Oral antidiabetics (2)

Lecture 6

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C) Insulin sensitizers (Thiazolidinediones)

Mechanism:

They stimulate nuclear peroxisome proliferator activated receptor γ (PPAR-γ), in muscles, fat, liver & adipose tissue. PPAR-γ receptors modulate expression of genes for insulin signal transduction and glucose & fat metabolism.

They ↑release adiponectin and ↓resistin (from adipocytes) which ↑& ↓tissue sensitivity to insulin respectively. They ↑expression of GLUT4 and ↓blood glucose, free fatty acids & triglycerides. They *↓LDL & ↑HDL*. They improve fatty liver. They also ↓prothrombotic & proinflammatory (as CRP) diabetic effects

Uses:

Type 2 diabetics as monotherapy or combination with oral hypoglycemics or euglycemics. They do not cause hypoglycemia.

Adverse effects & contraindications

1. Hepatotoxicity. Contraindicated in liver diseases.
2. Fluid retention: edema, CHF and ↑body wt. (also by ↑total fat mass). Also macular edema & dilutional anemia.
3. ↓ bone density & ↑fracture risk: by ↓osteoblast formation.
4. Contraindicated in pregnancy and may induce ovulation.

e.g. pioglitazone is metabolized by CYP to active metabolite.

Orally, once daily, 7.5 → 45 mg.

N.B.

- GLUT4:↑ by insulin (& metformin & pioglitazone) , translocated by exercise & ↑genetic coding by T4.
- Lipoprotein lipase: lipemia clearing. ↑by insulin.
- Hormone sensitive lipase: ↑ lipolysis in adipose tissue. ↓by insulin,

↑by epinephrine (β1) & cortisol, → ↑cholesterol e.g. in stress.

↑genetic coding by T4 →….but → more cholesterol secretion →↓cholesterol.

D) Incretins

Glucagon – like peptide -1 (GLP- 1) is a gut hormone with rapid proteolysis (also renal clearance). It amplifies insulin release by oral glucose more than by IV glucose. ↓early in type 2 diabetics (& in prediabetics).

Actions:

1. Amplifies glucose – induced insulin release & ↑insulin sensitivity peripherally. Unlike sulfonylurea, it causes mild ↑insulin release during fasting and at normoglycemic concentration → less hypoglycemic risk.

Unlike sulfonylurea, which accelerate β cell failure, it preserves islet integrity, with ↑regeneration & ↓apoptosis.

2. ↓glucagon secretion.
3. ↓gastric emptying → sensation of abdominal fullness + ↓ intestinal absorption.
4. Central anorexia.

GLP-1R agonists .1 •
(GLP-1 analogs)

Mechanism:

Synthetic long acting analogs of GLP-1. They are full agonists in GLP-1 receptor. They have **actions of GLP-1** but less proteolysis.

Uses:

In type 2 diabetics, it may be given as adjuvant if there is inadequate control by oral antidiabetics.

Adverse effects:

1. Anorexia & nausea in 40% of pts. (↓body wt.).
2. Hypoglycemia: more if combined with sulfonylurea.
3. Acute pancreatitis.
4. Nephrotoxicity.
5. Delay gastric emptying → ↓absorption of e.g. antibiotics & oral contraceptives (should be taken 1 hour before exenatide).

Preparations

1. Exenatide:

By SC injection before meals twice daily, as fixed- dose pens (5 &10 ug) 1 hour before breakfast & dinner .

Contraindicated in renal dysfunction.

- Exenatide LAR is long acting (once weekly), as powder diluted just before use.

2. Liraglutide:

3. Dulaglutide.

DPP-4 inhibitors .2•

Mechanism:

Selective oral inhibitors of dipeptidylpeptidase (DPP-4), the plasma enzyme which rapidly inactivates GLP-1 → prolonged action .

They ↑ plasma GLP-1 & insulin concentration.

They have other actions of GLP-1 but do not cause nausea, vomiting, with less wt. loss .

By inhibition of proteolysis, it also prolongs actions of GIP (gastric inhibitory polypeptide), neuropeptide Y, substance P, cytokines and growth factors.

Mainly renal clearance.

Uses:

Oral, once daily in type 2DM, with or without food, alone or combined with other oral antidiabetics or insulin. Dose is ↓in renal dysfunction.

Adverse effects:

Much lower incidence than other oral antidiabetics.

1. GIT upset.
2. Minimal hypoglycemia, except if combined with sulfonylurea or insulin.
3. Nasopharingitis & upper respiratory tract infection.
4. Headache.
5. Hypersensitivity reactions.
6. Pancreatitis.

Preparations:

1. Sitagliptin: 100 mg.
2. Vildagliptin: 50 mg.
3. Alogliptin: 25 mg.

2 & 3 are not used in liver dysfunction.

4. Linagliptin: 5 mg, no dose adjustment in renal or hepatic impairment. Not with enzyme inducers.

E) Sodium glucose co-transporter 2 (SGLT2) inhibitors

Mechanism:

Inhibit **SGLT2** in renal PCT (.....1 in intestine) → lowering of plasma glucose threshold from 180 to 90 mg%. This inhibits 90% of glucose reabsorption → glycosuria.

They ↓ body Wt. & BP by glucose loss & diuresis respectively.

Efficacy is reduced and are contraindicated in renal dysfunction.

Uses:

Type 2 DM with normal renal function.

Effective in advanced cases with loss of β- cells reserves.

Oral, once daily before 1st meal.

Adverse effects:

1. Polyuria & genitourinary infection. Mild, more in women.
2. Mild hypoglycemia in combination with insulin or sulfonylurea.
3. Bone fractures. Mainly canagliflozin.

Preparations:

1. Canagliflozin: 100mg.
2. Dapagliflozin: 10mg (5 mg in liver dysfunction).
3. Empagliflozin: 10mg.

Used in Type 2 DM with cardiovascular disease (↓cardiovascular morbidity & mortality