Anti-Diabetic Drugs
Review and update 2012

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Content

• Review in OAD (oral anti-diabetic drugs)
  – Insulin secretagogue: SU, Glinide
  – Insulin sensitizer: MFM, TZD
  – Inhibit glucose absorption in GI tract: AGI

• Update in anti-diabetic drugs
  – Incretin based therapy
  – SGLT-2 inhibitor
OADs mechanism

Hyperglycemia
SU or Glinides

Insulin secretagogue
Sulfonylurea

- Lower A1C 1-2%
- Side effect
  - Hypoglycemia
    - After exercise or missed meal
    - High dose
    - Use longer-acting (glibenclamide)
    - Undernourished or abuse alcohol
    - Impaired renal or cardiac function
    - Being in hospital
  - Weight gain
Meglitinides

• Efficacy~ SU (Neteglinide < repaglinide)
• Start before each meal
  – Postprandial hyperglycemia and erratic eating habits
• Principally metabolized by liver: not adjust in renal insufficiency
• May be used in allergy to SU
• SE: hypoglycemia and weight gain
• Inhibit alpha glucosidase enzyme
• Slow absorption glucose and ↓post prandial glucose
• Acarbose, miglitol, voglibose
• C/I: Cr >2 mg/dl
• Adverse effect: Flatulence
Metformin

- METFORMIN
- AMP-K
- Glucose → ChREBP
- Insulin → SREBP-1c
- Beta Oxidation
- TG
- VLDL
- FFA
- VLDL, Chylomicron remnant
Metformin

- Side effect
  - GI side effect
  - Vitamin B12 deficiency
    - ↓ absorption: altered intestinal Ca metabolism within distal ileum (vit B12 uptake is Ca dependent)
    - Dose dependent and time
    - No consensus available on screening or prevention
  - Rare risk of lactic acidosis
    - C/I: renal (Cr >1.5 in male, > 1.4 mg/dl in female or GFR < 60 ml/min) and liver dysfunction, heart failure, dehydration or hemodynamic compromise and alcohol abuse

Ting R. Arch Intern Med 2006;166:1975
De Jager. BMJ 2010;340:c2181
Kimmel B. clinical diabetes 2005;23:64-71
Thiazolidinediones

- Pioglitazone, (Rosiglitazone), Troglitazone
- Insulin sensitivity acting on adipose, muscle and liver
- Bind to and activate PPARs (Peroxisome proliferator-activated receptor-γ)
  - Regulate gene expression
    - Improve insulin sensitivity
    - Promoting lipid storage
    - ↓Expression gene associated with inflammation
  - Preserved pancreatic β cell function
- (Pioglitazone) ↑HDL-C, ↓LDL-C and small dense LDL
Rosiglitazone

• Meta-analysis: ↑MI 45% and CV death 64%
• RECORD trial: no significant difference
  (funded by manufacturer, open-lable, under-powered, ITT analysis of interim analysis)
• Meta-analysis included RECORD: ↑ MI, not CV death
• Retrospective observational study: ↑ stroke, CHF and death (compared to PIO)
• FDA: restrict access
Pioglitazone

• Side effect
  – Fluid retention and Congestive heart failure
    • C/I in class III, IV CHF
  – Weight gain
  – Fracture esp. postmenopausal women
  – Macular edema
  – Hepatotoxicity (troglitazone)
    • C/I in ALT > 2.5x ULN
FDA Drug Safety Communication: Ongoing Safety Review of Actos (pioglitazone) and Potential Increased Risk of Bladder Cancer After Two Years Exposure

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary
References
Assessing the Association of Pioglitazone Use and Bladder Cancer Through Drug Adverse Event Reporting

Carlo Piccinni, PHD, Domenico Motola, PHD, Giulio Marchesini, MD and Elisabetta Poluzzi, PHD

Risk of Bladder Cancer Among Diabetic Patients Treated With Pioglitazone Interim report of a longitudinal cohort study

James D. Lewis, MD, MSCE, Assiamira Ferrara, MD, PHD, Tiffany Peng, MA, Monique Hederson, PHD, Warren B. Bilker, PHD, Charles P. Quesenberry Jr., PHD, David J. Vaughn, MD, Lisa Nessel, MSS, MLSP, Joseph Selby, MD and Brian L. Strom, MD, MPH
European Medicines Agency recommends new contraindications and warnings for pioglitazone to reduce small increased risk of bladder cancer

Benefit-risk balance remains positive in a limited population of type 2 diabetics

Epidemiological studies
(Kaiser Permanente Northern California cohort study, French CNAMTS cohort study, GPRD case control study)
Pioglitazone

• US FDA: caution in previous Hx of bladder cancer and avoided in active bladder cancer
• AACE, ADA, Endocrine society and EMA: continued use
• France: suspended use
• Germany: against commencing pioglitazone therapy
## Efficacy

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Expected ↓ HbA1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5%</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5%</td>
</tr>
<tr>
<td>Glinides</td>
<td>1-1.5% (repaglinide more effective)</td>
</tr>
<tr>
<td>TZDs</td>
<td>0.5-1.4%</td>
</tr>
<tr>
<td>AGI</td>
<td>0.5-0.8%</td>
</tr>
</tbody>
</table>

Nathan DM Diabetic care 2006;29:1963
Unmet need

- Hypoglycemia
- Weight gain
- GI side effects
- Edema, CHF
- Renal impairment
- Other possible risk: cancer
Ideal drug for T2DM

- Safe
- Efficacious
- Durable control
- Well tolerated
- Low risk for hypoglycemia
- Weight neutral or weight loss
- Can be used in all stages of disease: CKD
Incretin

GLP-1: Glucagon-like Peptide-1

GIP: Glucose-dependent Insulinotropic Peptide

Amino acids shown in orange are homologous with the structure of glucagon.
Incretin Effect

Oral Glucose Tolerance Test and Matched IV Infusion

![Graph showing plasma glucose and insulin levels during oral and IV glucose tolerance tests. The graph includes a solid green line for oral glucose and an orange line for IV glucose, with data points for glucose levels at various time intervals. The graph shows a comparison of plasma glucose and insulin responses to oral and IV 50 g glucose loads in 6 subjects.](image)

Comparison of the Incretins

<table>
<thead>
<tr>
<th>Site of production</th>
<th>GLP-1 (L-cells; ileum and colon)</th>
<th>GIP (K-cells; duodenum and jejunum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓secretion in T2DM</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>↓Glucagon secretion</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>↓food intake</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Slow gastric emptying</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Stimulate β-cell growth</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Promote insulin synthesis</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Glucose dependent insulin secretion
Current Strategies to Enhances GLP-1 Activity

Meal → Intestinal GLP-1 release → Active GLP-1 → DPP-4 → GLP-1 t½=1–2 min → GLP-1 analogue

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1
Current Strategies to Enhances GLP-1 Activity

**GLP-1 receptor agonist**
- Exenatide twice daily* or only weekly
- Liraglutide once dialy

**DPP-IV inhibitor**
- Sitagliptin*
- Vildagliptin*
- Saxagliptin
- Linagliptin
- Alogliptin
GLP-1 agonist vs DPP-IV inhibitor

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GLP-1</th>
<th>DPP-IV inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Injection</td>
<td>Oral</td>
</tr>
<tr>
<td>↑GLP-1 Level</td>
<td>&gt;5x</td>
<td>~2x</td>
</tr>
<tr>
<td>Inhibit Gastric emptying time</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>↓satiety</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Yes</td>
<td>weight neutral</td>
</tr>
<tr>
<td>(animal) B-cell proliferation</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
GLP-1 Receptor agonist

- Exenatide
  - Prefilled syringes
  - SC twice daily premeal (0-1h) (dose 5 or 10 ug)
  - Currently in clinical trial exenatide LAR (T1/2~2wk)
    - Less freq. adverse effect
    - 2 mg wkly
  - Reduce SU dose on start and titrating exenatide
  - Not use in GFR < 30 ml/min

*Heloderma suspectum (Gila monster)*
GI: N/V, wanes with duration of Rx, reduced with dose titrations (caution use in gastroparesis)

GLP-1 and C-cell

- In Rat:
  - Liraglutide: C-cell hyperplasia (pre-neoplastic MTC)
  - GLP-1 receptor in C cell of thyroid – dose and duration dependent
    - rodent C cell GLP-1 receptor are particularly sensitive
- No changes in calcitonin in short term in human
- FDA: contraindicated in FamHx of MTC and MEN-2

DPP-IV inhibitor

• Orally
• Sitagliptin
  • Approved as initial Rx, 2\textsuperscript{nd} agent or 3\textsuperscript{rd} agent (MFM, TZD and SU)
  • Usual dose 100 mg OD
  • 50 mg OD if GFR <50 ml/min
  • 25 mg OD if GFR<30 ml/min or ESRD requiring dialysis
DPP-IV inhibitor

- Vildagliptin
  - Selective, reversible and competitive inhibitor DPP-IV
  - 85% metabolized in liver
  - monoRx, or combination with MFM, TZD or insulin
  - 50 mg twice daily
DPP-IV inhibitor: SE

• Meta-analysis: sitagliptin and vildagliptin
  – Nasopharyngitis risk ratio 1.2 (1-1.4)
  – UTI 1.5 (1.0-2.2)
  – Headache 1.4 (1.1-1.7)
  
  (Amori RE; JAMA 2007;298:194)

• Hepatic dysfunction
  – vildagliptin ➔ check LFT before and 3 mo-after start

• Saxagliptin: ↓absolute lymphocyte
Pancreatitis, Pancreatic, and Thyroid Cancer With Glucagon-Like Peptide-1–Based Therapies

MICHAEL ELASHOFF, ALEKSEY V. MATVEYENKO, BELINDA GIER, ROBERT ELASHOFF, and PETER C. BUTLER

Larry L. Hillblom Islet Research Center at David Geffen School of Medicine and Department of Biomathematics, University of California, Los Angeles, California

- US FDA AERS (adverse event reporting system)
- Sitaglipitin or exenatide
  - ↑ 6x pancreatitis
  - ↑ reports of pancreatic cancer
- Exenatide: thyroid cancer

- Failure to validate specific Dx
- No information regarding
  - Comorbidites
  - Confounding factors
  - Duration of drug exposure
- Patients and doctor report
Preclinical studies and clinical study

- Preclinical studies: no link between incretin and pancreatitis
  
  *(Drucker D. JCEM 2011)*

- Clinical study: No link between incretin and pancreatitis
  - Claims-based active drug (exenatide and sitagliptin) safety surveillance system
    *(Dore DD. Curr Med Res Opin 2009)*
  
  - Cohort study of acute pancreatitis in relation to exenatide
    *(Dore DD. Diabetes Obes Metab 2011)*
  
  - Pooled analysis of RCT (10,246) with sitagliptin
    *(Engell SS. Int J Clin Pract 2010)*
  
  - Medco National Integrated Database (exenatide and sitagliptin)
    *(Garg R. Diabetic care 2010)*

Large RCT, longer duration should provide more accurate data
### Approved clinical indication

<table>
<thead>
<tr>
<th>Drug</th>
<th>MonoRx</th>
<th>Add on to</th>
<th>Triple Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MFM</td>
<td>SU</td>
</tr>
<tr>
<td>Exenatide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vildagliptin (not US)</td>
<td>✓ (only US)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

European Medicines Agency (EMA) April 2011
US FDA
OADs mechanism (2)

Hyperglycemia

Insulin secretion
- ↑ Sulfonyureas
- ↑ Meglitinides

Glucagon secretion
- ↓ Incretins

GI
- α glucosidase inhibitors

Appetite control
- Incretins

Hepatic glucose output
- ↓ Metformin
- ↓ Thiazolidinediones

Lipotoxicity
- Thiazolidinediones

Glucose uptake and utilization
- ↑ Thiazolidinediones
- ↑ Metformin

Glucose reabsorption
- ↓ SGLT2 inhibitors
**SGLT2-inhibitors**

- Glucose transporters – blood glucose is freely filtered.

Glomeruli filter 144 g of glucose/24hr

Nearly 100% reabsorbed in renal tubules

BS reach renal threshold for reabsorption (180 mg/dL)

No Hypoglycemia

Glucosuria
Adverse effect

- UTI
- Symptomatic vulvovaginal candidiasis
Dapagliflozin rejected by FDA Panel

• July 2011: the FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) vote 9 to 6 against approval of dapagliflozin

• January 19, 2012: USFDA declined approval of the dapagliflozin,
  – asking Bristol-Myers Squibb and AstraZeneca to provide more data
    • Breast cancer: 0.4 vs 0.1 %
    • Bladder cancer: 0.3 vs 0.05 %
  – more study of the possible cancer risks and other safety questions would be needed.
Conclusion

- Insulin secretagogue
- Insulin sensitizer
- Incretin base
- SGLT-2 inhibitor

- Preserve beta-cell
- Side effect
  - Cancer
  - CV outcome
THANK YOU FOR YOUR ATTENTION