  - (require assistance to administer insulin)²