Insulin Cases: Inpatient and Outpatient

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Disclosures/Conflict of Interest

Justin Schmidt, PharmD., BCPS, BC-ADM declares no conflicts of interest, real or apparent, and no financial interests in any company, product or service mentioned in this program, including grants, employment, gifts, stock holdings and honoraria.

OR

Susan Cornell, BS, PharmD., CDE, FAPhA, FAADE declares the following:

• Novo-Nordisk Advanced Practitioner Advisory Board
• Sanofi Speaker Bureau

Objectives

Pharmacists

- Describe the pathophysiology of insulin resistance in type 1 and type 2 diabetes.
- Discuss the clinical, pharmacokinetic and pharmacodynamic profiles for current and emerging concentrated insulins.
- Describe safe and effective insulin administration and use.
- Identify strategies that allow safe transition between regimens containing concentrated insulins.
- Describe the role of pharmacists in counseling patients in inpatient and outpatient settings, to minimize the risk of insulin-related errors and hospital readmissions.

The Diabesity Epidemic

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

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| Percent | | | |
|---------| | | |
| 0 - 12.5| | | |
| 12.6 - 15.0| | | |
| 15.1 - 17.5| | | |
| 17.6 - 20.0| | | |
| ≥ 20.1  | | | |

Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet

- Decreased Insulin Secretion
- Increased Glucagon Secretion
- Increased Lipolysis
- Increased Glucose Reabsorption
- Increased Glucose Uptake
- Decreased VEGF
- Neutrophil Infiltration

3. Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet. See image for sources.
Insulin Resistance

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


Insulin Resistance: Diet & Exercise

• Additive effects: 3X higher improvement than diet or exercise alone
• Even if a person cannot exercise, can improve insulin sensitivity with 5-10% weight loss
• Calorie-reduced diet of any composition is effective
• Exercise typically 30-45 minutes at moderate level, 3-5 times per week

12 Pharmacotherapy Options

• Basal insulin
  - Insulin NPH
  - Insulin detemir (Levemir)
  - Insulin glargine (Lantus)
  - Insulin aspart (Novolog)
  - Insulin glulisine (Apidra)
  - Regular human insulin (Humulin R, Novolin R)

• Bolus insulin
  - Insulin lispro (Humalog)
  - U100
  - U200
  - Insulin degludec

• α-glucosidase inhibitors (AGI)
• Biguanides
• Bile acid sequestrants (BAS)
• Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)
• Dopamine agonists
• Glitazones
• Sodium Glucose Co-Transporter-2 inhibitors (SGLT-2s)
• Amylinomimetic

Glucose-Lowering Comparison

| Medication | Route of Administration | Target insulin resistance | Target Glucose | A1C Reduction (%) | And Reduction (%)
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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

Diabetes Medication Use Trends: CDC-National Health Interview Survey

New oral/non-insulin options have reduced insulin use... however
• Type 2 DM increasing (2x from 4.3% in 1995 to 8.6% in 2010)
• U-500 use increased ~97% between 2008-2010
• Proportion of basal insulin use increased 4% between 2008-2010
Pharmacokinetic Profile of Currently Available Insulins

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
  - 10–20% of total daily insulin requirement at each meal
- Correction dose (sensitivity factor)
  - Correct hyperglycemia reactively

High Doses of Insulin

- Concerns:
  - Hypoglycemia
  - Medication errors in dosing
  - Absorption issues
- Problems:
  - Over-basalization
  - Failure to treat the physiological defects
    - Insulin resistance
    - Decrease satiety

Concentrated Insulin

Rationale for Concentrated Insulin Use

- When daily insulin requirements are in excess of 200 units/day, the volume of U-100 injected insulin may become an issue
  - Physically too large for a single SC administration
  - Multiple injections are required to deliver a single dose
  - Increased injections may lead to compliance issues and poor glycemic control
  - Discomfort
  - Unpredictable absorption (rate-limiting step in insulin activity)

U-100 Insulin vs U-500 Insulin

- Humulin R U-500 is highly concentrated and contains 5 times as much insulin in 1 mL as standard U-100 insulin
- 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
Pharmacodynamics of Regular Insulin U-500 vs U-100

- Earlier peak at lower doses of U-500 (similar to U-100)
- Extended duration of U-500 vs U-100
- Somewhat like NPH/Rig Prepar

Pharmacodynamics of U-100 vs U-300 Glargine

- Type 1 diabetes:
  - Start with 0.5 to 1 U/kg/day of the total daily insulin dose calculated by using 0.2-0.4 U/kg/day
  - Give remainder of total daily insulin dose as short-acting insulin and divide between each daily meal
- Type 2 diabetes:
  - Start with 0.5 U/kg/day

U-300 Insulin Glargine

- FDA approved February 2015 (Toujeo®)
- Available only as a pen: 450 units/1.5 mL
- Maximum 80 units per injection
- Smaller depot surface area leading to a reduced rate of absorption
- Provides flatter and prolonged pharmacokinetic and pharmacodynamic profiles and more consistency
- Onset after first dose ~ 6 hours
- Half-life is ~23 hours
- Steady state in 4-5 days
- Duration of action ~36 hours

U-300 Insulin Glargine Dosing: Insulin-Naïve Patients

- Type 1 diabetes:
  - Start with 1/3 to 1/2 of the total daily insulin dose calculated by using 0.2-0.4 U/kg/day
  - Give remainder of total daily insulin dose as short-acting insulin and divide between each daily meal
- Type 2 diabetes:
  - Start with 0.2 U/kg/day

U-300 Insulin Glargine Dosing: Changing Insulins (Type 1 or Type 2 DM)

- Changing from QD long-acting or intermediate-acting insulin:
  - Initial dose can be same as QD long-acting dose, for patients controlled on U-100 insulin glargine
  - Expect that higher daily dose of U-300 insulin glargine will be needed to maintain the same level of glycemic control (~15% higher)
- Changing from BID NPH insulin:
  - Initial dose is 80% of the total daily NPH dosage (similar to conversion to U-100 insulin glargine)

U-100 and U-200 Insulin Degludec

- FDA denied approval in 2013 (signals for increased MACE/MACE+); research continues
- Approved in EU – Tresiba®
- Available only as FlexTouch pens
  - U-200: 600 units/pen, max 160 units/inj
  - U-100: 300 units/pen, max 80 units/inj
- Duration of action ≥42 hours
- Half-life ≥25 hours
- Detectable for at least 5 days
- Steady state in 2-3 days
Pharmacodynamics of Degludec*


Glucose Lowering Effect on Day 6 (mg/kg/min)

Time since Injection (hours)

Ideg 0.4 U/kg

Ideg 0.8 U/kg

Ideg 0.6 U/kg

U-200 Insulin Lispro

• FDA approved in May 2015
• Only available as a pen
• 200 units/mL, 3 mL, max 60 units/ inj
• Mfr advises against use in subcutaneous infusion pumps and intravenously
• No need to adjust dose when switching from another rapid-acting insulin
• PD study demonstrated bioequivalence
• Max glucose infusion rate was 534 vs. 559 mg/min (~5% greater w/ U-100 insulin lispro)
• Time to max effect 2.8 vs. 2.4 h (~15% faster w/ U-100 insulin lispro)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205747s000lbl.pdf

Prandial Insulin Lispro: U-200

Inhaled Insulin Delivery

Concentrated Insulins: Summary

• U-100 Regular Insulin
• Basal and bolus properties
• High risk of errors in dosing due to availability in a vial
• U-300 Insulin Glargine
• Slow initial onset and up to 5 days until steady state
• 15% higher dose than U-100 glargine (but unit-unit conversion initially advised)
• Less glycemic variability results in slightly less nocturnal hypoglycemia vs U-100 insulin glargine
• U-200 Insulin Degludec
• Not FDA approved
• Similar anticipated benefits of reduced nocturnal hypoglycemia
• U-200 Insulin Lispro
• Rapid-acting
• Bioequivalent to U-100 insulin lispro
Issues with concentrated insulin in the hospital setting

Transitions in care
- Transitions in diet, insulin formulations and insulin requirements complicate management in the hospital
- Concentrated insulins and pen devices have unique risks in the hospital
- Important to know onset and duration of insulins to allow safe transitions

U-500 in the hospital
- Retrospective study of 61 patients that were on U-500 prior to hospitalization
  - Switching associated with fewer days w/ hypoglycemia (3% vs 15% of days w/ hypoglycemia, p<0.01)
- ISMP
  - Tuberculin syringe preferred
  - Volume + units ideal on labeling

Perioperative management
- General approach
  - Omit rapid/short acting insulins when fasting to prevent hypoglycemia
  - Continue but possibly reduce intermediate/long acting insulins to prevent hyperglycemia (and DKA in type-1)
- Type-2 Pre-operative
  - Basal – 0-50% reduction of the dose before surgery
  - Mixed – 50% reduction of the dose before surgery
  - Basal/bolus – omit bolus doses, 0-50% reduction of basal dose before surgery
  - U-500 – not addressed, 50-75% reduction of AM dose reasonable given variability in kinetics and bolus properties
  - Alternatively, 1/3 TDD could be administered as basal insulin upon arrival

Pen use in the hospital
- ISMP
  - Major risk: HIV/HBV/HCV transmission from pen use for multiple patients
- Other concerns: pen labeling, use of cartridges as multi-dose vials, risk of needlestick injuries, user technique errors
- Veterans Health Administration (VA) National Center for Patient Safety
  - Prohibited multi-dose pen use in patient care units in 2013 (still in effect)
Cases

Case # 1-- George

- **History and Presentation**
  - George is a 67-year-old retiree who has been visiting your pharmacy/clinic for over 2 years. He was diagnosed with T2DM 6 years ago. He has tried both metformin and sulfonylureas but has since discontinued them because of intolerable GI side effects and efficacy concerns, respectively. Three months ago, he had an A1C of 8.4%, with no changes to his diabetes therapy at that time. He presents today for a follow-up visit.

- **Medical History**
  - T2DM x 6 years
  - HTN x 5 years
  - Dyslipidemia for 2 years

- **Social History**
  - Retired bank manager
  - Active health insurance
  - Nonsmoking with no illicit drug use
  - Infrequent caffeine use (~2 times per week)
  - Occasional alcohol use (~1 drink per week)
  - Self-reported largest meal of the day is dinner with evening snacks

- **Current Medications**
  - Insulin glargine (pen) 80 units twice per day
  - Insulin aspart (pen) 30-60 units per meal + Correction
  - Lisinopril 10 mg daily
  - Atorvastatin 10 mg daily

- **Physical Examination**
  - Height - 5 feet 6 inches
  - Weight - 280 lbs
  - Body Mass Index (BMI) - ~45 kg/m²
  - Blood Pressure - 124/76 mm Hg
  - Heart rate - 74 bpm
  - Slightly decreased sensation in both feet bilaterally; no evidence of retinopathy

- **Laboratory Results (Sample obtained this morning)**
  - A1C - 8.7%
  - Serum Creatinine (SCr) - 1.2 mg/dL
  - Urinary albumin-creatinine ratio (ACR) - <10 mg/g creatinine
  - Estimated glomerular filtration ratio (eGFR) - >100 mL/min/1.73 m²
  - Low-density lipoprotein cholesterol (LDL-C) - 105 mg/dL
  - High-density lipoprotein cholesterol (HDL-C) - 50 mg/dL
  - Triglycerides - 140 mg/dL

Case # 2-- Donna

- **History and Presentation**
  - Donna is 56 years old and has been visiting your pharmacy/clinic for just over 4 years. She was diagnosed with T2DM 4 years ago. The only problem she reports is occasional episodes of nocturnal hypoglycemia (about 3 to 5 per month). She was just discharged from the hospital today due to a severe hypoglycemic event at 3am two days ago. Three months ago, she had an A1C of 9.6% and presents today with a new prescription for insulin lispro pen 10 units TID before meals. However, she does not want to start bolus insulin due to erratic meal and work schedules. She tells you to throw the prescription for lispro away, as she will never use it.

- **Medical History**
  - T2DM x 4 years
  - Dyslipidemia x 1 year

- **Social History**
  - High school principal
  - Active health insurance
  - Nonsmoking with no illicit drug use
  - Infrequent caffeine use (~3 cups daily)
  - Infrequent alcohol use (~1 drink per 2 weeks)
  - Meal schedule and size is erratic because of her work

- **Current Medications**
  - LVP (pen) 80 units twice per day; morning (7 AM) and 6 hours before bed (1 PM)
  - Metformin 1000 mg daily
  - Sitagliptin 100 mg daily
  - Simvastatin 20 mg daily
**Case #2-- Donna**

- **Physical**
  - Height: 5 feet 8 inches
  - Weight: 220 lbs
  - Body Mass Index (BMI): 32 kg/m²
  - Blood Pressure: 136/84 mm Hg
  - Heart rate: 72 bpm
  - No evidence of retinopathy or neuropathy
  - Examination

- **Laboratory Results** (Sample obtained this morning)
  - A1C: 8.6%
  - Serum Creatinine (SCr): >1.1 mg/dL
  - Urinary albumin creatinine ratio (ACR): >20 mg/g creatinine
  - Estimated glomerular filtration rate (eGFR): >60 mL/min/1.73 m²
  - Low-density lipoprotein cholesterol (LDL-C): <100 mg/dL
  - High-density lipoprotein cholesterol (HDL-C): >40 mg/dL
  - Triglycerides: >150 mg/dL

**Case #3: William**

- **All: NKDA**
- **Meds:**
  - Insulin U-500 TID 120/90/90
  - ASA 81/d
  - Atorvastatin 40/d
  - Lisinopril 10/d
  - Tamsulosin 0.4/d

- **Obj data:**
  - Weight: 150 kg, BMI: 47 kg/m²
  - Clcr: 72 mL/min
  - Recent HbA1c: 7.6%
  - Glucose trends: fasting range 140-170, post-prandial 170-220

  - William is a 64 y/o obese AA male w/ h/o Type 2 DM, carotid stenosis, CAD s/p NSTEMI 2007 w/ DES x 1 and BPH.
  - Elective carotid endarterectomy considered given symptoms assoc w/ CVD.
  - The procedure will be performed under local anesethesia with anticipated discharge the next day.
  - William has been instructed to be NPO after midnight for the AM procedure. He is anticipated to resume meals w/ lunch.

**Case #4 Lindsey**

- **Ht: 68”  Wt: 88 kg  BMI: 29.5 kg/m²**
- **HbA1c prior to admission:** 6.5%
- **Capillary glucose readings over the last 24 hrs range** 100-140 mg/dL
- **Units of insulin infused over the last 6 hours:** 15 units

- Lindsey is a 33 y/o F with type 1 DM who was in a MVA 7 days ago. She was intubated and received blood transfusions and has recently regained consciousness. She has since been extubated, but is still on an IV insulin infusion. She is going to start a PO diet today.

**Case #4 Lindsey**

- **Is insulin pen use safe in the hospital?**
- **What are the pharmacokinetic/pharmacodynamic properties of U-300 insulin glargine?**
- **What adjustments should be made to ensure a safe transition between U-300 insulin glargine and other insulin products?**

**Key Barriers to Insulin Therapy**

**Patient Barriers**
- Patient reluctance
- Sense of failure
- Loss of independence
- Belief that insulin is ineffective
- Fear of injections
- Fear of hypoglycemia
- Weight gain

**Provider Barriers**
- Clinical inertia
- Lack of insulin training, time, and/or support
- Fear of hypoglycemia
- Weight gain
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 finger stick; give an injection in the office
• Teach patient to recognize and treat hypoglycemia; use basal analog insulin to minimize hypoglycemia
• Meet with dietitian before initiation of insulin

Considerations for Insulin Titration and Education

• First, do no harm
• Halt the hypoglycemia
• Fix the fastings
• Pare the postprandials

Product Expiration

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How to Use an Insulin Pen: 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 2-3 units; hold up, depress the button
• Repeat process until a drop of insulin appears at tip of the needle
• Dial up the dose

Injection

• 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

Patient Adherence

• Always have patients demonstrate their technique
  - At first education of the device
  - At first follow-up visit
  - At frequent intervals thereafter
• Basal-bolus dosing will mimic natural insulin physiology
  • Requires BG monitoring
  • Requires healthcare provider and patient education

• Insulin resistance is a MAJOR problem
  • Concentrated insulin may help people on large doses of insulin
  • However, need to use combination drug therapy to improve insulin sensitivity