These Aren’t Your Average Rookies: A Primer on New and Emerging Insulins

Alissa R. Segal, Pharm.D, CDE, CDTC, FCCP

Disclosures

- Eli Lilly & Company: Advisory board member
- Boehringer Ingelheim: Advisory board member
Objectives

- Evaluate how recently available insulin formulations (including concentrated & follow-on biologic) may overcome challenges of inpatient insulin needs
- Distinguish the role of pharmacists in minimizing prescribing, dispensing & insulin administration errors, particularly during transitions in & out of inpatient settings
- Discuss how to evaluate & integrate new & emerging insulins into treatment plans in hospital settings & transitions in care

Robert

- 54 year-old obese male with T2DM
- Admitted for lower extremity infection & cellulitis
- T2DM before admission:
  - Glucoses higher than typical in the last week
  - Last A1C: 7.5%
- Regimen:
  - Metformin 2000 mg/day
  - Insulin degludec U-200 45 units QHS
  - Insulin lispro U-200 12 – 16 units before meals
What are the issues/challenges when someone like Robert comes into the hospital?

What should his initial glycemic treatment in the hospital?

How should Robert be transitioned home?

Insulin use in the hospital

- Most appropriate agent for the majority of hospitalized patients
- Insulin is a high-alert medication
- For effective and safe use of insulin, institutions need to consider
  - Standardized pharmacy & practice operations
  - Education of nursing & support staff
  - Implementation of hospital-wide initiatives
  - Effective communication & collaboration among caregivers
Pharmacist’s Role in the Safe Use of Insulin in the Inpatient Setting

- Minimizing medication errors
- Discouraging the use of sliding scale insulin
- Development of treatment protocols
- Formulary decision-making
- Supporting the education of patients in advance of discharge

Key Information for Pharmacists to Understand

- Treatment options
- Treatment protocols
- Potential medication errors & methods to reduce errors
- Importance of pharmacy’s role on the multidisciplinary teams to ensure safe & effective management of hyperglycemia in the hospital setting
### Selected Insulin Errors

<table>
<thead>
<tr>
<th>Phase</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing</td>
<td>Unintended drug ordered due to new formulations</td>
</tr>
<tr>
<td></td>
<td>Dosage conversion from outpatient agents</td>
</tr>
<tr>
<td></td>
<td>Lack of individualization of regimen</td>
</tr>
<tr>
<td>Transcription</td>
<td>Transcription of incorrect dose</td>
</tr>
<tr>
<td>Dispensing &amp; Storage</td>
<td>Failure to double-check insulin products</td>
</tr>
<tr>
<td></td>
<td>Look-alike containers</td>
</tr>
<tr>
<td></td>
<td>Same name for different concentrations of insulin</td>
</tr>
<tr>
<td>Administration</td>
<td>Incorrect doses or insulin given</td>
</tr>
<tr>
<td></td>
<td>Incorrect use of administration device</td>
</tr>
<tr>
<td></td>
<td>Relationship between administration &amp; nutrition</td>
</tr>
<tr>
<td></td>
<td>Incorrect omission of doses (ie: surgical, T1DM)</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Failure to monitor for insulin effect &amp; adjust dose</td>
</tr>
</tbody>
</table>

*Cobaugh DJ. et al. Am J Health-System Pharm, 2013; 70: 1404-1413*

### Common Types of Medication Errors Associated With Insulin Therapy

- **Insulin omission**
  - Leads to hyperglycemia
  - Poor outcomes including increased risk of mortality

- **Improper dose or quantity of insulin**
  - Leads to hyperglycemia or hypoglycemia
  - Hyperglycemia $\rightarrow$ ketoacidosis
  - Hypoglycemia $\rightarrow$ range of symptoms from nausea to falls to increased risk of myocardial ischemia

*Adapted from: Cohen MR. Am J Health-Syst Pharm. 2010;67 (suppl 8):S17-S21.*
Strategies for Error Minimization

- Establish & assist in utilization of user-friendly protocols
- Staff education on new insulin products & any changes to protocols
- Computerized provider order entry systems & tools
- Multidisciplinary glucose management teams
- Active participation in multidisciplinary task force to oversee glycemic control in institution

Formulary Review

- Include insulin delivery devices that have safety features, perform reliably, and are easy to administer
- Request that the pharmacy and therapeutics (P&T) committee limits types of insulin on formulary and eliminates duplicate types
Insulin Developments (US)

- Technosphere Insulin
- Degludec U-100
- Degludec U-200
- Degludec/Aspart 70/30
- Other Follow-on Insulins
- Faster rapid-acting insulins

- 2014
  - Glargine U-300
  - Lispro U-200

- 2015
  - 1st Follow-on Biologic Insulin Glargine

- 2016
  - Fixed Dose LA Insulins/GLP-1 Agonists

- 2017 & Upcoming

Profiles of Current Insulins

- Rapid (insulin lispro, aspart, glulisine)
- Short (Regular Insulin)
- Intermediate (NPH insulin)
- Long (insulin detemir)
- Long (insulin glargine)
- Ultralong (U300 glargine)
- Ultralong insulin degludec

PK = pharmacokinetic; NPH = neutral protamine Hagedorn.
Robert

- T2DM admitted for LE infection & cellulitis with A1C 7.5%
- Regimen: Metformin 2000 mg/day, Insulin degludec U-200 45 units QHS, Insulin lispro U-200 12 – 16 units before meals
- What should his initial glycemic treatment for his stay in the hospital?

Adjustment of home insulin dosing for hospital admission

- ~ 70 – 100% of home regimen

<table>
<thead>
<tr>
<th>Consider higher dose if:</th>
<th>Consider lower dose if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>High admission A1C</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>High glucose levels on home dose</td>
<td>History of hypoglycemia (without previous insulin adjustment)</td>
</tr>
<tr>
<td>Steroids being started</td>
<td>Large dietary intake as outpatient, with expected lower intake as inpatient</td>
</tr>
<tr>
<td>On non-insulin agents being DC’d as inpatient</td>
<td></td>
</tr>
</tbody>
</table>
**Ideal Characteristics of Prandial/Bolus Insulin**

- Action closely mimics the normal physiological insulin response to meals
- Rapidly absorbed to control post-prandial hyperglycemia
- Quickly eliminated to avoid hypoglycemia
- Adjustable for pre-meal blood glucose concentration & content of the meal
- Easily administered

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**Review of Rapid Acting Insulins**

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Product</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart analog</td>
<td>Novolog</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glulisine analog</td>
<td>Apidra</td>
<td>10 - 30 min</td>
<td>30 min - 3 h</td>
<td>3 - 5 h</td>
</tr>
<tr>
<td>Insulin lispro analog</td>
<td>Humalog</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro conc.</td>
<td>Humalog U-200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin human inhalation</td>
<td>Afreeza</td>
<td>12 - 30 min</td>
<td>30 - 90 min</td>
<td>3 h</td>
</tr>
</tbody>
</table>
Inhaled technosphere insulin

Inhaled insulin: Pharmacodynamics

Adapted from Kipnis D. Ann Intern Med, 1968; Mudaliar SR et al. Diabetes Care, 1999; Afrezza® Prescribing Information
**Inhaled Insulin Dosing**

- **Insulin Lispro**
  - U-200 vs U-100
  - Comparable PK & PD to U-100

![Graphs comparing glucose infusion rates and mean peak serum insulin concentrations](Image)

**Lispro U-200: Administration**

- Designated administration device
  - Contains total of 600 units
  - Dosed by actual units
  - Dosage interval: 1 unit
  - Maximum dose per injection: 60 units

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**Inpatient considerations for the newer prandial insulins**

- No data on use within care settings other than outpatient
- Insulin lispro concentrations have same proprietary name
- Unique administration devices
- Confusion regarding dosage conversion in & out of care facilities
- Matching insulin to nutritional intake
- Pulmonary function – inhalation
### Short and Intermediate Acting Insulins

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Product</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human Regular</td>
<td>Humulin R</td>
<td>30 - 60 min</td>
<td>2 - 5 h</td>
<td>up to 12 h</td>
</tr>
<tr>
<td></td>
<td>Novolin R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Human Regular Conc.</strong></td>
<td>Humulin R U-500</td>
<td>30 - 60 min</td>
<td>2 - 5 h</td>
<td>6.5 - 10 h</td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human NPH</td>
<td>Humulin N</td>
<td>90 - 4 h</td>
<td>4 - 12 h</td>
<td>up to 24 h</td>
</tr>
<tr>
<td></td>
<td>Novolin N</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### New administration devices for Regular U-500 Insulin

- Administration devices calibrated for the concentration, so dosing in ACTUAL units
- Vial
  - Recommended to dispense with U-500 Syringe
- Insulin pen
Challenges with Regular U-500 Insulin

- Fears of hypoglycemia
- Dosing confusion
- Administration errors
- Different action profile compared to the 100 unit/mL formulation


Addressing Safety Concerns: U-500 in a Hospital Setting

- Pharmacist (or CDE) verify outpatient regimen
- U-500 is not stocked or stored on the units
- When ordered,
  - Pop-up message to verify choice of concentrated formulation
  - Total dose in units is entered
  - Computer converts units to volume
- Checklist and dispensing kit stored with product
- Pharmacist delivers insulin to nurse
  - Safety time out taken to review drug, orders, & medication administration record
- Patient and staff education

**Desired Characteristics of Replacement Basal Insulin**

- Mimics natural pancreatic basal insulin secretory pattern
- No distinct peak effect
- Continued effect over 24 hours
- Minimizes risk of nocturnal hypoglycemia
- Administered once daily for optimal patient adherence
- Reliable absorption pattern

**Long-Acting Insulins**

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Product</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>Levemir</td>
<td>45 min - 4 h</td>
<td>Minimal peak</td>
<td>up to 24 h</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Basaglar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine conc.</td>
<td>Toujeo</td>
<td>6 h</td>
<td>Minimal peak</td>
<td>24 h</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>Tresiba</td>
<td>1 h</td>
<td>Minimal peak</td>
<td>Up to 42 h</td>
</tr>
<tr>
<td>Insulin degludec conc.</td>
<td>Tresiba U-200</td>
<td>1 h</td>
<td>Minimal peak</td>
<td>Up to 42 h</td>
</tr>
<tr>
<td><strong>Pre-Mixed Long-Acting Insulin Combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin degludec/ aspart 70/30</td>
<td>Ryzodeg</td>
<td>30 – 60 min</td>
<td>2 – 5 h</td>
<td>&gt; 24 h</td>
</tr>
</tbody>
</table>
Pharmacodynamic Profiles of Basal Insulins Glargine U-100 & Detemir

Glargine
- 0.3 U/kg T1D
- 0.35 U/kg T1D
- 0.4 U/kg T1D
- 0.5 U/kg T2D
- 0.8 U/kg T2D

Detemir
- 0.35 U/kg T1D
- 0.4 U/kg T1D
- 0.4 U/kg T2D
- 0.8 U/kg T2D

GIR (mg/kg/min)
Time (hours)

Glucose Infusion Rates (GIR) after Basal Insulin Injection

T1D = type 1 diabetes; T2D = type 2 diabetes.

Basal Insulin: Variability of Effect

- Variability in effects of an insulin can cause unexplainable variations in glucose control from day to day

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Within Subject Variability (CV% of AUC GIR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>68</td>
</tr>
<tr>
<td>Glargine U-100</td>
<td>48 – 99</td>
</tr>
<tr>
<td>Detemir</td>
<td>27</td>
</tr>
<tr>
<td>Glargine U-300</td>
<td>34.8</td>
</tr>
<tr>
<td>Degludec</td>
<td>20</td>
</tr>
</tbody>
</table>

**Insulin Glargine U-300: Pharmacodynamics vs U-100**

- The U-300 glargine has a flatter more prolonged effect
- The time it takes for 50% of the effect of a single injection:
  - U-100 = 12.1 hours
  - U-300 = 16.7 hours

GIR = glucose infusion rate.


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**Glargine U-300: Efficacy vs. U-100**

- Glargine U-300 is non-inferior to U-100
- Similar reduction in A1C
- Similar reduction in FPG
- Less nocturnal hypoglycemia
- Likely need 15% higher dose

Ritzel et al. *Diabetes*. 2015; 90-LB.
Administration Device

- Administration via designated device
  - Contains 450 units of insulin (1.5mL)
  - Stable for 28 days at room temperature
  - Dosed in actual units
  - Dosing intervals of 1 unit
  - Maximum dose per injection 80 units

Insulin Degludec

**Insulin Degludec: Pharmacodynamics vs Insulin Glargine U-100**

- **Insulin degludec**
  - 0.4 U/kg: 25.9 hours
  - 0.6 U/kg: 27.0 hours
  - 0.8 U/kg: 23.9 hours
- **Insulin glargine**
  - 0.4 U/kg: 11.8 hours
  - 0.6 U/kg: 14.0 hours
  - 0.8 U/kg: 11.9 hours

*Insulin glargine was undetectable after 48 hours*

Heise T et al. Diabetologia, 2011

**Insulin Degludec U-100: Efficacy**

- Compared to Glargine U-100
  - Similar A1C lowering
  - Lower FPG achieved
  - Numerically less overall hypoglycemia
  - Significantly less nocturnal hypoglycemia

Insulin Degludec U-100 vs U-200 Pharmacodynamics


- Designated administration FlexTouch device
- Contains 300 units or 600 units (3 mL)
- Dosed by actual units
  - Dosage interval: 1 or 2 units
  - Maximum dose per injection: 80 or 160 units
- Stable at room temperature for 56 days

U100 pen
Up to 80U in 1U increments

U200 pen
Up to 160U in 2U increments
Follow-on Insulin Glargine: Pharmacokinetics & Dynamics

Linnebjerg et al, ADA, 2014; Heise et al, ADA, 2014

Follow-on Insulin Glargine

- Clinical studies
  - Healthy
    - PK/PD studies (n=91)
  - Type 1 Diabetes
    - PD study (n=19)
    - 24-week Efficacy study (n=268)
  - Type 2 Diabetes
    - 28-week Efficacy study (n=376)

- Developed for purely financial reasons

- Challenges
  - Pharmacovigilance
  - Same Non-proprietary name
  - Administration via Kwikpen
Inpatient considerations with newer long-acting basal insulins

- Very limited data for use in hospital setting
- Only available in disposable pens
- Insulin degludec concentrations have same proprietary name
- Dosing conversion confusion
- Longer duration of action for some
- Smoother action profile
- Less hypoglycemia

Reminder: Robert

- Outpatient insulin: IDeg U-200 45 units QHS, ILis U-200 14 – 16 units QAC

- How would you convert Robert’s insulin regimen?

- Do you need to adjust for the concentration?
**Strategies for Discharge: Prior to & at Discharge**

- Assist in conversion back to pre-admission regimen or to an adjusted/new regimen
- Ensure patient discharged with all necessary prescriptions and devices
- Begin educating the patient as soon as the patient is able to participate
- Communicate with PCP any changes made to regimen
- Post-discharge follow-up appointment with PCP

**Factors to consider for transition (discharge) regimen**

- Home regimen & control (A1C & hypo freq)
- Changes due to current illness/hospitalization
- Inpatient regimen & control
- Discharge use of steroids
- Patient preferences
- Financial/social/insurance
- Expected follow-up
Robert

- Outpatient insulin: IDeg U-200 45 units QHS, ILis U-200 14 – 16 units Q AC (A1C 7.5%)
- Inpatient insulin: IGlar U-100 50 units QHS, ILis U-100 8 – 10 units Q AC

What would you recommend for Robert’s discharge regimen?

Summary

- Insulin
  - Primary agent used within institutions
  - Offers effective treatment
  - Poses high risk of hyper- & hypoglycemia
- Newer insulins
  - Offer opportunities primarily in the outpatient setting
  - Create challenges/confusion in determining the conversion & administration in inpatient settings
  - Longer-acting basal insulins might provide smoother basal action
Summary

- For effective and safe use of insulin, pharmacists need to play a role in:
  - Standardizing pharmacy & practice operations
  - Education of patients, nursing & support staff
  - Implementation of hospital-wide initiatives
  - Effective communication & collaboration among caregivers for patient care as transition through care systems.