Lecture 8 & 9

Oral Hypoglycemic drugs

Objectives:

- ★ Classify different categories of oral hypoglycemic drugs.
- ★ Identify mechanism of action, pharmacokinetics and pharmacodynamics of each class of oral hypoglycemic drugs.
- ★ Identify the clinical uses of oral hypoglycemic drugs
- ★ Know the side effects, contraindications of each class of oral hypoglycemic drugs.

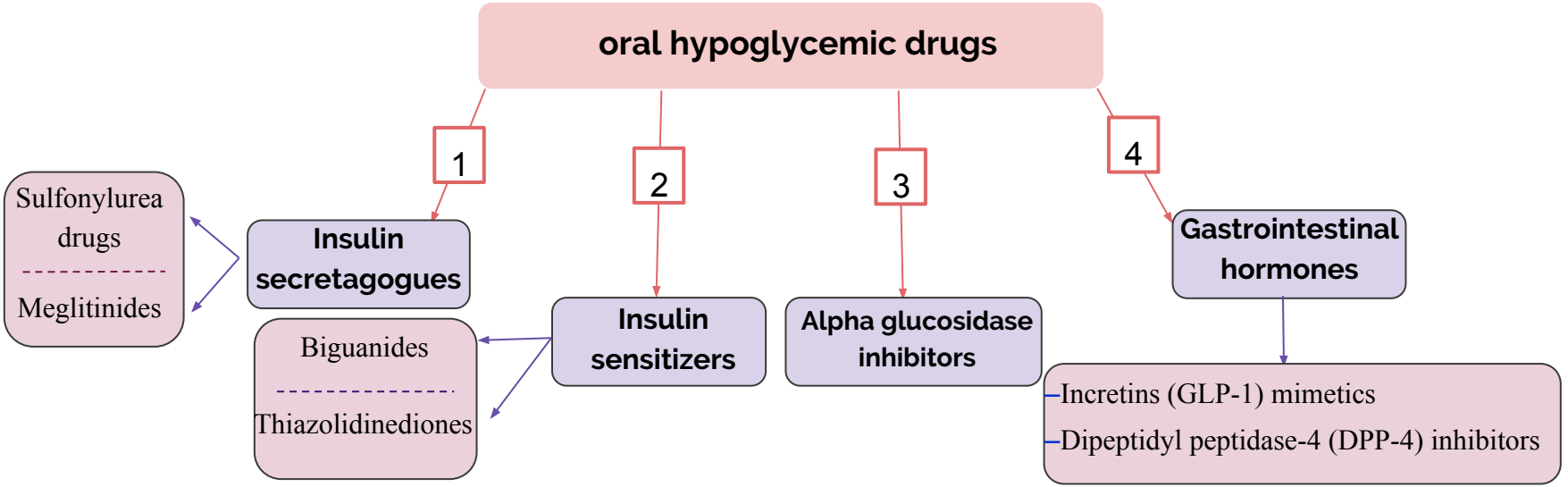
- Additional Notes
- Important
- Explanation –Extra-

before starting, please check our Endocrine block correction

For any correction, suggestion or any useful information
do not hesitate to contact us: Pharmacology434@gmail.com

Type II Diabetes

- ★ 80-90% occurrence
- ★ Over age 35
- ★ Pancreatic β-cells are not producing enough insulin.
- ★ Obesity is an important factor.
- ★ Insulin resistance in peripheral tissues.
- ★ Treated by **oral hypoglycemic drugs**.



Insulin secretagogues

Are drugs which increase the amount of insulin secreted by the pancreas

Sulfonylureas

MOA

★ **(**↑ Hyperglycemia ⟶ Blockade of ATP dependent K^+channels ⟶ Opening of voltage-dependent Ca^{++}channels ⟶ ↑ intracellular calcium in the beta cells ⟶ ↑ Insulin release **)**

★ **This drug** Stimulate insulin release from functioning B cells by blocking of **ATP-sensitive K channels** which causes depolarization and opening of **voltage- dependent calcium channels**, which causes an increase in intracellular calcium in the beta cells, which stimulates **insulin release**.

Pharmacokinetics

- Orally, well absorbed.
- Reach peak concentration after 2-4 hr.
- All are **highly** bound to plasma proteins.
- Duration of action is variable.
- **Second generation has longer duration than first generation ⟶ next slide**
- Metabolized in liver
- Excreted in urine (elderly and renal disease)
- Cross placenta, stimulate fetal β-cells to release insulin ⟶ fetal hypoglycemia at birth .

Adverse effect

1. Hyperinsulinemia & Hypoglycemia:

–More common in long acting sulfonylureas. particularly chlorpropamide, glyburide, and glimepiride)

–More in old age, hepatic or renal diseases.

–Less in tolbutamide.

2. Weight gain due to increase in appetite unless the diabetic diet and exercise program are followed.

	First generation sulfonylureas				second generation sulfonylureas		
drugs	Tolbutamide short-acting	Acetohexamide intermediate-acting	Tolazamide intermediate-acting	Chlorpropamide long- acting	Glipizide short -acting	Glyburide (Glibenclamide) long-acting	Glimepiride long-acting
Absorption	well	well	slow	well	well, reduced by food	well	well
Metabolism	yes						
Metabolites	inactive	active	active	inactive	inactive	inactive	inactive
Duration of action	Short (6 – 8 hrs)	Intermediate (12 – 20 hrs)	Intermediate (12 – 18 hrs)	Long (20 – 60 hrs)	10 – 16 hrs short	12 – 24 hrs long	12 – 24 hrs long
Doses	-				Divided doses 30 min before meals	Single dose	Single dose 1 mg
Excretion	urine						
Notes	**Tolbutamide:** • has short duration of action • safe for elderly diabetic patients or patients with renal impairment.				• More potent than first generation • Have longer duration of action. • Less frequency of administration • Have fewer adverse effects • Have fewer drug interactions		

Insulin secretagogues

Meglitinides

Drug	**Repaglinide** (Rapidly acting insulin secretagogues)
MOA	❑ Insulin secretagogue ❑ Identical to **sulfonylureas**
kinetics	❑ Orally, well absorbed ❑ Very **Fast onset acting** peak 1h ❑ Short duration of action within 4h ❑ Metabolized in liver and excreted in bile. ❑ Taken just before each meal
Uses	❑ **Type II diabetes**:monotherapy or in combination with other oral hypoglycemic drugs ❑ In patient allergic to sulfur (in Sulfonylureas)
ADRs	Less incidence than sulfonylureas ❑ Hypoglycemia ❑ Weight gain.

Insulin sensitizers

Increase the sensitivity of target organs to insulin

drugs	**E.g** 1- Biguanides (Metformin) 2-Thiazolidinediones (Pioglitazone)
1- Biguanides (Metformin)	
MOA	❑ Increases peripheral glucose utilization (tissue glycolysis) ❑ Reduce insulin resistance ❑ Inhibits hepatic gluconeogenesis ❑ Reduce LDL and VLDL ❑ Increase HDL
kinetics	❑ Orally. ❑ NOT bound to serum protein. ❑ NOT metabolized. t ½ 3 hours. (patient should use it 3 times a day) ❑ Excreted **unchanged** in urine
Uses	❑ Overweight patients with type 2 diabetes (first-line therapy). ❑ Type II diabetes as monotherapy or in combination.

Metformin

ADRs	❏ **GIT disturbances**: Metallic taste in the mouth ,nausea, vomiting, diarrhea ❏ **Lactic acidosis**. (rare) lactic acid accumulation usually occurs only in the presence of a predisposing conditions **such as** : Renal insufficiency, liver disease or alcohol abuse Heart failure, hypoxic states ❏ Interference with vitamin **B12 absorption** (long term use). ❏ Should be taken with meals and should be started at a low dose to avoid intestinal side effects then increase gradually
Advantages	❏ No risk of hypoglycemia or weight gain ❏ Improvement of lipid profile ❏ Inexpensive
C/I	❏ Renal disease. (cause it excreted in urine) ❏ Liver disease. (cause it metabolite in liver) ❏ Alcoholism.(can increase lactic acid) ❏ Cardiopulmonary dysfunction. ❏ Pregnancy.

2- Thiazolidinediones (glitazones)
E.g Pioglitazone

MOA	• Activate peroxisome proliferator-activated receptor -γ (PPAR-γ) (nuclear receptors in muscles and adipose tissue). • Increase glucose uptake and utilization in muscle and adipose tissue. • Increase sensitivity of target tissues to insulin.
kinetics	❖ Orally (once daily dose). ❖ Highly bound to plasma albumins (99%) ❖ Slow onset of activity ❖ Half life 3-4 h ❖ Metabolized in liver & Excreted in urine 64% & bile
Uses	• Type II diabetes with insulin resistance. • Used either **alone** or **combined** with sulfonylurea, biguanides or **insulin**. • No risk of hypoglycemia when used alone
Adverse effects	• Hepatotoxicity (liver function tests for 1st year of therapy) • **Fluid retention (Edema)** so it will cause **weight gain**.. • Congestive heart failure • Failure of estrogen-containing oral contraceptives

a-Glucosidase inhibitors

Eg: Acarbose ,Miglitol

MOA	★ **Reversible** inhibitors of intestinal a-glucosidases in intestinal brush border that are responsible for carbohydrate digestion which leads to decrease carbohydrate digestion and glucose absorption in small intestine (so it lower postprandial glucose level).		
kinetics (Acarbose)	• Given orally • is not absorbed • Excreted in feces • Taken just before meals • No hypoglycemia if used alone.		
Uses	• are effective alone in the earliest stages of impaired glucose tolerance • are not recommended alone as therapy for moderate to severe hyperglycemia • are **most useful** in combination with other oral hypoglycemic drugs or with insulin**.**		
ADRs	**GIT side effects**: Flatulence, diarrhea, abdominal pain, bloating.	**C/I**	irritable bowel syndrome, Inflammatory bowel disorders, Intestinal obstruction.

Incretins mimetics
GLP-1 agonists (hormone analog)
e.g. Dulaglutide, Exenatide, Liraglutide, Albiglutide

Incretins: are GI hormones secreted from intestine in response to food even before blood glucose level becomes elevated. They are carried through circulation to beta cells.

They leads to Increase insulin secretion & decrease in glucagon secretion *(regulate blood glucose).*

Incretins include:

1) GLP-1(glucagon-like peptide-1)
2) GIP (gastric inhibitory peptide)

★ **Both(1&2) are inactivated by dipeptidyl peptidase-4 (DPP-4).**

- **given s.c. once a week.**
- Therapy of patients with type 2 diabetes who are not controlled with oral medication.

Adverse effects

Nausea & vomiting (most common). Abdominal pain, decreased appetite & fatigue

Dipeptidyl peptidase-4 inhibitor (DPP- 4 inhibitors)
e.g. Sitagliptin, vildagliptin

- Inhibit DPP-4 enzyme thus increase incretin hormone (GLP-1).
- Orally.
- Given once daily.

Clinical uses:

Type II DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs.

Adverse effects:

Nausea, abdominal pain, diarrhea

SUMMARY

Class	Mechanism	Site of action	Main advantages	Main side effects
Sulfonylureas Tolbutamide	Stimulates insulin secretion	Pancreatic beta cells	• Effective • Inexpensive	• Hypoglycemia • Weight gain
Meglitinides repaglinide		Pancreatic beta cells	Sulfa free	•Hypoglycemia •Weight gain
Biguanides Metformin	Decreases insulin resistance	Liver	• mild weight loss • No hypoglycemia	• GIT symptoms, • Lactic acidosis • Metallic taste
Thiazolidinediones pioglitazone		Fat, muscle	No hypoglycemia	Hepatoxicity Edema, mild weight gain
α-Glucosidase inhibitors Acarbose	Inhibits α-glucosidase	GI tract	Low risk	•GI symptoms, flatulence
Incretins mimetics Dulaglutide	Increase incretin	GI tract	Once/week, s.c.	Nausea & vomiting
DPP-4 inhibitors Sitagliptin	Inhibit incretin breakdown	GI tract		Nausea & abdominal pain

MCQs

1) A patient with renal disease came to you with hyperglycemia what is the best oral hypoglycemic drug for him?

a-Chlorpropamide b-Glipizide
c-Tolbutamide d-Tolazamide

2)An obese patient who have diabetes type 2 need an oral hypoglycemic what is the recommended drug for him?

a-Glimepiride b-Metformin

c-Pioglitazone d-Miglitol

3) A diabetic lady who was on contraceptives came to you pregnant with increased numbers of ALT and AST, what oral hypoglycemic she is most likely taking?

a-Glitazones b-Metformin
c-Pioglitazone d-Tolbutamide

4)a diabetic patient with irritable bowel syndrome what oral hypoglycemic is contraindicated in this case?

a-Acarbose b-Pioglitazone
c-Metformin d-Acetohexamide

5) A patient taking Repaglinide skipped his lunch so he should skip his dose with this meal too?

a-true b-false

6)a pregnant lady came to the clinic with gestational diabetes what drug should describe for her?

1-Acarbose b-Exenatide

c-Pioglitazone d-insulin

answers:

1-c
2-b
3-c
4-a
5-a
6-d

Good luck!

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