Treatment of Type 2 Diabetes: Combination Therapy

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Objectives
• Identify the cluster of signs and symptoms that suggest the earliest presence of abnormal glucose disposal
• Discuss the goals for fasting and post meal blood sugars
• Contrast the various classes of medications used to treat diabetes by mode of action
• Outline combination therapy opportunities for treating diabetes
• Employ a case study to outline the plan of care for a diabetic with abnormal glucose disposal.

Case Study #1
Meet Jeff

• CC: Complete physical examination
  – Additional pertinent information: 47 year-old white male who presents for a complete physical examination
  – He has not seen a health care provider for 10 years.
  – Sleepy after meals, polyuria, blurry vision after larger meal

• PHM: Usual childhood diseases
  – No previous illnesses

• Surgery:
  – Tonsillectomy - age 5
  – Vasectomy – age 35

Jeff

• Family History:
  – Mother alive – age 77; hypertension and COPD
  – Father alive – age 79; unknown medical history

• Social History:
  – Non-smoker
  – Software engineer working 60 hours per week
  – No routine exercise program – “active life”
  – Diet: no particular plan
  – Alcohol: 1 beer, 2-3 times per week
  – Drugs: none

Jeff

• Medications:
  – No daily medications
  – Occasional multivitamin
Jeff – Physical Examination

- Weight: 257 lbs
- Height: 5'8"
- Waist: 47 inches
- BMI: 39.1
- Blood Pressure:
  - 3 readings 140/88 mm
- Pulse: 95 bpm
- Respirations: 18/min
- EKG: WNL

Jeff – Laboratory Parameters

- FBS: 93 mg/dL
- 2 hr PP Blood Sugar 185 mg/dL
- BUN: 18 mg/dL
- Creatinine: 0.8 mg/dL
- Total Cholesterol: 220 mg/dL
- HDL: 34 mg/dL
- Triglycerides: 156 mg/dL
- LDL: 155 mg/dL
- VLDL: 41 mg/dL
- AST: 54 mg/dL
- ALT: 67 mg/dL
- Serum Insulin 46 UU/ml

Conclusions:

- Impaired fasting glucose?
  - Fasting > 109
- Diabetes, Type 2
  - Fasting > 126 on two separate occasions
  - One time over 200 random

Does he need medications now?
Case Study # 2

Meet Allen

- **CC:** My diabetes is not in control
  - Additional pertinent information: 43 year-old white male who employs lifestyle therapy for type 2 diabetes and is reluctant to start oral agents
- **PHM:** Usual childhood diseases
  - Diabetic Dyslipidemia
  - Early retinopathy per ophthalmologist
  - Hypertension – proteinuria 130 micromgms/L
- **Obesity (central, abdominal)**
- **Surgery:**
  - Tonsillectomy - age 5
  - Vasectomy – age 35
## Allen

### Family History:
- Mother died age 64, DM and complications
- Father alive – age 73; estranged

### Social History:
- Non-smoker
- Software engineer working 60 hours per week
- No routine exercise program – “active life”
- Diet: no particular plan
- Alcohol: 1 beer, 2-3 times per week
- Drugs: none

## Allen

### Medications:
- None, feels that he gets on meds he will never get off.

## Allen – Physical Examination

<table>
<thead>
<tr>
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<th>Measurement</th>
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<tbody>
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- FBS: 146 mg/dL
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- Total Cholesterol: 220 mg/dL
- HDL: 34 mg/dL
- Triglycerides: 156 mg/dL
- LDL: 155 mg/dL
- VLDL: 41 mg/dL
- AST: 54 mg/dL
- ALT: 67 mg/dL
- A1C: 7.1%

Obesity and Diabetes: Prevalence Continues to Increase

Obesity From 1994-2005
Diabetes From 1994-2004

- No Data
- 10%-14%
- 15%-19%
- 20%
- <4%
- 4%-4.9%
- 24%
- 25%-29%
- >30%
- 5%-5.9%
- 6+

*Obesity defined as body mass index (BMI) ≥ 30, or about 30 lbs overweight for a
5'4" person.

Pathophysiology
Diabetes

• Group of metabolic diseases characterized by hyperglycemia
  – It results from:
    • Defects in insulin secretion
    • Impaired action of insulin
    • Combination of both


Pre-Diabetes

• Impaired Glucose Tolerance
  – 2 hour post load plasma glucose ≥ 140 and < 200

• Impaired Fasting Glucose
  – Fasting glucose ≥ 100 but < 126

www.diabetes.org/pre-diabetes/faq.jsp accessed 01/28/07
Classifications of Diabetes

• Gestational Diabetes
  – Glucose intolerance that begins or is detected during pregnancy
  – Increased risk of developing Type 2 diabetes
  – Current estimates reveal that 50% of women with gestational diabetes will go on to develop Type 2 diabetes at some point in her lifetime
  – Complicates 1% - 12% of all pregnancies or 135,000 pregnancies yearly


Classifications of Diabetes

• Type 1 Diabetes
  – Beta Cell Destruction
  – Immune Mediated or Idiopathic
  – Accounts for 5 – 10% of all individuals with diabetes

• Type 2 Diabetes
  – Insulin resistance with a relative insulin secretory defect to complete insulin deficiency
  – Formerly referred to as adult onset
  – Vast majority are obese


Diabetes – Type 1.5

• Slowly progressing type 1 or latent autoimmune diabetes in adults
  – Up to 20% of individuals labeled as Type 2 actually have Type 1.5
  – 50% need insulin within 4 years of being diagnosed

• Characterized by presence of antibodies (GAD65) which destroy the pancreas

• Clues: thin, relatively young
  – Usually no elevated blood pressure, normal triglycerides, normal HDL

Stages of Type 2 Diabetes

1. Beta Cell Death
   - Patient loses first phase insulin secretion; this is the first defense against postprandial hyperglycemia.
   - Time of diagnosis for most individuals is when 50% beta cell death occurs.

2. IGT Post-Prandial Hyperglycemia
   - Type 2 Diabetes Phase I
   - Type 2 Diabetes Phase II
   - Type 2 Diabetes Phase III


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CAD mortality rates related to glucose tolerance

- Normal glucose tolerance
- IGT
- Type 2


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Common Problems in Type 2 Diabetes

- Gradual Loss of Glucose Control
- Decreased Insulin Production
- Insulin Resistance
- Increased Glucagon Production
- Increased Hepatic Glucose Output
- Weight Gain
- Abnormal or Accelerated Gastric Emptying
- Hypertension
- Vascular Complications
- Dyslipidemia


Assessed 9-3-07.
When and How do we measure blood sugars

Measuring and Treating Impact of Diabetes

• Fasting Blood Sugar?
• 2 hrs after the beginning of a meal?
• A1C quarterly?
• CGMS
  – Continuous glucose monitoring system (Medtronic)

Factors Influencing Duration of Postprandial State

Data from Service J. Diabetologia. 1983;25:316.
Glucose Contributions to HbA\textsubscript{1c}

\[
HbA_{1c} = \text{Fasting Glucose} \quad + \quad \text{Postprandial Glucose}
\]

- Fasting Glucose
  - Influenced by:
    - Hepatic glucose production
    - Hepatic sensitivity to insulin

- Postprandial Glucose
  - Influenced by:
    - Preprandial glucose
    - Insulin secretion
    - Glucose load from meal
    - Insulin sensitivity in peripheral tissues


Changes in A1c Standardization

- A1c = chronic glycemic control
- Blood Glucose = measure of acute control
- These are different and unrelated units
- How can we better look at acute vs chronic control without difficult conversion equations that may not be accurate
- So – ADAGE Research group started a new correlation study

Poor Correlation between A1C & BS

ADAG Study
Design
- A1c measured centrally q month x 4 mo
  - with OGTT away
- Plasma and ISF Glucose Monitored
- Continuous glucose monitoring (CGM) for 2 days every month for 4 months
- 8 point SMBG daily profile during CGM days
- 7 point SMBG for 3 days per week (minimum)
- Timeline goals:
  - Began recruitment April 2006
  - Summary Data Presented at EASD Sept 2007
  - Article in press

ADAG Study Outcomes
New Correlation A1c & BS

Correlation Between A1C and Mean Plasma Glucose Levels


New Acute number on lab slips
A1c Derived Average Glucose

A1c Derived Average Glucose


Glucose Excursions in Normal and Diabetic Individuals

Type 2 diabetic
Normal
Limitations of HbA1c

• Masks high and low fluctuations...does not reveal glycemic variability.
• Normal to low HbA1c values can be achieved with frequent hypoglycemic episodes.
• Anemia can alter accuracy of A1C.

Medications: May Increase Glucose

• Atypical antipsychotics
• Centrally acting alpha blockers
• Beta blockers
• Corticosteroids
• Minoxidil
• Diuretics
• Cyclosporine
• Estrogens
• Lithium
• Niacin
• Phenytoin
• Protease inhibitors
• Rifampin
• Thyroid preparations


How do I target my treatment of DM?

• Postprandial hyperglycemia is a significant contributor to A1C levels, particularly at the lower end of A1C's
  – For instance:
    • A1C of 7.3% to 9.2%: postprandial glucose accounts for 50% of this number
    • A1C < 7.3%: postprandial glucose accounts for 70% of this number
  • Take away message – Allen with an A1C of 8.6% - need work on basal and post meal excursions

Assessing the Damage of Diabetes by A1C

- For every 1% rise in A1c above 6%:
  - 14% increase in fatal and non fatal MI
  - 12% increase in strokes
  - 43% increase in peripheral vascular disease
  - 16% rise in congestive heart failure


Glycemic Control Reduces Risk of Type 2 Diabetes Complications

- Risk reduction with 1% decline in updated A1c
  - P<0.0001
  - P=0.035
  - P=0.021
  - P<0.0001

37% 43% 16% 12% 16% 15%
Microvascular disease PVD MI Stroke Heart failure Cataract extraction


Tight Control...?? !!

- ADVANCE – more mortality
- ACCORD – no change in mortality
- UKPDS – 10 years later
  - Intensive glucose lowering, not tight BP control decreased MI and all cause mortality
  - Early and aggressive glycemic control showed protective effects on macrovascular damage

Case Study

Assessing the Damage of Diabetes

Allan = 7.1%
- 28% increase in fatal and non-fatal MI
- 24.2% increase in strokes
- 86% increase in peripheral vascular disease
- 36% rise in congestive heart failure


Major Pathophysiologic Defects in Type 2 Diabetes

Del Prato S, Marchetti P. Horm Metab Res. 2004;36:775–781.
Allen – Initial Intervention

- Life Style Changes
  - Discussion on Diabetes
  - Discussion on Target Organ Damage
  - Carb Counting
  - Glycemic Index
  - Blood Glucose Testing
  - Exercise
    - After stress testing?
  - Then what if the post meal numbers are high?

Major Targeted Sites of Oral Drug Classes

- Pancreas
  - Sulfonylureas
  - Meglitinides
  - DPP-4 inhibitors
  - Incretin Memetics

- Muscle and fat
  - Beta-cell dysfunction

- Liver
  - Hepatic glucose overproduction
  - Insulin resistance

- Gut
  - Glucose absorption
  - Incretin Memetics
  - DPP-4 inhibitors

- Alpha-glucosidase inhibitors

- Biguanides
  -TZDs
  - Biguanides
  -TZDs
  - Biguanides

Major Classes of Medications

1. Drugs that sensitize the body to insulin and/or control hepatic glucose production
   - Thiazolidinediones
   - Biguanides

2. Drugs that stimulate the pancreas to make more insulin
   - Sulfonylureas
   - Meglitinides

3. Drugs that slow the absorption of starches
   - Alpha-glucosidase inhibitors
Thiazolidinediones

- Thiazolidinediones decrease insulin resistance by making muscle and adipose cells more sensitive to insulin. They also suppress hepatic glucose production.
- Efficacy
  - Decrease fasting plasma glucose ~35-40 mg/dl (1.9-2.2 mmol/L)
  - Reduce A1C ~0.5-1.0%
  - 6 – 12 weeks for maximum effect

Other Effects
- Weight gain, edema
- Hypoglycemia (if taken with insulin or agents that stimulate insulin release)
- Contraindicated in patients with abnormal liver function or CHF
- Improves HDL cholesterol and plasma triglycerides; usually LDL neutral

Medications in this Class: pioglitazone (Actos), rosiglitazone (Avandia), [troglitazone (Rezulin) - taken off market due to liver toxicity]
- WATCH DOSE WITH INSULIN!!

FDA and Avandia (rosiglitazone)

- Nov 14th release
- FDA adds boxed warning for Heart-related risks to Anti-Diabetes Drug Avandia

"At this time, FDA has concluded that there isn’t enough evidence to indicate that the risks of heart attacks or death are different between Avandia and some other oral type 2 diabetes treatments."

- FDA has requested that GSK conduct a new long-term study to evaluate the potential cardiovascular risk of Avandia.
**Biguanides**

- Biguanides decrease hepatic glucose production and increase insulin-mediated peripheral glucose uptake.
- **Efficacy**
  - Decrease fasting plasma glucose 60-70 mg/dl (3.3-3.9 mmol/L)
  - Reduce A1C 1.0-2.0%
- **Other Effects**
  - Diarrhea and abdominal discomfort
  - Lactic acidosis
  - Cause small decrease in LDL cholesterol level and triglycerides
  - No specific effect on blood pressure
  - No weight gain, with possible modest weight loss
  - Contraindicated in patients with impaired renal function (Serum Cr > 1.4 mg/dL for women, or 1.5 mg/dL for men)
- **Medications in this Class:** metformin (Glucophage), metformin hydrochloride extended release (Glucophage XR)

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**Sulfonylureas**

- Sulfonylureas increase endogenous insulin secretion
- **Efficacy**
  - Decrease fasting plasma glucose 60-70 mg/dl (3.3-3.9 mmol/L)
  - Reduce A1C by 1.0-2.0%
- **Other Effects**
  - Hypoglycemia
  - Weight gain
  - No specific effect on plasma lipids or blood pressure
  - Generally the least expensive class of medication
- **Medications in this Class:**
  - Second generation sulfonylureas: glyburide (Micronase, Glynase, and DiaBeta), glimepiride (Amaryl), glipizide (Glucotrol, Glucotrol XL)

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**Meglitinides**

- Meglitinides stimulate insulin secretion (rapidly and for a short duration) in the presence of glucose.
- **Efficacy**
  - Decreases peak postprandial glucose
  - Decreases plasma glucose 60-70 mg/dl (3.3-3.9 mmol/L)
  - Reduce A1C 1.0-2.0%
- **Other Effects**
  - Hypoglycemia (although may be less than with sulfonylureas if patient has a variable eating schedule)
  - Weight gain
  - No significant effect on plasma lipid levels
  - Safe at higher levels of serum Cr than sulfonylureas
- **Medications in this Class:** repaglinide (Prandin), nateglinide (Starlix)
**Alpha-glucosidase Inhibitors**

- Alpha-glucosidase inhibitors block the enzymes that digest starches in the small intestine
- **Efficacy**
  - Decrease peak postprandial glucose 40-50 mg/dl (2.2-2.8 mmol/L)
  - Decrease fasting plasma glucose 20-30 mg/dl (1.4-1.7 mmol/L)
  - Decrease A1C 0.5-1.0%
- **Other Effects**
  - Flatulence or abdominal discomfort
  - No specific effect on lipids or blood pressure
  - No weight gain
  - Contraindicated in patients with inflammatory bowel disease or cirrhosis
- **Medications in this Class:** acarbose (Precose), miglitol (Glyset)

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**Efficacy of Monotherapy with Oral Diabetes Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fasting Plasma Glucose Reduction (mg/dl)</th>
<th>A1C Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinedione</td>
<td>35-40</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>60-70</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>Biguanide</td>
<td>60-70</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>60-70</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitor</td>
<td>20-30</td>
<td>0.5-1.0</td>
</tr>
</tbody>
</table>

DeFronzo Annals of Internal Medicine 1999;131:281-303

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**Fixed dose combinations for diabetes**

- **Sulfonylurea + Biguanide**
  - Glyburide + Metformin = Glucovance
  - Glipizide + Metformin = Metaglip
- **Sulfonylurea + Thiazolidinedione**
  - Glimpiride + Rosiglitazone = Avandaryl
  - Glimpiride + Pioglitazone = Duetact (4/30)
- **Thiazolidinedione + Biguanide**
  - Rosiglitazone + Metformin = Avandamet
  - Pioglitazone + Metformin = ActoPlus Met
- **Gliptins + Biguanide**
  - Sitagliptin + Metformin = Janumet (50/500; 50/1000)
The Role of Incretins in Type 2 Diabetes

Incretin Effect

In 1964, it was demonstrated that the insulin secretory response was greater when glucose was administered orally through the gastrointestinal tract than when glucose was delivered via IV infusion.

The incretin effect implies that nutrient ingestion causes the gut to release substances that enhance insulin secretion beyond the release caused by the rise in glucose secondary to absorption of digested nutrients.

New Medications

- **Exenatide (Byetta)** –
  - Incretin mimic
- Exenatide - synthetic version of exendin-4
  - A naturally-occurring hormone first isolated from the saliva of a Gila monster (lizard).
- Exenatide lowers blood glucose by increasing insulin secretion, suppresses glucagon secretion and slows gastric emptying
  - Because it only has this effect in the presence of elevated blood glucose levels, it does not tend to increase the risk of hypoglycemia on its own

Product insert, 2006
Exenatide

- **Indications**
  - Adjunct to metformin, sulfonylureas or combination
  - For individuals who have not achieved glycemic control with the above products

- **Dosage**
  - Exenatide is injected with morning and evening meals (bid)
  - 5 mcg bid x 30 days then 10 mcg bid if able to tolerate injected subcutaneously
  - Inject in arm, thigh or abdomen 60 minutes before meals
  - Prefilled pens

Product insert, 2006

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**AMIGO trials: GLP-1 analog in type 2 diabetes**

<table>
<thead>
<tr>
<th>Active treatment</th>
<th>Change from baseline</th>
<th>Exenatide 5 µg bid</th>
<th>Exenatide 10 µg bid</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Sulfonlylurea²</td>
<td>A1C (%)</td>
<td>–0.46</td>
<td>–0.56</td>
<td>+0.12</td>
</tr>
<tr>
<td>(N = 377)</td>
<td>Weight (lb)</td>
<td>–2.0</td>
<td>–3.6</td>
<td>–1.3</td>
</tr>
<tr>
<td>Metformin²</td>
<td>A1C (%)</td>
<td>–0.40</td>
<td>–0.76</td>
<td>+0.08</td>
</tr>
<tr>
<td>(N = 336)</td>
<td>Weight (lb)</td>
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<td>–4.3</td>
<td>–0.7</td>
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<td>Metformin + sulfonlylurea²</td>
<td>A1C (%)</td>
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<tr>
<td>(N = 733)</td>
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<td>–3.6</td>
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Exenatide

- **Biggest side effect:** nausea
  - Up to 40% of individuals

- **Dosing information:**
  - Consider reducing sulfonylurea dosage when initiating

- **Benefits:**
  - Modest weight loss sustained through 82 weeks
  - Improved glycemic control
  - ? Beta cell preservation
Incretins Play an Important Role in Glucose Homeostasis

Food ingestion

Glucose Dependent
- Insulin from beta cells
  (GLP-1 and GIP)

Release of gut hormones—Incretins
Pancreas
Glucose Dependent
- Glucagon from alpha cells
  (GLP-1)

↓

Blood

GI tract

Food ingestion

↑

Glucose uptake by peripheral tissue

Beta cells

Glucose Dependent

Active GLP-1 & GIP

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

Sitagliptin: Indications and Usage

- Monotherapy
  - JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

- Combination therapy
  - JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a PPARγ agonist (e.g., thiazolidinediones) when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

- Important limitations of use
  - JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Caution

- Caution:
  - Gastroparesis
  - Medications that require rapid GI absorption
    - Contraceptives
    - Antibiotics

Product insert, 2006
Pramlintide

- Pramlintide (Symlin) - synthetic form of the hormone amylin, produced by the beta cells in the pancreas.
- Amylin, insulin, and glucagon work together to maintain normal blood glucose levels.
- Pramlintide injections are taken with meals
  - No hypoglycemia (alone) or weight gain
  - May even promote modest weight loss
  - Biggest side effect: nausea - which tends to improve over time
  - Pramlintide cannot be combined in the same vial or syringe with insulin

Product insert, 2006

Case Study

Allen - Physical Examination

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- AST: 54 mg/dL
- ALT: 67 mg/dL
- A1C: 7.1%

Allen

- Medications:
  - None at this time

So, what to do

- Sensitizers
  - TZD
  - Metformin “bring the body back to baseline”
- Incretins
  - Oral – Januvia / Janumet
- SUs
  - Lets burn out the pancreas and get to insulin sooner?
- Inhaled Insulin – now off the market due to $$$
- Insulin sub q
  - Lispro + basal
- Insulin Pump
Guideline Recommendations Are Becoming More Aggressive

- 2007 ADA standards
  - "The A1C goal for patients in general is an A1C goal of <7%.
  - "The A1C goal for the individual patient is an A1C as close to normal (<6%) as possible without significant hypoglycemia."
- ADA/EASD consensus statement
  - "If lifestyle intervention and maximal tolerated dose of metformin fail to achieve or sustain glycemic goals, another medication should be added within 2–3 months of the initiation of therapy or at any time when A1C goal is not achieved."

How do I target my treatment of DM?

- Postprandial hyperglycemia is a significant contributor to A1C levels, particularly at the lower end of A1C's
  - For instance:
    - A1C of 7.3% to 9.2%: postprandial glucose accounts for 50% of this number
    - A1C < 7.3%: postprandial glucose accounts for 70% of this number
  - Take away message – Jeff with an A1C of 7.2% - look very closely at reducing postprandial glucose

Insulin Therapy

Food becomes a medicine to maintain Blood sugars!

Must have fixed carbohydrate intake
For fixed AC insulin dose – (bad)
Starting Insulin

• Prepare for the WORST (MDI)
  – Needle phobia
  – Hypoglycemia
  – Increased intravascular volume
  – Bad insulin and weird values
  – Ketoacidosis
  – Weight gain
  – Sick days

Back to the Basics

• Significant patient education now--- face time

• Start with description of what goals are
  – AC 100 mg/dL; 2 hour post meal < 135 mg/dL
• Revisit carbohydrate counting
• Revisit glycemic index
• Revisit hypoglycemic protocol
• Revisit lactic acidosis (DKA)
• Introduce strict regimen of blood sugar testing and multiple dosing of insulin (about 4 day)

Label Reading

<table>
<thead>
<tr>
<th>Nutrition Facts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serving Size: 1 oz (28g/oz) / 6 servings</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>Calories: 180</th>
<th>Fat: 10g (15%)</th>
<th>Carbohydrates: 10g (4%)</th>
</tr>
</thead>
</table>

What is the serving size?

How many grams of Fat?

How many grams of Carbohydrates?
Preparing the patient for insulin

- Carbohydrate Counting
- 1 piece of white bread
- 12 cherries
- 2” apple
- ½ cup strawberries
- ½ cup watermelon
- M&M Choc Peanut
- Individual serving

- Glycemic Index
- 72
- 22
- 38
- 32
- 72
- 33

- Peanut Butter

Hypoglycemic Protocol

- Feel low (or check low)
- Check blood sugar if can
- 15 grams of glucose
  - Not something that has to be converted to glucose
- Wait 15 minutes
- Take Blood Sugar
- 15 grams of glucose
- If blood sugar is now acceptable, have a low glycemic snack to maintain blood sugar
  - Evaluate why hypoglycemia occurred.
Insulin Choices

- Rapid Acting Insulin
- Short Acting Insulin
- Intermediate Acting Insulin
- Mixes
- Long Acting Insulin
- Combination Insulin
- rapid acting only (The Pump)
Rapid Acting Insulin

<table>
<thead>
<tr>
<th>Examples</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glulisine (Apidra)</td>
<td>10-15 min</td>
<td>40-70</td>
<td>3-5 hr</td>
<td>Rapid absorption (even in obese patients) Short half life</td>
<td>High cost vs regular</td>
</tr>
<tr>
<td>Lispro (Humalog)</td>
<td>15 min</td>
<td>40-70</td>
<td>3-5 hr</td>
<td>Short half life</td>
<td>High cost vs regular</td>
</tr>
<tr>
<td>Aspart (NovoLog)</td>
<td>15 min</td>
<td>40-50</td>
<td>3-6 hr</td>
<td>Short half life</td>
<td>High cost vs regular</td>
</tr>
</tbody>
</table>

Slightly longer duration of action than other rapid acting insulins.

Product inserts accessed 2-1-08

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Rapid Acting Insulins

- NovoLog®
- Humalog®

Hedman, Diabetes Care 2001; 24(6):1120-21

Product inserts

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Short Acting Insulin

<table>
<thead>
<tr>
<th>Examples</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular Insulin</td>
<td>30 – 60 min</td>
<td>50 – 120 min</td>
<td>3-8 hrs</td>
<td>Low cost</td>
<td>Long duration of action may lead to: Nocturnal hypoglycemia</td>
</tr>
<tr>
<td>Regular Iletin, Humulin R, Novolin R, Velosulin BA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Product inserts accessed 2-1-08
### Intermediate Acting Insulin

<table>
<thead>
<tr>
<th>Example</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>1-3 hrs</td>
<td>8 hrs</td>
<td>20 hrs</td>
<td>Low cost</td>
<td>Peak at 6-8 may lead to hypoglycemia</td>
</tr>
<tr>
<td>NPH Iletin II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novolin N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lente</td>
<td>1-2.5 hrs</td>
<td>7-15 hrs</td>
<td>18-24 hrs</td>
<td>Low cost</td>
<td>Unpredictable peaks may lead to hypoglycemia</td>
</tr>
<tr>
<td>Lente Iletin II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Product inserts accessed 2-1-08

### Intermediate & Short/Rapid Acting Mixes

<table>
<thead>
<tr>
<th>Examples</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/50</td>
<td>Depends</td>
<td>Depends</td>
<td>Depends</td>
<td>Convenient administration</td>
<td>Not possible to customize delivery of short and rapid acting insulin to patients</td>
</tr>
<tr>
<td>70/30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75/25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH with Regular Lispro Protamine Aspart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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### Long Acting – Basal Insulin

<table>
<thead>
<tr>
<th>Examples</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detemir (Levemir)</td>
<td>1-2 hrs</td>
<td>None</td>
<td>12-24 hrs</td>
<td>Continuous dose prevents hypoglycemia</td>
<td>Shorter duration than insulin glargine</td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td>1 hr</td>
<td>None</td>
<td>24 hrs</td>
<td>Continuous dose level prevents hypoglycemia; can be administered once daily</td>
<td>High cost; Not effective for postprandial glucose elevations; can not be mixed with short acting insulin</td>
</tr>
</tbody>
</table>

Product inserts accessed 2-1-08
### Basal Insulins

<table>
<thead>
<tr>
<th>Glargine, Detemir</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Glucose infusion rate (mg/dL/min)</th>
<th>Time (h) after s.c. injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
</tr>
</tbody>
</table>

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Just wanted to say it FORMALLY!

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Find Lane

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