Insulin Therapy: 2016

Chris Lamer
Objectives

• Compare the different types of insulin in regards to onset, peak, duration, and their role in treatment of type 2 diabetes
• Review issues related to the initiation and monitoring of insulin therapy
• Discuss factors that affect insulin therapy such as expectations, adverse reactions, fear of treatment
What is Insulin and Why Do We Need it?

• Insulin is a hormone released by beta cells of the pancreas

• Insulin is a protein

• Insulin binds to insulin receptors to lower blood glucose by:
  • Stopping glucose production
  • Stopping glycogen breakdown
  • Promoting glucose uptake into cells to be used as energy
  • Storing glucose as glycogen
Glucose is Continuously Used for Energy

SOME Factors that affect glucose levels:

- Exercise
- Insulin resistance
- Stress
- Emotion
- Illness, Injury, or Infection
- Temperature
Insulin is Released to Control Blood Glucose Levels

• **Basal Insulin** - to help manage the glucose our bodies make

• **First Phase (Bolus) Insulin** – to tell our body to stop making glucose

• **Second Phase (Bolus) Insulin** – to help utilize the glucose we eat
Basil Insulin Release

Basal Insulin Release

Glucose in the blood
First Phase Release

Gluconeogenesis/Glycogenolysis

First Phase
Insulin Release
Second Phase Release

Second Phase Insulin Release
Progression of Diabetes

Insulin Secretion

Nutrition and Physical Activity

Non-Insulin Medications

Insulin
Using Insulin

• Augmentation
  • Improve glucose control when the pancreas is still functioning

• Replacement – mimic the pancreas
  • Pancreas unable to make insulin
  • Desire to utilize insulin as primary therapy
Use Insulin as Primary Therapy

- FPG > 250
- Casual Glucose > 300
- A1C > 10%
- Ketonuria
- Weight Loss
Diabetes Treatment Algorithms

- https://www.ihs.gov/diabetes/clinician-resources/
What Makes Insulin Different?

- How long it takes to work (onset)?
- How long it works (duration)?
- When (if) the insulin spikes (peak)?

- How concentrated is the insulin?
Insulin Concentrations

1mL U-100 contains 100 units of insulin
1mL U-200 contains 200 units of insulin
1mL U-300 contains 300 units of insulin
1mL U-500 contains 500 units of insulin
RX 52 year old man
Diagnosis of T2DM x 14 years
Current A1C = 9.9%
Random blood glucose (POC) = 248
Works and lives on a small farm 45 miles from clinic
Managing Blood Glucose with Insulin

Fasting Plasma Glucose (FPG) Target = 70-130mg/dl*

HS Basal insulin – start 10 units or 0.2 units/kg

Increase dose 2 units every 3 days until FPG is 70 - 130mg/dl*

May increase by 4 units every 3 days if FPG is > 180mg/dl*
Considerations

- What are the goals of therapy?
  - Immediate risks
  - Long term risks
  - Quality of Life

- Targets
  - A1C < 7%
  - Fasting 70-130
  - Pre-Meal 70-130
  - Bedtime < 140
  - 2h Post Prandial <160-180

Goals must be individualized to the patient
Considerations (cont.)

What should you consider before starting insulin?

• Other health conditions
• Caregiver support
• Risk of hypoglycemia
• Barriers to insulin technique
• Monitoring plan
• Education
Considerations (more)

What concerns may Rx have?
- Will it hurt?
- I don’t have time to monitor blood sugar?
- Will this interfere with my life?
- Is this dangerous – can it hurt me?
- How will it make me feel?
- Can I still work while taking it?
  - What about driving?
- Will I gain more weight?
- Does this mean I’m going to die?
Basal Insulin

- Intermediate Acting
  - NPH
- Long Acting
  - Glargine
  - Detemir (Levemir®)
- Ultra Long Acting
  - Glargine U300 (Toujeo®)
  - Degludec (Tresiba®)
## Intermediate Acting Insulin

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>1-2 hours</td>
<td>4-12 hours</td>
<td>12-16 hours</td>
</tr>
</tbody>
</table>
# Long-Acting Insulin

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine (Basaglar®, Lantus®)</td>
<td>1-2 hours</td>
<td>None</td>
<td>20-26 hours</td>
</tr>
<tr>
<td>Detemir (Levemir®)</td>
<td>1-2 hours</td>
<td>6-8 hours</td>
<td>18-24 hours</td>
</tr>
</tbody>
</table>
Ultra-Long-Acting Insulin

- Steady insulin levels for over 24 hours
- Injected once daily
- May be combined with short-acting insulin to cover meals

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine U300</td>
<td>1-2 hours</td>
<td>None</td>
<td>Up to 36 hours</td>
</tr>
<tr>
<td>(Toujeo®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degludec</td>
<td>30-90 min</td>
<td>None</td>
<td>&gt;42 hours</td>
</tr>
<tr>
<td>(Tresiba®)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Insulin Glargine U300 (Toujeo®)

- Concentrated insulin
  - 1ml of Glarine U100 contains 100 units
  - 1ml of Glargine U300 contains 300 units

- 3ml of Glargine has the same amount of insulin as 1ml of Glargine 300U
Insulin Degludec (Tresiba®)

- Available as:
  - U100 (100 units/mL)
  - U200 (200 units/mL)
- Good for 8 weeks after opening
Division of Diabetes Algorithm

**STEP 2:** Target **Premeal Glucose** (target one at a time)

Premeal Glucose Target = 70-130mg/dl*

- If Pre-lunch glucose > 130mg/dl*
  - Start 4 units Bolus Insulin before breakfast

- If Pre-supper glucose > 130mg/dl*
  - Start 4 units Bolus Insulin before lunch
  - OR Add/Increase morning NPH/levemir

- If Bedtime glucose above target (e.g. > 140mg/dl*), Start 4 units Bolus Insulin before supper OR Increase evening NPH/levemir

  Increase Bolus insulin by 2 units every 3 days

  *As insulin doses get larger, (over 10 units), begin to change insulin dose by 10-20%*
## Self Monitoring Blood Glucose

<table>
<thead>
<tr>
<th></th>
<th>Before Breakfast</th>
<th>After Breakfast</th>
<th>Before Lunch</th>
<th>After Lunch</th>
<th>Before Dinner</th>
<th>After Dinner</th>
<th>Bed Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>115</td>
<td>139</td>
<td>149</td>
<td>175</td>
<td>129</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td>159</td>
<td>182</td>
<td>122</td>
<td>169</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td>98</td>
<td>154</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturday</td>
<td>135</td>
<td>180</td>
<td>151</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunday</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Bolus Insulin

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular (Humulin®, Novolin®)</td>
<td>30-60 min</td>
<td>2-5 hours</td>
<td>5-8 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro (Humalog®)</td>
<td>15-30 min</td>
<td>30-90 min</td>
<td>3-5 hours</td>
</tr>
<tr>
<td>Aspart (Novolog®)</td>
<td>10-20 min</td>
<td>30-90 min</td>
<td>3-5 hours</td>
</tr>
<tr>
<td>Glulisine (Apidra®)</td>
<td>15-30 min</td>
<td>30-90 min</td>
<td>3-5 hours</td>
</tr>
</tbody>
</table>
Regular Insulin U500

<table>
<thead>
<tr>
<th></th>
<th>U-100</th>
<th>U-500</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 units</td>
<td>0.5mL</td>
<td>0.1 mL</td>
</tr>
<tr>
<td>100 units</td>
<td>1 mL</td>
<td>0.2 mL</td>
</tr>
<tr>
<td>200 units</td>
<td>2 mL</td>
<td>0.4 mL</td>
</tr>
<tr>
<td>400 units</td>
<td>4 mL</td>
<td>0.8 mL</td>
</tr>
<tr>
<td>Type of Insulin</td>
<td>Onset</td>
<td>Peak</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>NPH/Reg 70/30 (Humulin®, Novolin®)</td>
<td>30-60 min</td>
<td>2-4 hours</td>
</tr>
<tr>
<td>NPH/Reg 50/50 (Humulin®)</td>
<td>30-60 min</td>
<td>2-5 hours</td>
</tr>
<tr>
<td>Aspart protamine/ Aspart 30/70</td>
<td>5-15 min</td>
<td>1-4 hours</td>
</tr>
<tr>
<td>Aspart protamine/ Aspart 50/50</td>
<td>15-30 min</td>
<td>1-4 hours</td>
</tr>
<tr>
<td>Aspart protamine/ Aspart 70/30</td>
<td>5-15 min</td>
<td>1-12 hours</td>
</tr>
<tr>
<td>Lispro protamine/ Lispro 50/50</td>
<td>10-15 min</td>
<td>1-4 hours</td>
</tr>
<tr>
<td>Aspart protamine/ Aspart 75/25</td>
<td>10-15 min</td>
<td>1-12 hours</td>
</tr>
</tbody>
</table>
What to do with Other Medications When Starting Insulin?

- Metformin 500mg
  - Take 2 tablets by mouth two times daily after meals.

- Glyburide 5mg
  - Take 2 tablets by mouth two times daily.

- Pioglitazone 30mg
  - Take 1 tablet by mouth daily.
What to do with Other Medications When Starting Insulin? (cont.)

- **Metformin**: Recommend that it be continued
- **Sulfonylureas**: questionable benefit
- **TZD**: May increase risk of edema and weight gain; may reduce insulin resistance
- **SGLT2 Inhibitors**: Lower risk of hypoglycemia compared with other agents and less weight gain
- **DPP4 Inhibitors**: Modest A1C lowering; may be weight neutral
- **GLP-1 Agonist**: Can reduce A1c and body weight; longer acting have more effect than shorter acting; low risk of hypoglycemia
Insulin Costs

Is Insulin the New EpiPen? Families Facing Sticker Shock Over 400 Percent Price Hike

In the last eight years, the average price per vial of insulin has skyrocketed by over 200 percent, but there’s one major difference: If you can’t get an EpiPen, there’s a chance you might die. If your body doesn’t have insulin, you certainly will die.

“It feels like they’re holding my kid ransom,” said Tiffany Arey, whose son has diabetes.

Only three major companies make insulin in the U.S. and each has steadily raised its prices, sometimes in secret. Since 2009, the manufacturer for Novo Nordisk’s insulin Novolog has up 380 percent. Eli Lilly’s Humalog is up 280 percent and Humulin has increased by 240 percent, according to data from Truven Health Analytics.

That’s sending some diabetic families into sticker shock.

Competing insulin prices increase in tandem, ’08-’16

Average wholesale prices up over 200%.
## Insulin Costs (cont.)

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Cost/1ml (vial)</th>
<th>Cost/1ml (pen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novolin N</td>
<td>$0.54</td>
<td></td>
</tr>
<tr>
<td>Novolin R</td>
<td>$0.54</td>
<td></td>
</tr>
<tr>
<td>Novolin 70/30</td>
<td>$0.54</td>
<td></td>
</tr>
<tr>
<td>Aspart (Novolog(R))</td>
<td>$2.01</td>
<td>$2.01</td>
</tr>
<tr>
<td>Aspart/NPH</td>
<td>$2.58</td>
<td>$2.56</td>
</tr>
<tr>
<td>Detemir</td>
<td>$2.15</td>
<td>$2.86</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Cost/1ml (vial)</th>
<th>Cost/1ml (pen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humulin U500</td>
<td>$28.20 (500 units)</td>
<td>$28.20 (500 units)</td>
</tr>
<tr>
<td>Glargine U300</td>
<td></td>
<td>$15.99</td>
</tr>
<tr>
<td>Degludec U100</td>
<td>$19.76</td>
<td></td>
</tr>
<tr>
<td>Degludec U200</td>
<td>$39.71</td>
<td></td>
</tr>
</tbody>
</table>
Insulin Pens (1)

• Eliminate the need to carry and transport vials and syringes
• Improve convenience and adherence
  • Persistence with pens 65.3% compared to vials 49.8%
• Easier to administer the correct dosage
• Thinner, shorter needles
• Improved acceptance of insulin therapy
Insulin Pens (2)

- Manual/physical dexterity issues
- Visual impairment
- Extreme age categories (i.e., pediatrics, elderly)
- Trypanophobia (fear of needles and injections)
- Small insulin dosage requirements
- Lack of social acceptance
- Poor (prior) adherence to insulin with vials and syringes
- Erratic schedules and changing doses
Insulin Pens (3)

- Cost similar to vials and syringe
- Acquisition costs increase, but so do reimbursements
  - Consider formulary selection based on insurance
Insulin Pens (4)

Inhaled Insulin (1)

- Exubera: pulled by manufacturer (Pfizer)
  - Complicated to use
  - Large delivery device
  - High cost
  - Lung cancer (6/4740 patients compared to 1/4292 untreated); both groups included previous smokers
Inhaled Insulin (2)

- Afrezza
  - Dreamboat delivery

- Increase insulin in 15-30 minutes,
- Peak 12-15 (sooner than SQ)
- Duration 3 hours (mimic IV administration)
Inhaled Insulin (3)
Inhaled Insulin (4)

<table>
<thead>
<tr>
<th>Injected mealtime insulin dose</th>
<th>Afrezza® dose</th>
<th>Number of cartridges needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 4 units</td>
<td>4 units</td>
<td>4 unit (blue)</td>
</tr>
<tr>
<td>5-8 units</td>
<td>8 units</td>
<td>8 unit (green) +</td>
</tr>
<tr>
<td>9-12 units</td>
<td>12 units</td>
<td>12 unit (yellow) OR</td>
</tr>
<tr>
<td>13-16 units</td>
<td>16 units</td>
<td></td>
</tr>
<tr>
<td>17-20 units</td>
<td>20 units</td>
<td></td>
</tr>
<tr>
<td>21-24 units</td>
<td>24 units</td>
<td></td>
</tr>
</tbody>
</table>
Inhaled Insulin (5)

AFREZZA® inhalers

<table>
<thead>
<tr>
<th>Item</th>
<th>Storage Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opened package</td>
<td>May be used for up to 15 days</td>
</tr>
</tbody>
</table>

AFREZZA® cartridges

<table>
<thead>
<tr>
<th>Item</th>
<th>Storage Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not in use: Refrigerated storage</td>
<td>Refrigerated</td>
</tr>
<tr>
<td>Sealed (unopened)</td>
<td>May be stored until the expiration date</td>
</tr>
<tr>
<td>blister cards and strips</td>
<td></td>
</tr>
<tr>
<td>Sealed (unopened)</td>
<td>May be stored for 1 month</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Storage Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>In use: Room temperature storage</td>
<td>Room temperature</td>
</tr>
<tr>
<td>blister cards and strips</td>
<td></td>
</tr>
<tr>
<td>Sealed (unopened)</td>
<td>Must be used within 10 days</td>
</tr>
<tr>
<td>Strips</td>
<td></td>
</tr>
<tr>
<td>Opened</td>
<td>Must be used within 3 days</td>
</tr>
</tbody>
</table>

Do not put a blister card or strip back into the refrigerator after being stored at room temperature.

Before use, cartridge and inhaler should be at room temperature for 10 minutes.
Inhaled Insulin (6)

- Afrezza is not recommended for:
  - Treatment of DKA
  - People with COPD or asthma (risk of bronchospasm)
  - Smokers or cessation smokers
    - Smoking documentation in RPMS
      - Current smoker
      - Cessation smoker (quit within 6 months)
      - Previous smoker
Insulin in Development - Bolus Insulin

• PH20 - rapid acting
  • Faster absorption

• Linjeta
  • Faster onset of action and peak effect, reduced variability

• Combining other agents with insulin to increase onset:
  • edetic acid, hyaluronidase, nicotinamide + arginine, biochaperone
Insulin in Development - Basal Insulin

- Pegylated Lispro
  - Delays absorption, longer half life (less filtration by kidney)
  - Half life 44-75 hours
  - Preferential hepatic effect - reduced glucose output (increased suppression)
  - Lower weight effects
Insulin in Development

• Smart insulin
  • Glucose responsive
• Oral insulin spray - starts in 5 minutes peaks 30, gone in 2 hours
• Oral gel capsule - given HS
• Insulin patch to provide basal and bolus of insulin
  • Uses ultrasound to enlarge sweat and hair follicle pores
• Insulin pad - warms skin in 10 minute intervals to encourage cutaneous absorption
• Intradermal insulin using micro-needles
  • More rapid delivery of insulin compared to subcutaneous; less pain
Insulin Basics

- Warm the insulin - cold insulin hurts!
- Draw up in syringe and let sit out for a while
- Roll vial in hands (do not shake)

- Abdomen  Fastest absorption
- Arm
- Thigh
- Buttock  Slowest absorption

- *Atrophy* - Concave, pitting; More common with animal products
- *Hypertrophy* - Thickening of lipid tissue; Prevent by rotating sites
Insulin and the Joint Commission

- Lack of dose check systems
  - Recommendation is to have another ‘nurse’ review the insulin dose prior to administration
- Insulin and heparin vials kept in close proximity to each other on a nursing unit, leading to mix-ups
- Use of "U" as an abbreviation for "units" in orders (which can be confused with "O," resulting in a 10-fold overdose)
  - Recommendation to write/type out “units” on prescriptions
Special Situations

- Supplemental insulin
- Carbohydrate counting
- Insulin:Carbohydrate ratios
Conclusion

Thank you!