Insulin: A Powerful Weapon in the Diabetic Arsenal

Diana Cowell, PharmD
PGY-1 Pharmacy Resident

Objectives

• Identify the mechanism of action of insulin
• Describe the onset and duration for the various types of insulin
• Identify important safety precautions

Mechanism of Action

• Produced by pancreatic beta cells
• Acts at insulin receptor
• Allows glucose to enter cell
• Prevents liver glucose production
• Type 1 DM – Absence of Insulin
• Type 2 DM – Insulin Resistance
Effects of Insulin

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Effects</th>
</tr>
</thead>
</table>
| Liver        | Inhibits glycogenolysis; promotes glycogen storage  
Inhibits conversion of FA and AA to keto acids  
Inhibits conversion of AA to glucose |
| Muscle       | Increased protein synthesis  
Increased glycogen synthesis |
| Adipose      | Increased TG storage |

Katzung BG, Masters SB, Trevor AJ: Basic and Clinical Pharmacology, 12th Ed.

Structure of Insulin

- 51 Amino Acids in 2 chains  
- Disulfide bridges

Insulin Dimers and Hexamers

- Form dimers and hexamers when concentrated  
- Stabilize around zinc ions  
- Monomers are biologically active  
- Degradation to monomers = delayed absorption
Types of Insulin Analogs

Short Acting Insulin

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Pen/Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>Novolin R</td>
<td>30 min – 1 hr</td>
<td>2-4 hrs</td>
<td>6-12 hrs</td>
<td>Vial</td>
</tr>
<tr>
<td>Regular</td>
<td>Humulin R</td>
<td>30 min – 1 hr</td>
<td>2-4 hrs</td>
<td>6-12 hrs</td>
<td></td>
</tr>
</tbody>
</table>

Rapid Acting Insulin

- **Lispro**
  - Reverse B28 Proline and B29 Lysine

- **Aspart**
  - Replace B28 Proline with aspartic acid

- **Glanine**
  - Replace B29 Lysine with Glutamic Acid
  - Replace B3 Asparagine with Lysine
Rapid Acting insulin

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Pen/Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspart</td>
<td>Novolog</td>
<td>&lt; 15 min</td>
<td>0-2 hrs</td>
<td>3-4 hrs</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Novolog FlexPen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>Humalog</td>
<td>&lt; 15 min</td>
<td>1-2 hrs</td>
<td>3-4 hrs</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Humalog KwikPen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glulisine</td>
<td>Apidra</td>
<td>&lt; 15 min</td>
<td>1-2 hrs</td>
<td>3-4 hrs</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>Apidra SoloStar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Origins of NPH

- Protamine = strongly basic protein
  - Delays absorption of subcutaneous injections
- NPH = Neutral Protamine Hagedorn
  - Used zinc and protamine to prolong insulin effects
- Mixing of NPH and Regular Insulin
  - Can mix up to 15 minutes prior to use
  - “Clear” then “Cloudy”

Intermediate Acting Insulin

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Pen/Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>Novolin N</td>
<td>1-2 hrs</td>
<td>4-14 hrs</td>
<td>10-16 hrs</td>
<td>Vial</td>
</tr>
<tr>
<td>NPH</td>
<td>Humulin N</td>
<td>1-2 hrs</td>
<td>4-14 hrs</td>
<td>10-16 hrs</td>
<td>Vial</td>
</tr>
</tbody>
</table>

- Can be mixed with regular insulin
- Always draw up clear insulin first
Long Acting Insulin

Glargin
- Replace asparagine (A21) with glycine on A Chain
- 2 arginines added to B Chain

Detemir
- Lysine (B29) bound to myristic acid

Long Acting Insulin

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Pen/Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargin</td>
<td>Lantus</td>
<td>2-5 hrs</td>
<td>None</td>
<td>24 hrs</td>
<td>Both</td>
</tr>
<tr>
<td>Detemir</td>
<td>Levemir</td>
<td>2-5 hrs</td>
<td>None</td>
<td>24 hrs</td>
<td>Both</td>
</tr>
</tbody>
</table>

Mixed Insulins

- Aspart Protamine + Aspart
  - NovoLOG Mix 70/30
  - NovoLOG Mix 70/30 Flexpen
- Lispro Protamine + Lispro
  - HumaLOG Mix 50/50
  - HumaLOG Mix 50/50 KwikPen
  - HumaLOG Mix 75/25
  - HumaLOG Mix 75/25 KwikPen
- NPH + Regular
  - Humulin 70/30
  - Novolin 70/30
What is Protamine?

- Protamine = strongly basic protein
  - Delays absorption of subcutaneous injections

- NPH and Regular Insulin Mixed
  - Stability Issues
  - Use of protamine bound aspart/lispro gives an NPH-like effect


### Insulin Mixtures

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Pen/Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>70% NPH/30% Regular</td>
<td>Novolin 70/30</td>
<td>30 min</td>
<td>4-8 hrs</td>
<td>24 hrs</td>
<td>Vial</td>
</tr>
<tr>
<td>70% NPH/30% Regular</td>
<td>Humulin 70/30</td>
<td>30 min</td>
<td>4-8 hrs</td>
<td>24 hrs</td>
<td>Vial</td>
</tr>
<tr>
<td>50% Lispro Protamine/50% Lispro</td>
<td>Humalog 50/50 (KwikPen)</td>
<td>&lt;30 min</td>
<td>2-5.5 hrs</td>
<td>6-12 hrs</td>
<td>Vial</td>
</tr>
<tr>
<td>75% Lispro Protamine/25% Lispro</td>
<td>Humalog 75/25 (KwikPen)</td>
<td>&lt;30 min</td>
<td>1-6 hrs</td>
<td>6-12 hrs</td>
<td>Vial</td>
</tr>
<tr>
<td>70% Aspart Protamine/30% Aspart</td>
<td>Novolog 70/30 (FlexPen)</td>
<td>10-15 min</td>
<td>1-4 hrs</td>
<td>12-24 hrs</td>
<td>Vial</td>
</tr>
</tbody>
</table>

### Duration of Various Insulins

Katzung BG, Masters SB, Trevor AJ: Basic and Clinical Pharmacology, 12th Ed.
Insulins at MMC

Latest on Inhaled Insulin

Technosphere Technology
- Novel small molecule FDKP
- Self-assembles into microspheres in acidic environment
- Insulin attached during precipitation process
- Particles are freeze-dried for inhalation purposes
- Readily dissolve upon inhalation
PK and Dosing

• Similar to rapid-acting insulin
  - Reaches max concentration in 15 min
  - Faster elimination
• Cartridges come in 2 strengths: 4 and 8 units

Safe Use of Insulin in Hospitals

• Percentage of Med Errors Involving Insulin
  - 1998: 11%  
  - 2004: 16.3%  
  - 2008: 16.2%
• Insulin implicated in 33% of med error-related deaths

Common Insulin Errors

<table>
<thead>
<tr>
<th>Phase</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing</td>
<td>Incorrect dosage/irrational orders</td>
</tr>
<tr>
<td></td>
<td>Nomenclature-related errors</td>
</tr>
<tr>
<td>Transcribing/Verification</td>
<td>Incorrect transcription of verbal / telephone orders</td>
</tr>
<tr>
<td></td>
<td>Transcription of an incorrect dose</td>
</tr>
<tr>
<td></td>
<td>Poor verification procedures</td>
</tr>
<tr>
<td>Dispensing and Storage</td>
<td>Failure to double-check insulin products</td>
</tr>
<tr>
<td></td>
<td>Look-alike containers</td>
</tr>
<tr>
<td></td>
<td>Unsecure and/or non-segregated storage</td>
</tr>
<tr>
<td>Administration</td>
<td>Incorrect doses</td>
</tr>
<tr>
<td></td>
<td>Incorrect use of insulin pens</td>
</tr>
<tr>
<td></td>
<td>Name confusion</td>
</tr>
<tr>
<td></td>
<td>No nutritional assessment</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Failure to monitor and/or adjust dose</td>
</tr>
</tbody>
</table>


Prescribing

- Which insulin?
- Dose in UNITS vice “u” or “mL”
- Indication – basal, prandial, correction, etc.
- Administration time – time, prior to meal, etc.
- Regimen adjustments
- BG monitoring
- Hypoglycemia management

Order Verification

- Clarifying errors or omissions
- Improper dose/quantity
- Timing in relation to meals
- Assessment of dose adjustments
- Drug interactions
- BG monitoring ordered
- Hypoglycemia protocol ordered
Administration

- Incorrect dosage, drug, infusion rates
- Patient nutrition status
- Independent double-check of all doses
- Proper pen use – 1 pen per patient

Extra Reading


Cases
Examples of Insulin Regimens

2014 Standards of Diabetes Care

Pre-Prandial Goal: 70-130 mg/dL

Peak Post Prandial Goal: < 180 mg/dL

Case 1

A.B. 50 yo F who injects:
14 units glargine subcut QHS
4 units aspart subcut AC

<table>
<thead>
<tr>
<th>Time</th>
<th>BG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0700</td>
<td>155</td>
</tr>
<tr>
<td>1215</td>
<td>248</td>
</tr>
<tr>
<td>1730</td>
<td>172</td>
</tr>
<tr>
<td>2300</td>
<td>167</td>
</tr>
<tr>
<td>0300</td>
<td>162</td>
</tr>
</tbody>
</table>

What should we do?
A. No change – BG is perfectly managed!
B. Increase mealtime coverage at lunch to 6 units
C. Add 4 units aspart subcut at 2300 to cover high nighttime BG
D. Increase glargine to 16 units subcut QHS
Case 2
A.B. 50 yo F who injects:
  14 units glargine subcut QHS
  4 units aspart subcut AC

<table>
<thead>
<tr>
<th>Time</th>
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</tr>
</thead>
<tbody>
<tr>
<td>0700</td>
<td>160</td>
</tr>
<tr>
<td>1215</td>
<td>130</td>
</tr>
<tr>
<td>1730</td>
<td>115</td>
</tr>
<tr>
<td>2300</td>
<td>104</td>
</tr>
<tr>
<td>0300</td>
<td>65 (w/ night sweats)</td>
</tr>
</tbody>
</table>

What should we do?
A. No change – BG is perfectly managed!
B. Decrease glargine to 12 units subcut QHS
C. Decrease dinner dose to 2 units aspart subcut
D. Add 2 units aspart subcut at breakfast

Case 3
A.B. 50 yo F who injects:
  12 units glargine subcut QHS
  4 units aspart subcut AC

<table>
<thead>
<tr>
<th>Time</th>
<th>BG (mg/dL)</th>
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</thead>
<tbody>
<tr>
<td>0700</td>
<td>88</td>
</tr>
<tr>
<td>1215</td>
<td>105</td>
</tr>
<tr>
<td>1730</td>
<td>105</td>
</tr>
<tr>
<td>2300</td>
<td>104</td>
</tr>
<tr>
<td>0300</td>
<td>95</td>
</tr>
</tbody>
</table>

What should we do?
A. No change – BG is perfectly managed!
B. Increase glargine to 16 units subcut QHS
C. Increase dinner dose to 6 units aspart subcut
D. Increase lunch dose to 6 units aspart subcut

Quiz Question 1
Which of the following is NOT an effect of insulin?

a. Inhibits glycogenolysis
b. Increased protein synthesis
c. Decreased glycogen synthesis
d. Increased triglyceride storage
Quiz Question 2
Which is the onset, peak, and duration of action for rapid, short, intermediate and long acting insulins?

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5 hrs</td>
<td>None</td>
<td></td>
<td>24 hrs</td>
</tr>
<tr>
<td>30 min – 1 hr</td>
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<td>6-12 hrs</td>
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<tr>
<td>1-2 hrs</td>
<td>4-14 hrs</td>
<td></td>
<td>10-16 hrs</td>
</tr>
<tr>
<td>&lt; 15 min</td>
<td>1-2 hrs</td>
<td></td>
<td>3-4 hrs</td>
</tr>
</tbody>
</table>

Quiz Question 3
Which is not an important safety consideration with regards to insulin?

a. Insulin orders should be written in units vice in “u” or “mL”

b. Complete orders should address an indication (basal, prandial, correction) and administration timing

c. Patient nutrition status is not relevant to insulin dosing orders

d. Insulin orders should include instructions for blood glucose monitoring and hypoglycemia management
References


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