Examining the Necessity of Newer Insulins for In-Hospital Diabetes Management

Presented in partnership with the ICHP Annual Meeting

Faculty

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Disclosures

• Susan Cornell, PharmD, CDE, FAPhA, FAADE: Speakers’ Bureau—Sanofi

Learning Objectives

• Describe the reasons for use of concentrated insulin formulations in the treatment of diabetes
• Discuss the clinical, pharmacokinetic, and pharmacodynamic profiles for current and emerging basal insulins
• Describe the pharmacist’s role in counseling patients from inpatient to outpatient settings to minimize the risk of insulin administration errors and hospital readmissions

Technician Learning Objectives

• Describe the reasons for use of concentrated insulin formulations in the treatment of diabetes
• List the available formulations of newer insulins
• Explain how to use an insulin pen

Concentrated Insulin:

The Diabesity Epidemic
Type 2 Diabetes with Severe Insulin Resistance
Due to Obesity and Physical Inactivity

Obesity
Diagnosed with Diabetes
Physically Inactive

<table>
<thead>
<tr>
<th>Age-adjusted Percent</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 19.4</td>
<td>0 - 20.5</td>
</tr>
<tr>
<td>19.5 - 23.8</td>
<td>20.6 - 24.6</td>
</tr>
<tr>
<td>23.9 - 27.8</td>
<td>24.7 - 28.2</td>
</tr>
<tr>
<td>27.1 - 30.8</td>
<td>28.3 - 32.7</td>
</tr>
<tr>
<td>&gt; 30.8</td>
<td>32.8 - 36.9</td>
</tr>
</tbody>
</table>


Obesity
Age-adjusted Percent
0 - 20.0
20.1 - 24.4
24.5 - 28.2
28.3 - 32.7
> 32.8

Physically Inactive
Percent
0 - 20.0
20.1 - 24.4
24.5 - 28.2
28.3 - 32.7
> 32.8

Diagnosed with Diabetes
Age-adjusted Percent
0 - 6.3
6.4 - 7.5
7.6 - 8.8
8.9 - 10.5
> 10.6

Insulin Resistance
• Major defect in individuals with type 2 diabetes
• Reduced biological response to insulin
• Closely associated with obesity
• Associated with cardiovascular risk
• Type 1 diabetes patients can be insulin resistant as well


Glucose-Lowering Comparison

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Route of Administration</th>
<th>Target Insulin Resistance</th>
<th>Target Glucose (FPG or PPG)</th>
<th>A1C Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonureas</td>
<td>Oral</td>
<td>No</td>
<td>Both</td>
<td>1.5 - 2.0</td>
</tr>
<tr>
<td>Metformin</td>
<td>Oral</td>
<td>Yes</td>
<td>FPG</td>
<td>1.5</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Oral</td>
<td>Yes</td>
<td>Both</td>
<td>0.5 - 1.0</td>
</tr>
<tr>
<td>Meglitinidases</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.5 - 1.0</td>
</tr>
<tr>
<td>AGIs</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.5 - 1.0</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.5 - 0.7</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.4</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Injectable</td>
<td>No</td>
<td>Steady-state – PPG</td>
<td>0.8 - 1.5</td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>Injectable</td>
<td>Yes (to a degree)</td>
<td>Basal – FPG</td>
<td>0.6</td>
</tr>
<tr>
<td>Insulin</td>
<td>Injectable</td>
<td>Yes (to a degree)</td>
<td>Basal – FPG</td>
<td>as much as needed</td>
</tr>
</tbody>
</table>


Insulin Therapy for Insulin Resistance
• Insulin, insulin, and yet more insulin!
  - Causes weight gain and fluid retention
  - Increased risk of hypoglycemia
  - Expensive at high volumes (especially the pens)
  - Multiple injections per day often needed
  - Pumps not practical with high-volume insulin usage


Pharmacokinetic Profile of Currently Available Insulins

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>NPH (Neutral protamine Hagedorn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Insulin levels rise quickly</td>
</tr>
<tr>
<td>10</td>
<td>Insulin levels peak</td>
</tr>
<tr>
<td>24</td>
<td>Insulin levels decline</td>
</tr>
</tbody>
</table>

NPH = neutral protamine Hagedorn.

The Basal-Bolus Concept
• Basal insulin: 50% of daily needs
  - Controls nighttime and between-meal glucose at a nearly constant level
• Bolus insulin: 50% of daily needs
  - Controls mealtime glucose
  - 10% to 20% of total daily insulin requirement at each meal
  - Correction dose (sensitivity factor)
    - Correct hyperglycemia reactively
Concentrated Insulin: The Pharmacokinetic, Pharmacodynamic, and Clinical Properties of Concentrated Insulin Products

U-100 Insulin vs U-500 Insulin

- Human Regular U-500 is highly concentrated and contains 5 times as much insulin in 1 mL as standard U-100 insulin
  - Truly used for patients on high doses of insulin (usually >200 units daily)
- Both have onset of action at 30 minutes
  - U-500 insulin exhibits a delayed and lower peak effect relative to U-100
  - U-500 insulin typically has a longer duration of action compared with U-100 (up to 24 hours following a single dose)
- Clinical experience has shown that U-500 insulin frequently has time-action characteristics reflecting both prandial and basal activity


PK and PD profiles for U-500 vs U-100 Human Insulin

IRI = immunoreactive insulin; PK = pharmacokinetic; PD = pharmacodynamic.

Human Regular U-500 Pen

- Can deliver up to 300 units in a single injection
  - No dose conversion for pen
    - Vials/syringes will need dose conversion
  - Dials in 5-unit increments
  - Holds 1500 units of insulin in every pen
- For severely insulin-resistant patients
  - When daily insulin requirements are in excess of 200 units/day


High-Concentration Glargine (U-300)

- Available only in a pen
  - U-300: 450 units/pen, max 80 units/injection
    - Can be used for patients on small and large volumes of insulin
  - Offers a smaller depot surface area, leading to a reduced rate of absorption
  - Provides flatter and prolonged PK and PD profiles and more consistency
    - Half-life is ~23 hours
    - Steady state in 4 days
    - Duration of action ≤36 hours


PK and PD of U-300 Insulin Glargine vs U-100 Insulin Glargine

U-300 glargine displays a more even and prolonged PK/PD profile compared with U-100 glargine, offering blood glucose control beyond 24 hours

LLOQ = lower limit of quantification; GIR = glucose infusion rate.
U-100 and U-200 Insulin Degludec

- Available only in a pen
  - U-200: 600 units/pen, max 160 units/injection
  - U-100: 300 units/pen, max 80 units/injection
- Can be used for patients on small and larger volumes of insulin
- Provides flatter and prolonged PK and PD profiles and more consistency
  - Duration of action >42 hours
  - Half-life ~25 hours
  - Detectable for at least 5 days
  - Steady state in 3 to 4 days

- Detectable for at least 5 days
- Steady state in 3 to 4 days


Basal Insulin Degludec

- Flat, stable profile of both 100 unit/mL and 200 unit/mL formulations

- Mean 24-Hour GIR Profile of the Two Insulin Degludec Formulations at Steady State

GIR = glucose infusion rate.

Importance of Patient Education

- Avoid using insulin as a “threat,” but as a solution; discuss it as an option early
- Use insulin pens and regimens that offer maximum flexibility
- Give a “limited” trial of insulin
- Tell patient that injection is less painful than a finger stick; give an injection in the office/hospital/pharmacy
- Teach patient to recognize and treat hypoglycemia
  - Use basal analog insulin to minimize hypoglycemia


Overcoming Barriers to Insulin Therapy

- Avoid using insulin as a “threat,” but as a solution; discuss it as an option early
- Use insulin pens and regimens that offer maximum flexibility
- Give a “limited” trial of insulin
- Tell patient that injection is less painful than a finger stick; give an injection in the office/hospital/pharmacy
- Teach patient to recognize and treat hypoglycemia
  - Use basal analog insulin to minimize hypoglycemia

What Patients Need to Know about Insulin AND Delivery Devices

- Storage and expiration
  - When it should be refrigerated
  - When it can be at room temperature
  - Time medication expires after first use
- How to prepare product for first use
- How to properly use the device
- How to dispose of the device

- Compare at home vs hospital (formulary) insulin
- Syringes or pen needles
- Blood glucose meter and strips
- Lancets and lancing device
- Glucagon emergency kit
- Contact information of diabetes care provider(s)
### Product Expiration

<table>
<thead>
<tr>
<th>Products/Device</th>
<th>Refrigerated</th>
<th>Unrefrigerated</th>
<th>Once used (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro U-100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin human N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin human R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro U-100, U-200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vials &amp; pens: Insulin detemir</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pens: Insulin degludec U-100, U-200</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled:</strong> Insulin human</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Expiration dates:
- **Vials**: 28 days
- **Pens**: 28 days
- **Glargine U-300**: 42 days
- **Lispro, glargine, glulisine**: 28 days
- **Aspart**: 14 days
- **Vials & pens**: 42 days
- **Insulin degludec U-100, U-200**: 56 days

Do not refrigerate:
- Lispro, glargine, glulisine: 28 days
- Aspart: 14 days

Usable for:
- **Insulin detemir**: 42 days
- **Insulin degludec U-100, U-200**: 56 days


### Basal Insulin Delivery Options

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Concentration</th>
<th>Vial</th>
<th>Pen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>U-100</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glargine</td>
<td>U-100</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glargine</td>
<td>U-300</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>U-100</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Degludec</td>
<td>U-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>U-200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular Human</td>
<td>U-500</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

### First-Time Preparation

- **Check the pen**
  - Make sure liquid is clear, colorless, and particle-free
  - (N insulin and mixed insulin will be cloudy)
  - Wipe the rubber stopper with alcohol
- **Attach the needle**
- **Prime the needle**
  - Dial 2 to 3 units; hold up, depress the button
  - Repeat process until a drop of insulin appears at tip of the needle
- **Dial up the dose**
- **Inject straight into the skin**
  - Depress button to release insulin into subcutaneous tissue
  - Hold for 5 to 10 seconds before removing needle from skin
  - Remove needle and dispose into sharps container

### Concentrated Basal Insulin Dosing Conversion Comparison

<table>
<thead>
<tr>
<th>Glargine U-300</th>
<th>Degludec U-200</th>
<th>Human R U-500</th>
</tr>
</thead>
<tbody>
<tr>
<td>True basal insulin</td>
<td>True basal insulin</td>
<td>Pseudo-basal insulin</td>
</tr>
<tr>
<td>1 daily injection</td>
<td>1 daily injection</td>
<td>1 to 1 multiple daily injections of basal-bolus</td>
</tr>
<tr>
<td>80% of total daily basal dose</td>
<td>80% of total daily basal dose</td>
<td>Total daily dose divided into 2 or 3</td>
</tr>
<tr>
<td>Maximum single-dose injection: 80 units</td>
<td>Maximum single-dose injection: 180 units</td>
<td>Maximum single-dose injection: 300 units</td>
</tr>
<tr>
<td>Dialed in 1-unit increments</td>
<td>Dialed in 2-unit increments</td>
<td>Dialed in 5-unit increments</td>
</tr>
<tr>
<td>450 units of insulin per pen</td>
<td>600 units of insulin per pen</td>
<td>1500 units of insulin per pen</td>
</tr>
</tbody>
</table>

- **Expect higher daily dose of Glargine U-300 to maintain glycemic control**
- **Monitor for hypoglycemia**

### Clinical Pearls

- **Watch for over basalization**
  - High basal dose with no or little bolus insulin
  - Continually increasing insulin doses does not reduce insulin resistance
  - Humulin R U-500 is useful for patients on very high total daily insulin doses (eg, >200 TDD/day)
  - Ultra long-acting basal insulins (Glargine U-300 and Degludec U-200) provide longer duration of action for better basal coverage with low nocturnal hypoglycemia

### Take Aways

- **Insulin resistance is a MAJOR problem**
  - Some concentrated insulin may help people on large doses of insulin
  - However, need to use combination drug therapy to improve insulin sensitivity
  - **Novel, long-acting basal insulin analogs in development may provide benefit compared with current agents**
    - Flatter time-action profiles with less variability
    - Less hypoglycemia, particularly nocturnal hypoglycemia
  - **Patients need to know how to properly use insulin devices**
    - Hospital pharmacists should review technique at discharge
    - Community pharmacists should review technique at initial fill and periodically thereafter
Questions?