Oral antidiabetics (1)

Lecture 5

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Oral antidiabetics

Pt.- centered approach > guidelines.

Antidiabetic combination is better than maximizing the dose.

A) Oral hypoglycemics (Insulin secretagogs)

1. Sulfonylurea

Mechanism:

1. Closure of K channels…
2. Direct ↑ insulin exocytosis.
3. ↑ sensitivity and number of insulin receptors.
4. ↓ plasma glucagon.

Uses:

Type 2 DM if pt. fails to respond to lifestyle modification for 3 months and no contraindications. Before meals.

Contraindications:

1. Uses of insulin except 7.
8. Decrease dose in old & renal disease.
9. Hypersensitivity reactions.

Adverse effects:

1. Hypoglycemia especially by glibenclamide. Caution in old & CV pts.
2. ↑body weight
3. 2ry failure & tachyphylaxis: by exhaustion of insulin stores
4. GIT upset.
5. Teratogenicity (pass placenta)
6. Allergic reactions as skin rash (related to sulfonamide).

Interactions:

1. β blockers → hypoglycemia.
2. Hyperglycemic drugs as corticosteroids ↓hypoglycemic effects.
3. Drugs highly bound to PP as NSAIDs & oral anticoagulants→ ↑free level → potentiation.
4. Enzyme inducers as rifampin → antagonism.

Preparations:

2nd generation: More potent & less adverse effects.

1. **Glipizide**:

Shortest t½ (3hs.). Also extended release preparations for 24 hours, once in the morning (but loss of benefit).

Preferred in old age & renal dysfunction to avoid hypoglycemia.

Gliclazide: .2 •

Intermediate potency and duration. 80mg .

Once daily (MR) tablets (30-60 mg) are used.

3. **Glibenclamide (glyburide):**

Most potent and longest duration (12-24 hs.).

CI in old age & renal dysfunction.

5mg. 1-4 tablet /day.

3rd generation:

Glimepride: binds to different receptors. Rapid association with receptors (→ rapid insulin release) and rapid dissociation (→ less ↑insulin & hypoglycemic risk and less ↑ Wt.).

Intermediate – long duration (12-24 hs.). Its peak effect is 4hs. Food at this time is important to avoid hypoglycemia.

Dose: 1-8 mg once daily orally just before major meal.

Meglitinides2. •

Mechanism:

Similar to sulfonylurea but no direct exocytosis.

Very rapid onset & peak (1 hour) achieve meal (PP) hyperglycemic control. Short duration (4 hours) due to effective hepatic clearance → less hypoglycemia & less ↑ body wt.

Uses, CI & adverse effects: Similar to sulfonylurea.

e.g. **repaglinide** orally 0.25, 0.5, 1 or 2 mg (according to amount of carbohydrate in meal) before each meal.

Caution in liver dysfunction. Affected by enzyme inducers & inhibitors and can be given in renal dysfunction & old pts .

Nateglinide is similar.

B) Euglycemics •

Unlike oral hypoglycemics:

1. No ↑ insulin release (Non insulin secretagog).
2. No ↓ blood glucose below normal.
3. No ↑ body wt.

1. Metformin

Mechanism:

A **biguanide**. It primarily ↓fasting glycemia and mildly PP hyperglycemia.

1. ↓ glucagon - dependent hepatic glucose production (↓glycogenolysis & gluconeogenesis) in fasting state →↓fasting blood glucose. Major action.

2. Inhibits mitochondrial respiratory chain (complex 1) → uncoupling of oxidative phosphorylation → ↑anerobic glycolysis →

↑ fatty acid oxidation & glucose uptake & utilization →↓ PP hyperglycemia.
↓lipogenesis & cholesterol synthesis →↓ postprandial hyperlipidemia .

3. ↓carbohydrates & fat absorption in GIT.

4. ↑insulin sensitivity by ↑ activation of insulin receptors & IRSs →↑ phosphorylation of GLUT4 → ↑peripheral glucose uptake.

5. ↓plasma glucagon.

6. Beneficial effect on gut microbiota (x intestinal dysbiosis).

Pharmacokinetics:

Absorbed orally, wide distribution into various tissues.

Not highly bound to plasma proteins & not metabolized.

Uses:

1. Type 2DM (1st line) with or without other oral antidiabetics.
   Mainly in middle (< 60 years) age, obese diabetics.

   ↓ diabetic complications & mortality.

2. Macrovascular & microvascular diabetic complications.

Other drugs affect only microvascular complications.

Cardiovascular diseases cause 50% of diabetic morbidity & mortality.

3. Metabolic syndrome & prevention of diabetes. It does not prevent diabetes in old & leaner prediabetics. Even by 250 mg.

4. Obesity. 5. NAFLD. 6. Polycystic ovary syndrome.

7. ↓cancer risk mainly in higher doses and ↑ cytotoxicity by cytotoxic drugs or radiotherapy.

Adverse effects:

1. GIT upset, flatulence.... Start with small dose.
2. ↓absorption of vit. B12. Deficiency after years.

   But neuropathy....
3. Lactic acid acidosis (by anerobic glycolysis).
4. Contraindicated (not absolute) in severe heart, lung, liver & renal dysfunction (risk of lactic acid acidosis).

Dose:

Metformin (Glucophage) 500 mg orally with meals.

Also slow (extended) release long acting formulations 850 & 1000mg. 1-3 times daily. They → less GIT side effects.

α glucosidase inhibitors .2•

Mechanism: compete with oligosaccharides (as sucrose) for α glucosidase in brush border of intestine, decreasing glucose absorption, reducing PP hyperglycemia .

Used alone or with oral hypoglycemics or metformin. Low efficacy.

If hypoglycemia: ttt by glucose & not sucrose.

Uses:

1. Type 2DM ttt & prophylaxis.

2. Obesity.

3. Prophylactic in hypertension and ↓cardiovascular risk & complications. By ↓ PP hyperglycemia, glucose variability, ↓Wt., on gut microbiota.

Adverse effects :

1. GIT upset, flatulence, diarrhea. Poor tolerance.
2. Reversible ↑ in liver enzymes (caution in liver diseases).
3. Contraindicated in renal dysfunction (excretion is renal).

e.g. acarbose. 25-100 mg before each meal.