Insulin and new oral hypoglycaemics

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23rd March 2011, Lister Hospital
Pharmacological treatments for Diabetes Mellitus

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What shall we cover?

• Insulin
• Oral Hypoglycaemics
• Others/Newer agents

...but not in this order!
Previously

Injections - insulin

Non-insulin treatment - oral

Nomenclature

IDDM and NIDDM

Pharmacological approach
Regulation of glucose

1-food
2-GIP release  3-β cells
4/5/6-inhibitory
7-incretin effect
Classification

- Insulin sensitisers
- Insulin secreatgogoues
- Alpha glucosidase inhibitors
- Amylin analogues
- SGLT-2 inhibitors
- Insulins
- Incretins/Gliptins
Insulin sensitisers

- Biguanides
- PPAR$\gamma$ agonist/Thiazolidinedione
- Dual PPAR agonist ($\alpha$ and $\gamma$)
Insulin sensitisers

• Biguanides
  – Metformin
    » Hepatic glucose output
    » Skeletal muscle uptake
  – Phenformin

• PPAR\(\gamma\) agonist/Thiazolidinediones

• Dual PPAR agonist (\(\alpha\) and \(\gamma\))
Insulin sensitisers

• Biguanides

• PPAR\(\gamma\) agonist/Thiazolidinediones
  – Pioglitazone
  – Rosiglitazone/Troglitazone

• Dual PPAR agonist (\(\alpha\) and \(\gamma\))
  – Aleglitazar

– \(\gamma\) : adipose tissue, \(\beta\) cells, vascular endoth, macrophages

– \(\alpha\) : liver, heart, skeletal muscle, vascular wall
Classification

✓ Insulin sensitisers
  • Insulin secretegogoues
  • Alpha glucosidase inhibitors
  • Amylin analogues
  • SGLT-2 inhibitors
  • Insulins
  • Incretins/Gliptins
Insulin secretagogues

ATP sensitive potassium channels
  • Sulfonylureas
  • Meglitinides
Insulin secretagogues

ATP sensitive potassium channels

- Sulfonylureas
  - 1st gen
  - 2nd gen
  - 3rd gen?

- Meglitinides
### Sulfonylureas

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration of biologic effect, h</th>
<th>Usual daily dose, mg</th>
<th>Dosing per day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-generation sulfonylureas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetohexamide</td>
<td>12 to 18</td>
<td>500 to 750</td>
<td>Once or divided</td>
</tr>
<tr>
<td>Chlorpropamide (Diabinese)</td>
<td>24 to 72</td>
<td>250 to 500</td>
<td>Once</td>
</tr>
<tr>
<td>Tolbutamide (Orinase)</td>
<td>14 to 16</td>
<td>1000 to 2000</td>
<td>Once or divided</td>
</tr>
<tr>
<td><strong>Second-generation sulfonylureas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide (Glucotrol)</td>
<td>14 to 16</td>
<td>2.5 to 10</td>
<td>Once or divided</td>
</tr>
<tr>
<td>Glipizide (Glucotrol XL)</td>
<td></td>
<td>5 to 10</td>
<td>Once</td>
</tr>
<tr>
<td>Gliclazide (Diamicron R)</td>
<td>24</td>
<td>40 to 240</td>
<td>Once</td>
</tr>
<tr>
<td>Gliclazide (Diamicron MR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide (Glibenclamide)</td>
<td>20 to 24+</td>
<td>2.5 to 10</td>
<td>Once</td>
</tr>
<tr>
<td>Glyburide (Diabeta)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide (Micronase)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide (Glynase)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>24+</td>
<td>2 to 4</td>
<td>Once</td>
</tr>
</tbody>
</table>
Insulin secretagogues

ATP sensitive potassium channels

- Sulfonylureas

- Meglitinides (prandial glucose regulators)
  - Repaglinide
  - Nateglinide
Classification

- Insulin sensitisers
- Insulin secretagogues
  - Alpha glucosidase inhibitors
  - Amylin analogues
  - SGLT-2 inhibitors
  - Insulins
  - Incretins/Gliptins
Alpha glucosidase inhibitor

- Acarbose
- Voglibose
- Miglitol

- Prevents carbohydrate digestion (complex poly to mono)
- Also blocks pancreatic alpha amylase

- SE
- Treatment of hypoglycaemia
- Use with caution in severe renal impairment
Classification

- Insulin sensitisers
- Insulin secretagogues
- Alpha glucosidase inhibitors
  - Amylin analogues
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Amylin analogues

(A) Twenty-four-hour plasma insulin and amylin profiles in healthy subjects. (B) Mean amylin +/- standard deviation versus time after a meal. Amylin response is absent in patients with type 1 diabetes and impaired in insulin-requiring patients with type 2 diabetes.

Amylin analogues

- Pramlintide
- Same as insulin
- Works by
  - slowing gastric emptying
  - regulation of post prandial glucose
  - reduction of food intake/increasing satiety - (wt loss)
Mean change ± standard deviation in A1c and body weight in patients with type 1 diabetes treated with insulin plus either pramlintide or placebo

![Graph showing mean change in HbA1c and body weight over weeks for patients treated with placebo + insulin, 30 μg/60 μg pramlintide + insulin, and 30 μg/60 μg pramlintide + insulin.](image)

* p<0.05.
• p<0.001.

Classification

- Insulin sensitizers
- Insulin secretagogues
- Alpha glucosidase inhibitors
- Amylin analogues
  - SGLT-2 inhibitors
  - Insulins
  - Incretins/Gliptins
SGLT-2 inhibitors

• Sodium dependent glucose cotransporters
  • SGLT1: sm intestinal mucosa
  • SGLT2 (and 1): proximal tubule of nephron

• 90% of glucose reabsorption
  – Canagliflozin
  – Dapagliflozin
Classification

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Back to basic...
Increase in plasma concentrations of insulin (top) and c-peptide (bottom) for type 2 diabetic patients and healthy subjects after ingestion of a mixed breakfast meal.

Data are means ±SE.
* p <0.05 for differences between type 2 diabetic patients and healthy subjects.

Relative acute insulin response to IV glucose

Insulin
Insulins

- Rapids
- Intermediates
- Long
<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Onset of action</th>
<th>Time to peak effect</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro, aspart,</td>
<td>5 to 15 min</td>
<td>45 to 75 min</td>
<td>2 to 4 h</td>
</tr>
<tr>
<td>glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>About 30 min</td>
<td>2 to 4 h</td>
<td>5 to 8 h</td>
</tr>
<tr>
<td>NPH</td>
<td>About 2 h</td>
<td>6 to 10 h</td>
<td>18 to 28 h</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>About 2 h</td>
<td>No peak</td>
<td>20 to &gt;24 h</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>About 2 h</td>
<td>No peak</td>
<td>6 to 24 h</td>
</tr>
<tr>
<td>NPL</td>
<td>About 2 h</td>
<td>6 h</td>
<td>15 h</td>
</tr>
</tbody>
</table>
Available insulins

- Humalog lispro
- Humalog mix25
- Humalog mix50
- Humulin I
- Humulin S
- Humulin M3
- Lantus (glargine)
- Novorapid
- Novomix30
- Insulatard
- Actrapid
- Mixtard 30
- Levemir (detemir)
• **Rapids**
  – Human (Actrapid/Humulin S)
  – Analogues (Novorapid, Humalog Lispro, Glulisine)
  – Inhaled insulin (exubera)

• **Intermediate**
  – Insulatard/Humulin I
  – Premixed (Mixtard 30/Humulin M3/Novomix 30/ Mumalog mix 25 and mix 50)

• **Long**
  – Glargine
  – Detemir
  – Degludec (trial)
Normal (Non-diabetic) Blood Glucose and Insulin Levels over 24 Hours

- **Blood Glucose**
- **Natural Insulin Secretion**

- Breakfast
- Lunch
- Supper

- Glucose Levels
- Insulin Levels
Effect of twice-daily insulin regimen

Twice-daily administration of regular (solid lines) and intermeing lente or NPH (dashed lines) insulins before breakfast and evening meal provides peaks of insulin after the injections as a relatively constant baseline level of insulin throughout the day after injections of the intermediate-acting insulins.
Variable serum insulin concentrations with premixed insulins

24-hour serum insulin profiles after the injection of two premixed insulin preparations: one containing a total of 0.3 units/kg of NPH and regular insulin in a 50:50 ratio (dashed line); and one containing the same total amount of NPH and regular insulin in a 70:30 ratio (solid line). Serum insulin concentrations were significantly higher during the first six hours with the 50:50 regimen which contained more regular insulin. To convert serum insulin values to µU/mL divide by 6.

Time-action profiles for NPH and insulin glargine

Serum insulin concentrations after subcutaneous injection of 0.4 U/Kg body weight of insulin glargine (shown in red) or NPH human insulin (shown in blue) on 2 different study days in 15 normal subjects. In contrast to NPH insulin, the time-action profile for insulin glargine has virtually no peak which may make it an ideal basal insulin for intensive insulin therapy in patients with type 1 diabetes. To convert serum insulin values to μU/mL, divide by 6.

Variation in pharmacokinetics of insulin detemir among six in the same dose on four separate occasions (note significant peak 8 to 12 hours and duration well short of 24 hours in some patients). Data from Heist, T, Nosek, L, Ronn, BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with diabetes. Diabetes 2004; 53:1614.
Classification

✓ Insulin sensitisers
✓ Insulin secretagogues
✓ Alpha glucosidase inhibitors
✓ Amylin analogues
✓ SGLT-2 inhibitors
✓ Insulins
  • Incretins/Gliptins
Incretins/Gliptins
Incretins/Gliptins

Incretins are a group of gastrointestinal hormones that cause an increase in the amount of insulin released from the beta cells of the islets of Langerhans after eating, even before blood glucose levels become elevated.

Eg. Gastric-inhibitory-peptide (GIP), Glucagon-like-peptide1 (GLP1)
GLP-1 concentrations (top) and GIP concentrations (bottom) using NH2-terminal assays

Data are means ±SE.
* p <0.05 for differences between type 2 diabetic patients and healthy subjects.

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Incretin effect after oral glucose was diminished in type 2 diabetes\textsuperscript{6}

*\(p \leq 0.05\) vs. respective value after oral load

IR = immunoreactive

6. Adapted from Nauck M et al Diabetologia 1986;29:46–52
Why are incretins important?

• Incretins are important:
  – The “incretin effect”
  – The incretin effect accounts for ~60% of total insulin release following a meal

• Incretin effect is due to Incretins (hormones) secreted by intestinal endocrine cells in response to nutrient intake

• Accessory effects..
GLP-1 secreted upon the ingestion of food

1. β-cell: Enhances glucose-dependent insulin secretion in the pancreas

2. α-cell: Suppresses postprandial glucagon secretion

3. Liver: Reduces hepatic glucose output

4. Stomach: Slows the rate of gastric emptying

5. Brain: Promotes satiety and reduces appetite

Incretins and glycaemic control\textsuperscript{7,8}

Mode of action of DPP-4 inhibitor

A DPP-4 inhibitor and inhibits the breakdown of incretins and thereby increases active incretin levels.

DPP-4 = dipeptidyl peptidase 4 inhibitor

Adapted from 8. Miller S, St Onge EL. Ann Pharmacother 2006;40:1336-1343.
Two main incretins...

<table>
<thead>
<tr>
<th>GLP-1</th>
<th>GIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 amino acid peptide&lt;sup&gt;1&lt;/sup&gt;</td>
<td>42 amino acid peptide&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Synthesised and released by L cells of ileum and colon</td>
<td>Synthesised and released from K cells of jejunum and duodenum</td>
</tr>
<tr>
<td>Sites of action:</td>
<td>Sites of action:</td>
</tr>
<tr>
<td>Pancreatic $\beta$-cells and $\alpha$-cells</td>
<td>Pancreatic $\beta$-cells</td>
</tr>
<tr>
<td>GI tract</td>
<td>Adiopocytes</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td></td>
</tr>
</tbody>
</table>

# Incretin based therapies

<table>
<thead>
<tr>
<th>GLP1 mimetics</th>
<th>GLP 1 enhancers (DPP-4 Inhibitor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S/C Inj)</td>
<td>(Oral)</td>
</tr>
<tr>
<td>Exenetide</td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>Exenetide LAR</td>
<td>Vildagliptin</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Saxagliptin</td>
</tr>
<tr>
<td>Taspoglutide</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Algoliptin</td>
</tr>
</tbody>
</table>

**Incretin based therapies**

- Exenetide
- Exenetide LAR
- Liraglutide
- Taspoglutide
- Albiglutide

- Sitagliptin
- Vildagliptin
- Saxagliptin
- Linagliptin
- Algoliptin
Mean (SE); N = 10; *P < 0.05.
GLP1 mimetics

• Exenatide/Liraglutide
Does it work?
Change in A1c (A) and weight (B) from baseline in patients with type 2 diabetes treated with metformin plus exenatide-coated placebo

Open-label extension study – combined 82-week completers data. Exenatide continued to reduce weight

Baseline body weight

- Placebo BD (N = 128)  98 kg
- Exenatide 5 µg BD (N = 128)  100 kg
- Exenatide 10 µg BD (N = 137)  100 kg

Mean Δ body weight (kg)

Time (week)

0 10 20 30 40 50 60 70 80 90

-5 -4 -3 -2 -1 0 1

Placebo-controlled Trials

Open-label extension (all patients exenatide 10 µg BD)

82-wk completers; Mean (SE); Weight was a secondary endpoint
Adapted from Blonde L, et al. Poster presented at the American Diabetes Association Meeting 2005 (Abstract 477P)
Exenatide vs. Insulin Glargine Comparator Trial: Achieved Equivalent Reductions in HbA$_{1c}$

(Pts on Exenatide were better off by 5-6 kg)

ITT population; Mean ± SE shown.
## Adverse events

Results of 30-week exenatide studies

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N = 483)</th>
<th>Exenatide 5 µg and 10 µg BD (N = 963)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>18%</td>
<td>44%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
<td>13%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>Feeling jittery</td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Overall incidence ≥5% and incidence of Exenatide > placebo
GLP1 mimetics

- Exenatide/Liraglutide
  - Caution in Cr Cl <50 ml/min (not used <30)
  - SEs: Nausea/vomting. Pancreatitis*
  - Wt reduction
  - Papillary thyroid/Thyroid C cell hyperplasia (Liraglutide)
GLP1 enhancers

- Sitagliptin/Vildagliptin/Saxagliptin
Does it work?

- **Sitagliptin**
  - **Monotherapy**
    - 0.6% reduction in HbA1c
    - -1.5% if starting >9%
  - **Combined**
    - +metformin: -0.6%
    - +pioglitazone: -0.85%
    - Sitagliptin+metformin vs glipizide+ metformin: 0.7% in both but hypo in glipizide group

- Functions as tumour suppressor
- Adjust dose in renal compromise
• Saxagliptin/Vildagliptin/Sitagliptin
  • Same efficacy overall
  • Abdo pain/nausea/vomiting common
  • Pancreatitis
  • Skin reaction
  • Vildagliptin - hepatic dysfunction
  • Renal safety - ? Saxagliptin
  • Weight neutral
Incretins/Gliptins

- Not as monotherapy
- Not with insulin
- Third agent or second agent
Classification

✓ Insulin sensitisers
✓ Insulin secretagogues
✓ Alpha glucosidase inhibitors
✓ Amylin analogues
✓ SGLT-2 inhibitors
✓ Insulins
✓ Incretins/Gliptins
Conclusion: we covered

• Insulin
• Oral Hypoglycaemics
• Others/Newer agents

...but not in that order!
Summary

• Will see various combinations of insulin therapy
• Will see various combinations of agents, oral and injections
• Be aware of new side effects for the newer agents
• Pump - still not widely available
• Transplant/artificial pancreas ......