Non-Insulin Agents in the Hospital

*Diabetes Education Conference*

*Diabetes Care:*

*From Hospital to Home* 2009 Community Hospital Program

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Disclosures

- Although I have attended advisory board meetings and/or given talks on behalf of most healthcare companies that have therapies used to treat patients with diabetes none of it has influenced my views presented in this talk.
Needs Assessment

- why and when conventional oral agents are held during hospital admission,
- update on the Avandia controversy,
- role of the newer agents (incretins)
Outline

– Diabetes in the hospital
– Tools
  • non-insulin agents
  • TZD’s
– Practice
Diabetes in the Hospital

- Diabetes is very different in the hospital

- po intake:
  - Interrupted, more, less, better, worse, continuous, etc...

- Exercise:
  - None, less, more
Diabetes in the Hospital

- Diabetes is very different in the hospital
- Stress
- Drugs
  - Up, down
- Organ dysfunction
  - Kidney, liver
DM2 is progressive: know where they are

Non-Insulin Agents for Diabetes

Incretin based therapies
- ↑ insulin
- ↓ glucagon

The Diabetes Doctor
<table>
<thead>
<tr>
<th>Class</th>
<th>A1C</th>
<th>Hypoglycemia</th>
<th>Other advantages</th>
<th>Other disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-glucosidase inhibitor</td>
<td>↓</td>
<td>Rare</td>
<td>Improved postprandial control weight neutral</td>
<td>GI side effects</td>
</tr>
<tr>
<td>Incretin agent: DPP-4i, GLP-1</td>
<td>↓ to↓</td>
<td>Rare</td>
<td>Improved postprandial control weight neutral</td>
<td>New agent (unknown long-term safety)</td>
</tr>
<tr>
<td>Insulin</td>
<td>↓↓↓</td>
<td>Yes</td>
<td>No dose ceiling Many types, flexible doses</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Insulin secretagogue:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinide</td>
<td>↓ to↓</td>
<td>Yes*</td>
<td>Improved postprandial control</td>
<td>Requires TID to QID dosing</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td></td>
<td></td>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td>Metformin</td>
<td>↓ to↓</td>
<td>Rare</td>
<td>Weight neutral Very safe</td>
<td>GI upset ?risk lactic acidosis</td>
</tr>
<tr>
<td>TZD</td>
<td>↓↓</td>
<td>Rare</td>
<td>Durable monotherapy</td>
<td>Requires 6-12 weeks for maximal effect Edema, rare CHF, rare fractures in females</td>
</tr>
<tr>
<td>Weight loss agent</td>
<td>↓</td>
<td>None</td>
<td>Weight loss</td>
<td>GI side effects (orlistat) Increased heart rate/BP (subutramine)</td>
</tr>
</tbody>
</table>
My Take on TZD’s

• Most of my patients with diabetes will die from CAD regardless of being on or off TZD’s
• Results of the various meta analysis out there are conflicting
• TZD’s cause fluid retention which in the susceptible heart can lead to CHF
• None of the meta analysis to date have commented on whether most of the MI’s were happening in patients with CHF or not
• Results of properly designed trials did not demonstrate increased risk
  – ACCORD, RECORD
• I have regrettably reduced the use of TZD’s (Avandia more so than Actos) solely due media hype and not because of concern for safety of my patients
Incretin Based Diabetic Therapies
After this portion of the talk you should...

- be able to explain the physiologic roles of incretins
- be able to explain the basis of the two main incretin-based diabetic therapeutic approaches
- be well aware of incretin-based therapies as they are now hitting the Canadian market
Which of the following is not a key defect in the pathophysiology of DM2?

1. Beta cell failure
2. Altered carbohydrate absorption
3. Glucagon dysregulation
4. Insulin resistance
Leo

- DM2 x 10 yrs
- A1c 8.1%
- Lipids and BP O.K.
- BMI 28
  - He has “tried everything”
- On maximum Metformin, fears further weight gain and won’t touch a TZD

- How will you manage such a patient?
Concept

- When A1c is high basal glucose is the main contributor to the elevation in A1c above normal
- When A1c is slightly elevated it is postprandial glucose that is the main contributor to the elevation in A1c above normal
Daily Glucose Profile: Poor Control

Daily Glucose Profile: Good Control

Both FPG and PPG Contribute to A1C

Antihyperglycemic Agents

**Postprandial hyperglycemia**

- Acarbose
- Nateglinide Repaglinide
- Rapid-acting insulin analogues

**Basal hyperglycemia**

- Metformin
- Sulfonylureas
- TZD’s
- Basal insulin

The balance between control and tolerability: data from DCCT

Concept

- The hyperglycemia in DM2 is not solely due to insulin resistance/insufficiency
- The lack of postprandial glucagon suppression also contributes to hyperglycemia
## Beta and Alpha Cells in Pancreas of Normal Individuals

<table>
<thead>
<tr>
<th>Beta Cells</th>
<th>Alpha Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Comprise about 50% of endocrine mass of pancreas¹</td>
<td>• Comprise about 35% of endocrine mass of pancreas¹</td>
</tr>
<tr>
<td>• Produce insulin and amylin²</td>
<td>• Produce glucagon²</td>
</tr>
<tr>
<td>• Insulin released in response to elevated blood glucose levels²</td>
<td>• Glucagon released in response to low blood glucose levels²</td>
</tr>
</tbody>
</table>

Postprandial Insulin, Glucagon Dynamics Abnormal in Type 2 Diabetes

Glucose (mg %)

- Type 2 diabetes
- Normal subjects

Insulin (µU/mL)

- Delayed/depressed insulin response

Glucagon (pg/mL)

- Nonsuppressed glucagon

The third defect in DM2

Back to Leo

- Wouldn’t it be nice if there was a drug that
  - Helped the pancreas secrete more insulin
    AND
  - Suppressed glucagon
    AND
  - Was more active when sugars were high
    AND
  - Was less active when sugars were low so as to avoid hypoglycemia?
INCRETINS: The Players

- The gila monster
- GLP-1
  - Glucagon-like peptide-1
- GIP
  - Glucose-dependant insulinotropic polypeptide
- DPP-IV inhibitor
  - dipeptidyl-peptidase IV inhibitor
The Gila Monster
What Are Incretins?

- Gut peptide hormones (GLP-1, GIP)
- Secreted in response to food ingestion
- Stimulate glucose-dependent insulin secretion
- Account for up to 60% of insulin response in healthy subjects
- Short half-life due to enzymatic degradation

GLP-1 Effects in Humans: Understanding Glucoregulatory Role of Incretins

- GLP-1 secreted upon the ingestion of food
- Promotes satiety and reduces appetite
- Alpha cells: ↓ Postprandial glucagon secretion
- Liver: ↓ Glucagon reduces hepatic glucose output
- Stomach: Helps regulate gastric emptying
- Beta cells: Enhances glucose-dependent insulin secretion
- ↑ Beta-cell response
- ↓ Beta-cell workload

Incretin Secretion and DPP-4–Mediated Inactivation

- Mixed meal
  - Intestinal GIP release
  - Intestinal GLP-1 release
- Decreased gastric emptying, food intake, and glucagon secretion
  - $T_{1/2} = 1$ to $2\text{ min}$

- GIP (1-42) active
- GLP-1 (7-36) active

- Increased insulin secretion
- Enhanced beta-cell proliferation
- Reduced beta-cell apoptosis

- DPP-4
  - GLP-1 (9-36) inactive (> 80% of pool)
  - DPP-4 inhibitor

Drucker DJ. Diabetes Care 2003;26:2929-2940.
GLP-1 Actions Glucose-Dependent in Patients with Type 2 Diabetes

Strategies for Incretin-Based Therapy

X GLP-1 continuous infusion: impractical
X GIP efficacy unproven
✓ Agents that mimic GLP-1 action:
  GLP-1 analogues (eg, exenatide, liraglutide)
✓ Agents that prevent incretin degradation:
  DPP-IV inhibitors (eg, sitagliptin, vildagliptin)

Sinclair EM, Drucker DJ. Physiology 2005;20:352-365
## Incretin-Based Therapies

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 Analogues</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administration</strong></td>
<td>Injection</td>
<td>Orally available</td>
</tr>
<tr>
<td><strong>GLP-1 concentrations</strong></td>
<td>Pharmacological</td>
<td>Physiological</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>GLP-1</td>
<td>GLP-1 + GIP</td>
</tr>
<tr>
<td><strong>Insulin secretion</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Glucagon secretion</strong></td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>HbA₁c ↓</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Expansion of beta-cell mass (animal studies)</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Nausea and vomiting</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Weight loss</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Gastric emptying</strong></td>
<td>Inhibited</td>
<td>+/-</td>
</tr>
</tbody>
</table>
## Incretin-Modifying Therapies

<table>
<thead>
<tr>
<th></th>
<th><strong>Incretin Mimetics</strong></th>
<th><strong>DPP-4 Inhibitors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exenatide</strong></td>
<td><strong>Byetta™</strong></td>
<td><strong>Saxagliptin</strong></td>
</tr>
<tr>
<td><strong>Liraglutide</strong></td>
<td><strong>Victoza</strong></td>
<td><strong>Onglyzas®</strong></td>
</tr>
<tr>
<td><strong>Saxagliptin</strong></td>
<td><strong>Merck</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sitagliptin</strong></td>
<td><strong>Januvia™</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Eli Lilly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Novo-Nordisk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Merck</td>
<td></td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Injection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td></td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>2-4 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(LAR 1 week)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12-14 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12-14 hours</td>
<td></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>b.i.d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>q.d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o.d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>q.d.</td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>5-10 ug b.i.d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(LAR 2 mg/week)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Up to 2 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg o.d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Insulin secretion</strong></td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td><strong>Glucagon secretion</strong></td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td><strong>A1c reduction</strong></td>
<td>-0.8% to 2.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.8% to 2.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.5% to -1.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.5% to -1.5%</td>
<td></td>
</tr>
<tr>
<td><strong>FPG reduction</strong></td>
<td>↓ (LAR better)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td><strong>Body weight reduction</strong></td>
<td>Yes (3-5 kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes (3-5 kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Antibody production</strong></td>
<td>Yes (45%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>β cell mass</strong></td>
<td>Robust</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probable</td>
<td></td>
</tr>
</tbody>
</table>
Use of Incretin-Modifying Therapies

- Incretin-modifying therapies are indicated after metformin monotherapy
  - They share with TZDs advantage of no hypoglycemia, unlike secretagogues
  - They have advantage over TZDs and secretagogues of weight loss or absence of weight gain
  - They share with TZDs potential benefits on beta cell preservation over secretagogues
Take Home Points About Incretins

- Incretins play an important role in glucose homeostasis by both increasing insulin secretion and suppressing glucagon in a glucose dependent manner.
- Medications such as GLP-1 analogues and DDP-IV inhibitors are safe and useful tools that are being added to our armamentarium of drugs to fight DM2.
- You will soon be seeing many patients like Leo on these medications.
In the Hospital

- Want to avoid complications of acute dysglycemia and maintain good control
- Think “can this drug cause hypoglycemia?”
  - No for metformin, TZD’s and incretin based therapies
- Has the medical condition altered drug metabolism
  - Decreased renal function – increases risk of hypoglycemia with secretagogues, possible increased risk of lactic acidosis with metformin
In the Hospital

- When and will the patient be eating
- What was their control like prior
  - Someone with very tight control is at increased risk of hypoglycemia

- You can predict a fair bit but you have to check and react if need be.

- Pharmacists and diabetes nurse educators are you friends
Thank You

- Diabetes is dynamic in the hospital setting
- Incretin therapies are the newest agents and more are coming
- Check, check, check
- Ask your friends!