CONFLICTS OF INTEREST

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Research grants from Sanofi and Amylin Pharmaceutical Companies

Mayer B. Davidson, MD
Advisory Board – Sanofi Pharmaceutical Company
Chief Medical Officer – Insulin Algorithms, Inc

ADJUSTING INSULIN DOSES

1. No one right way
2. Adjust insulin around usual eating pattern – not other way around
3. Inconsistent food intake – major issue
4. Response to insulin very variable
5. Because of 3 and 4, use pattern of glucose results over time
6. Pre-prandial testing easier than post-prandial and usually all that is needed

Self-Mixed Insulin Regimen – Case #1
30 NPH/10 Reg before breakfast; 20 NPH/10 Reg before dinner: Patient is obese

Self-Mixed Insulin Regimen – Case #1
30 NPH/10 Reg before breakfast; 20 NPH/10 Reg before dinner: Patient is obese

Self-Mixed Insulin Regimen – Case #2
80 NPH / 30 Reg before breakfast; 40 NPH / 32 Reg before dinner: Patient is obese

Self-Mixed Insulin Regimen – Case #2
80 NPH / 30 Reg before breakfast; 40 NPH / 32 Reg before dinner: Patient is Obese
Insulin Therapy
Basal & Bolus

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12/03/2014

Case

- John is a 62 year-old African American man, with type 2 diabetes, diagnosed 10 years ago
- He works as an electrician and has irregular meal times
- He tries to avoid sweets
- He smokes 1 pack a day and drinks 1-2 beers a night
- He has a history of CAD, depression, & hypertension

Case

- Current labs:
  - A1C: 9.4%
  - Home glucose ranges: FPG 180-200 mg/dL; premeal 200-250 mg/dL.
    - Serum creatinine: 2.3 mg/dL, LFTs normal.
  - TC 153 mg/dL, LDL 70 mg/dL, HDL 41 mg/dL, TG 225 mg/dL
Case

Current medications:
- Metformin, 1000 mg BID
- Glimepiride, 4 mg QD
- Sitagliptin, 100 mg QD
- ASA, 81 mg QD
- Benazepril, 40 mg QD
- Simvastatin, 40 mg QD
- Escitalopram, 10 mg QD

What do John’s symptoms of anxiety, trembling, sweating, and clammy hands suggest?
- a) Hyperglycemia
- b) Hypoglycemia
- c) Hypothyroidism
- d) GERD

Case

John’s Self-Blood Glucose Monitoring Download

- Frequent episodes of hypoglycemia due to sulfonylurea and CKD

Case

- HbA1c: 9.4%
- Patient is already on triple therapy with A1C still >9%; likely having hypoglycemia.
- He should not be on metformin with Cr >1.5
- He may continue sitagliptin, as this will decrease potential need for bolus insulin and reduce post-prandial glycemic variability; however, due to his increased Cr, his sitagliptin dose should be reduced to 50 mg.
- Basal insulin should be initiated.

Case

- John starts with basal analog insulin 10 units at bedtime
- John was counseled on diet and lifestyle changes including alcohol reduction, smoking cessation, increased physical activity, sodium reduction, and carbohydrate counting
- He was scheduled for a follow-up visit in 1 week to review BP progress and SMBG results.
- He was counseled on proper BP home monitoring to ensure accurate readings.

Case

3-month Checkup

- Height: 6’2”, Weight: 228 lbs, BMI: 29 kg/m²
- BP 130/84 mm Hg, HR 68 bpm
- Foot and fundoscopy exam: no change since prior visit
- Labs:
  - A1C: 7.9%
  - Serum creatinine: 2.3 mg/dL
  - Urine albumin: 60 mg/g
  - LFTs normal
Case 3-month Checkup

Current medications:
- Sitagliptin, 50 mg QD
- ASA, 81 mg
- Long acting Insulin 15 units SQ HS & titrate up to 34 u.
- Benazepril, 40 mg QD
- Simvastatin, 40 mg QD
- Escitalopram, 10 mg QD
- Carvedilol, 12.5 mg BID

Case SMBG Log

<table>
<thead>
<tr>
<th>Time</th>
<th>BG (mg/dL)</th>
<th>Time</th>
<th>BG (mg/dL)</th>
<th>Time</th>
<th>BG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 (fasting)</td>
<td>126</td>
<td>7:30 (fasting)</td>
<td>134</td>
<td>8:00 (fasting)</td>
<td>136</td>
</tr>
<tr>
<td>1:00 (post-lunch)</td>
<td>Missed reading</td>
<td>1:00 (post-lunch)</td>
<td>214</td>
<td>1:00 (post-lunch)</td>
<td>229</td>
</tr>
<tr>
<td>5:30 (post-dinner)</td>
<td>218</td>
<td>6:30 (post-dinner)</td>
<td>Missed reading</td>
<td>5:30 (post-dinner)</td>
<td>240</td>
</tr>
<tr>
<td>9:30 (bedtime)</td>
<td>242</td>
<td>10:00 (bedtime)</td>
<td>219</td>
<td>9:30 (bedtime)</td>
<td>197</td>
</tr>
</tbody>
</table>

Case

What is the best option?

a) Increase his basal insulin dose
b) Add a rapid-acting insulin with each meal
c) Add rapid acting analog to his largest meal
d) Switch to premix insulin

Case Options When Not at Goal with One Injection of Basal Insulin

- Basal Plus
- Add prandial insulin at main meal
- or
- Switch to Basal/Bolus
- or
- Switch to a premixed insulin analog

Case

Basal Plus Bolus Mealtime Insulin

- Use rapid-acting analogs, or regular insulin
- Easier timing, less postprandial hypoglycemia
- Can be taken up to 15 minutes after starting to eat
- May start with 1 injection at largest meal; however most patients need a dose with each meal
- 4 units and titrate OR by weight - 0.1 U/kg
- OR 1 U/15 gr CHO and titrate
- Titrate to:
  - <140 mg/dl 2 hours post-prandial OR
  - <110 mg/dl next meal or bedtime
- Stop oral SUs/glinides when prandial insulin is started.

Mealtime Insulin Rapid-Acting Analogs (Aspart, Glulisine, Lispro) vs Regular
Case 3-month Follow-up

- Height: 6'2", Weight: 210 lbs, BMI: 27 kg/m², BP: 130/78 mm Hg, HR: 80 bpm
- Foot and fundoscopy exam: no change since prior visit
- Labs:
  - HbA1c: 6.4%;
  - FPG: 94-100 mg/dL; 2-h PPG: 110-118 mg/dL
  - Serum creatinine: 2.1 mg/dL
  - Urine albumin: 20 mg/g, LFTs normal

Case 3-month Follow-up

- Current Medications:
  - 40 U long-acting analog insulin SQ hs
  - 12 U rapid-acting insulin SQ with breakfast and lunch
  - 15 U rapid-acting insulin SQ with dinner
  - Benazepril 40 mg QD
  - Simvastatin 40 mg QD
  - Escitalopram 10 mg QD
  - Carvedilol 12.5 mg BID
  - ASA 81 mg QD

How to Start Insulin?

- 2 methods: *Weight based* or *fixed dose*.
- A typical weight-based starting dose ranges from 0.15 to 0.6 Units/kg/day.
- Usual starting: 0.2 - 0.5 Units/kg/day.
- ~ 50% basal & 50% as prandial boluses.
- Fixed dose: low dose basal (NPH, glargine or detemir), & titrate the dose based on fasting BG.

Pre-Mixed (70/30) Insulin Regimen - Case #1

40 Pre-Mixed before breakfast; 30 Pre-Mixed before dinner: Patient is obese.
Pre-Mixed (70/30) Insulin Regimen - Case #2
40 Pre-Mixed before breakfast; 30 Pre-Mixed before dinner: Patient is obese.

Pre-Mixed (70/30) Insulin Regimen - Case #3
60 Pre-Mixed before breakfast; 20 Pre-Mixed before dinner: Patient is obese.

**Insulin U-500**

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**U-500 Human Regular Insulin: Clinical Pharmacology**

- Clinical experience has shown that U-500 human regular insulin frequently has **time action characteristics** reflecting both prandial and basal activity.
- U-500 human regular insulin has an onset within **30 minutes** and has a relatively long duration of action (up to 24 hours following a single dose) compared with other regular insulins; this effect has been attributed to the **high concentration** of the preparation.
- U-500 human regular insulin is **not** modified by any agent that might prolong its action.

U-500 = 500 units/mL, U-100 = 100 units/mL

Potential Candidates for U-500 Human Regular Insulin Therapy1-3

- Patients with the following medical conditions may be considered for U-500 human regular insulin therapy:
  - Type 2 diabetes with obesity and/or severe insulin resistance
  - Type 2 diabetes with insulin requirements >200 units per day
    - Postoperative or post-transplant state
    - High-dose glucocorticoid therapy
    - Severe systemic infection
    - Gestational diabetes mellitus with severe insulin resistance
    - Genetic defects of insulin action
    - Type A insulin resistance syndromes
    - Lipodystrophic diabetes
    - Rare forms of immune-mediated diabetes such as anti-insulin receptor antibodies (type B insulin resistance syndrome).


Humulin R U-500 Is Highly Concentrated

- Humulin R U-500 contains 500 units of insulin in each milliliter (5 times more concentrated than Humulin R U-100)
- Humulin R U-500 allows a patient to inject 1/5 the insulin volume when compared to injecting the same dose of a U-100 insulin.

U-500 = 500 units/mL; U-100 = 100 units/mL.
1 U-100 regular insulin syringe containing 100 units of insulin [20 unit markings] = 0.01 mL of U-500 regular insulin.

Algorithm for U-500 Regular Insulin Dosing1,2 (1 of 2)

<table>
<thead>
<tr>
<th>TDD Dose (units/day)</th>
<th>Injection Frequency/ Delivery Method</th>
<th>Dosage Distribution (% of TDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 - 300</td>
<td>2 injections/day (before breakfast and evening meal)</td>
<td>60/40 or 50/50</td>
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<tr>
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<td>3 injections/day (before meals)</td>
<td>40/30 or 33.3/33.3</td>
</tr>
<tr>
<td></td>
<td>CSII (1 “pump unit” = 0.01 mL, 0.01 mL of U-500 R insulin = 5 actual units)</td>
<td>3 mealtime boluses (30% TDD) with basal rate (50% TDD)</td>
</tr>
</tbody>
</table>


Algorithm for U-500 Regular Insulin Dosing1,2 (2 of 2)

<table>
<thead>
<tr>
<th>TDD Dose (units/day)</th>
<th>Injection Frequency/ Delivery Method</th>
<th>Dosage Distribution (% of TDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 - 600</td>
<td>3 injections/day</td>
<td>40/30/30 or 33.3/33.3/33.3</td>
</tr>
<tr>
<td></td>
<td>4 injections/day (before meals and bedtime)</td>
<td>30/30/30/10</td>
</tr>
<tr>
<td></td>
<td>CSII (1 “pump unit” = 0.01 mL, 0.01 mL of U-500 R insulin = 5 actual units)</td>
<td>3 mealtime boluses (30% TDD) with basal rate (50% TDD)</td>
</tr>
</tbody>
</table>

1 U-500 = 500 units/mL; U-100 = 100 units/mL. TDD: total daily dose. CSII: continuous subcutaneous insulin infusion. U-500: U-500 regular human insulin. TDD: total daily dose of insulin. A1C: glycated hemoglobin. 
2 Simplified algorithm for conversion from previous TDD of U-100 insulin to U-500 regular insulin.
3 When switching to U-500 regular insulin, the TDD may be reduced by 15%–20% for initial A1C ≥7%.
4 Increasing the dose by 10% to 20% for initial A1C ≥8% may be considered.
5 U-500 regular insulin is recommended 30 minutes before a meal; dosage may be titrated according to frequent, non-stressed blood glucose.
6 May initially use fixed ratios or distribute boluses according to the proportion of carbohydrates of meal or carbohydrate counting according to patient preference and physician judgment.

Case # 1

- Norman is 48 yo male with T2DM for ~ 15 years.
- His weight is 228 lbs with BMI of 36.4.
- PMHX: Dyslipidemia, HTN, Obesity, & Asthma.
- Enrolled in DMP first 10/10/11 & completed at HbA1c 7.3%.
- Second enrollment, 5/2012, with HbA1c 10.9%.
- Initial regime:
  - NPH 40 units AM, and 40 units HS
  - Reg 20 units am and 20 units HS + SS
  - Metformin 1000 mg BID AC meals
  - Pioglitazone 15 mg daily.
Case # 1

- Blood glucose values at the time of referral (while on 165 units daily):

<table>
<thead>
<tr>
<th></th>
<th>275</th>
<th>233</th>
<th>139</th>
<th>194</th>
<th>235</th>
<th>189</th>
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<tbody>
<tr>
<td>Pre</td>
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<td>238</td>
<td>127</td>
<td>121</td>
<td>201</td>
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<td>Dinner</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- Barriers to control:
  - Incorrect timing of meds (both Metformin and insulin)
  - Complaining of painful injection & nightmares.

- From 10/2013-2/6/14 titrated insulin, Pioglitazone stopped & had patient taking at correct time yet BG control remained elevated.

- 2/6/14 Insulin switched to RU-500
  - TDD of NPH/REG= (at time of insulin switch) was 178 units and HbA1c was 9.8%.

- Started on RU-500 at 17 insulin syringe units (85 units) BID AC BF & D.
  - Within 2 months HbA1c dropped to 6.8% & currently 6.6%.
  - Norman still reports weekly and SMBG is stable.
  - Ongoing problems with his diet/activity but better & improving.

U-500 Regular Insulin: Safety

- Fluid retention and heart failure with concomitant use of PPAR-gamma agonists
  - Thiazolidinediones, which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin
  - Fluid retention may lead to or exacerbate heart failure.
  - Patients treated with insulin, including Humulin R U-500 and a PPAR-gamma agonist, should be observed for signs and symptoms of heart failure.

Case # 2

- Steven, 56 yo male with h/o T2 DM for ~18 years.
- 3rd enrollment in DMP - previously completed not at goal X 2
- Referred once again on 12/2013 with HbA1c 11.4%.
- On insulin glargine 45 units BID & insulin Lispro 40 units AC BF/L/D with TDD 210 units (with 5 injections daily).
- Learned pt non adherent to diet, weight gain, injecting incorrectly at times (post vs. pre meals)
Case # 2

- Blood glucose values at the time of re:

<table>
<thead>
<tr>
<th>Time</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Dinner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBS</td>
<td>212</td>
<td>241</td>
<td>188</td>
<td>341</td>
<td>410</td>
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<tr>
<td></td>
<td>211</td>
<td>218</td>
<td>186</td>
<td>186</td>
<td>182</td>
</tr>
</tbody>
</table>

- 12/2013 started on RU-500 at enrollment due to high TDD and poor control with multiple daily injections.
- Starting dose: 20 syringe units BID (100 actual units) AC BF & Dinner.
- Current dose: 32 syringe units am (160 units) am and 24 syringe units pm (120 units)
- Current HbA1c 6.6% and SMBG stable- NO hypos.