Combination of OHA Therapy in Type 2 Diabetes Mellitus

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DIABETES MELLITUS

\[\downarrow\]

\[\beta\text{-Cell Dysfunction}\]

\[\downarrow\]

INSULIN

HOLDS TRUE
FOR
TYPE 1 D.M.
Worldwide prevalence of diabetes in 2000

Number of persons

- < 5,000
- 5,000–74,000
- 75,000–349,000
- 350,000–1,499,000
- 1,500,000–4,999,000
- > 5,000,000
- No data available

Worldwide prevalence of diabetes in 2030 (projected)

Number of persons

- < 5,000
- 5,000–74,000
- 75,000–349,000
- 350,000–1,499,000
- 1,500,000–4,999,000
- > 5,000,000
- No data available

Total cases > 300 million adults

Type 2 diabetes: a growing problem

- A serious, progressive disease, characterized by two fundamental defects
  - Insulin resistance
  - β-cell dysfunction
- Accounts for > 95% on diabetes cases worldwide
- Represents a significant disease burden
  - Associated with serious microvascular and macrovascular complications
  - Significant impact on overall healthcare costs
Characteristics of type 2 diabetes

- Chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism
- Defects in insulin action (insulin resistance), insulin secretion (β-cell dysfunction) or both
ORAL HYPOGLYCEMIC AGENTS

O.H.A. are the most common form of treatment of Type 2 D.M. worldwide. When used judiciously they are important agents in the management of the most common form of Diabetes.
O. H. A.

For economic, logistic and general effectiveness, oral agents are a dependable means of treating a large population of diabetics worldwide when used correctly.
ORAL HYPOGLYCEMIC AGENTS
SULFONYLUREAS
BIGUANIDES
MEGLITINIDES
ALPHA GLUCOSIDASE INHIBITORS
THIAZOLIDINEDIONES
CLINICAL BARRIERS TO O.H.A.S.

- HYPOGLYCEMIA
- DIURNAL GLUCOSE FLUCTUATIONS
- EXCESSIVE WEIGHT GAIN
- POST PRANDIAL HYPERGLYCEMIA
Ideal Therapeutic Agents

• improve the timing and amount of insulin secreted without unduly stressing the already maximally stimulated beta-cells

• enhance insulin actions

• restore inhibition of hepatic gluconeogenesis to normal
SULPHONYLUREAS
FIRST GENERATION

Tolbutamide

CH₂ -CH₂CH₂CH₂CH₂Cl

Chlorpropamide

Cl -CH₂CH₂CH₂CH₂
SULPHONYLUREAS
SECOND GENERATION

Gliclazide

GLIBENCLAMIDE

GLIPIZIDE
EFFECTS OF SULPHONYLUREAS

- Increased tissue sensitivity to insulin thus improved insulin action
- Reduced hepatic extraction of insulin from the circulation
- Effects on plasma lipids, i.e. Triglycerides and Cholesterol, Direct effects unlikely
- Effects on platelets and fibrinolysis
- Effects on Basement Membrane to reduce thickness
SULFONYLUREAS:

EXTRAPANCREATIC EFFECTS

1. Increased insulin receptor binding sites
2. Decreased hepatic gluconeogenesis.
   Augmentation of insulin-induced suppression of hepatic glucose release.
3. Inhibition of triglyceride lipase
4. Enteroinsular axis stimulation
OPTIONS FOR SULFONYLUREAS

CHLORPROPAMIDE

TOLBUTAMIDE

GLIBENCLAMIDE

GLIPIZIDE

GLICLAZIDE

GLIMEPIRIDE
BIGUANIDES
MODE OF ACTION

- Inhibition of glucose and aminoacid transport across small bowel
- Enhanced glycolysis in extra hepatic tissues
- Inhibition of hepatic gluconeogenesis
- Direct cellular effect
- Increase in glucose uptake
BIGUANIDES
MODE OF ACTION

- In isolated mitochondria there is interference with transfer of high energy bonds to A.D.P. suggesting that the compound inhibits oxidative phosphorylation.

- 1/3 is eliminated as metabolite. 2/3 is eliminated unchanged. 30% is excreted in urine in 5 hours and 90% in 24 hours.

- Toxicity associated with hypoxia, renal insufficiency and excessive alcohol intake.

- Hypoglycemia due to phenformin alone is actually unknown.
BIGUANIDES
CONTRA-INDICATIONS

- Patients with renal insufficiency
- Conditions that predispose to tissue hypoxia.
  - Severely uncontrolled diabetes
  - C.C.F., I.H.D., Malignant hypertension, Proliferative retinopathy
  - Pulmonary insufficiency
  - Acute infections, traumatic or inflammatory conditions
  - Advanced age.
BIGUANIDES
CONTRA-INDICATIONS

- Hepatic dysfunction (hepatitis, cirrhosis, fatty liver)
- Alcohol abuse
- Patients using barbiturates, salicylates, phenothiazines
- General debilitating conditions
- Pre and post operatively (1 week)
- During starvation diet
- Poorly complying patients
OPTIONS FOR BIGUANIDES

- Phenformin
- Metformin
NEWER O.H.A.

- GUAR GUM
- ACARBOSE
- GLIMEPIRIDE
- REPAGLINIDE
- GLITAZONES
ACARBOSE

- Inhibits $\alpha$ Glucosidase Activity
- GI Effects
GLIMEPIRIDE

- Less Hypos
- Less Weight gain
- Less Hyperinsulinemia
- Less early failure of $\beta$ cells
- Less skipped doses
INSULIN SECRETAGOGUES

Miglitinide Analog – Repaglinide

• No peripheral effects on muscle, liver and adipose tissue
• Excreted via bite – safe in patients with renal disease
• Lower risk for hypoglycemia even on skipping a meal!
• Good efficacy & safety profile even in the elderly
• First line therapy in type 2 patients with diet failure
• Good results when used in combination with Metformin
REPAGLINIDE

- Non Sulfonylurea
- Insulinotropic agent
GLITAZONES
Modes of Action

- It activates the nuclear peroxisome proliferator activated receptor - $\gamma$ (PPAR-$\gamma$)

- It also has partial agonist activity against PPAR $\alpha$
# DIFFERENT TYPES OF PPARS

<table>
<thead>
<tr>
<th>Tissue expression</th>
<th>α: Skeletal muscle, liver, kidney</th>
<th>β: Not known</th>
<th>γ: Adipose tissue, skeletal, cardiac muscle, liver, kidney Sl, bladder &amp; spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Control of lipoprotein metabolism, fatty acid oxidation</td>
<td>Not known</td>
<td>Adipocyte differentiation</td>
</tr>
<tr>
<td>Target Actions</td>
<td>Treatment of dyslipidemia</td>
<td>Not known</td>
<td>Improves insulin sensitivity</td>
</tr>
<tr>
<td>Natural ligands</td>
<td>Docosahexanoic acid</td>
<td>Not known</td>
<td>PG metabolite PGJ,</td>
</tr>
<tr>
<td>Synthetic ligand</td>
<td>Fibrates</td>
<td>-</td>
<td>Thiazolidinediones</td>
</tr>
</tbody>
</table>
GLITAZONES

- INHIBITS SMOOTH MUSCLE CELLS (SMC) PROLIFERATION IN PATIENTS WITH INSULIN RESISTANCE

- LIVER CELL INJURY IN 1.9% CASES IN CONTROLLED TRIALS

- SUBFULMINANT LIVER FAILURE

- RETENTION OF FLUID

- ANEMIA
GLITAZONES

- INCREASES INSULIN SENSITIVITY IN SKELETAL MUSCLE, HEPATIC AND ADIPOSE TISSUE
- DECREASES ENDOGENOUS INSULIN CONCENTRATION
- DECREASES EXOGENOUS INSULIN REQUIREMENTS
- INDUCES CYTOCHROME p 450 ISOENZYME 3 A 4
# Characteristics of Oral Antidiabetic Agents

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Insulin secretagogues</th>
<th>Metformin</th>
<th>α-Glucosidase inhibitors</th>
<th>Insulin</th>
<th>TZDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on FPG / HbA1C</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Effect on Plasma insulin</td>
<td>↑</td>
<td>↓</td>
<td>-</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Effect on insulin resistance</td>
<td>-</td>
<td>↓/-</td>
<td>-</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>Effect on β-cell function</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Safety and tolerability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of hypoglycaemia</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Weight gain</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Gastrointestinal side-effects</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>-</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oedema</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✓</td>
</tr>
</tbody>
</table>

Efficacy: ↓ = reduced levels; ↑ = increased levels; - = no documented change. Safety and tolerability: ✓ = treat-related adverse event; - no documented association with treatment. FPG = fasting plasma glucose. TZDs = thiazolidinedions.
TYPE 2 DIABETES MELLITUS
SECONDARY FAILURE

- Secondary failure rate 5% to 10% a year (UKPDS 7% a year)
  - Decreasing $\beta$-cell function
  - Obesity
  - Non-adherence to treatment
  - Lack of exercise
  - Intercurrent illness
PROBABILITY OF REQUIRING POLYThERAPY

- Young age at diagnosis
- Increased base line Obesity
- Increased base line Glycemia
- Increased baseline Triglycerides
TRADITIONAL STEPWISE APPROACH
EARLY COMBINATION APPROACH. OAD, ORAL ANTIDIABETIC DRUG
ADVANTAGES OF FIXED DOSE COMBINATIONS

- Improved compliance
- Synergism
- Enhanced efficacy
- Reduction of side effects
- Economy
GOALS OF THERAPY FOR THOSE WITH DIABETES MELLITUS SHOULD INCLUDE A SERIOUS EFFORT TO ACHIEVE BLOOD GLUCOSE LEVELS AS CLOSE TO NORMAL AS POSSIBLE

CONFIRMED BY DCCT UK PDS KUOMOTO TRIAL
IDEAL O.H.A.

- Combination Efficacy, Safety, Tolerability.
- Metformin
- Thiazolidinediones
ADA “Consensus” on Type 2 Diabetes Therapy

Nonpharmacologic Therapy
- Diet
- Exercise

Glycemic goals not achieved

Monotherapy
- Sulfonylureas
- Biguanides
- α-Glucosidase inhibitors
- Glitazones
- Meglitinides
- Insulin

Glycemic goals not achieved

Combination Therapy
Frequently used or well studied
- Sulfonylurea + Metformin
- Sulfonylurea + Troglitazone
- Sulfonylurea + Pioglitazone
- Sulfonylurea + Acarbose
- Repaglinide + Metformin
- Rosiglitazone + Metformin

Infrequently used and/or less well studied
- Sulfonylurea + Insulin
- Metformin + Insulin
- Pioglitazone + Insulin
- Troglitazone + Insulin
- Acarbose + Insulin

Insulin
- Intermediate BID
- Intermediate + Regular BID
- Multiple (3 or more) injections

Glycemic goals not achieved

Very symptomatic
- Severe hyperglycemia
- Ketosis
- Unrecognized IDDM
- Pregnancy

PRACTICAL MANAGEMENT OF TYPE 2 DIABETES MELLITUS

**FBG > 126**

- "All get diet and exercise"

**Monotherapy**

1. **126-140 mg/dL**
   - Glitazones
   - Metformin
   - Acarbose

2. **140-200 mg/dL**
   - Repaglinide
   - Glitazones
   - Metformin
   - Sulfonylurea

3. **200-240 mg/dL**
   - Acarbose
   - No Sx
   - Sx
   - Sulfonylurea

4. **240-300 mg/dL**
   - No Sx/Sx
   - Sulfonylurea

5. **> 300 mg/dL**
   - No Sx
   - Sx
   - Sulfonylurea
   - Insulin

**Oral Combination**
- Evolving criteria
  - If FBG > 140 mg/dL (126 mg/dL?)
  - HbA1c > 8% (7%?)
  - Add second oral agent and titrate to maximum dose

**Triple Therapy**
- If no improvement:
  - Try a different sensitizier
  - Or try triple therapy?
  - Or Continue oral agent(s) and add insulin Rx at PM or Hs
CONCLUSION

• MONOTHERAPY

• COMBINATION THERAPY
THANK YOU