Oral hypoglycemic drugs

Eman Alrashidi , Badra`a Almuharib , Sarah Bin Husain

Reham Alhenaki, Ala`a Alahmari

Special thanks FOR Badra`a ,, ☺

Imp >>> RED
Notes >>> green

Team Notes for introduction:

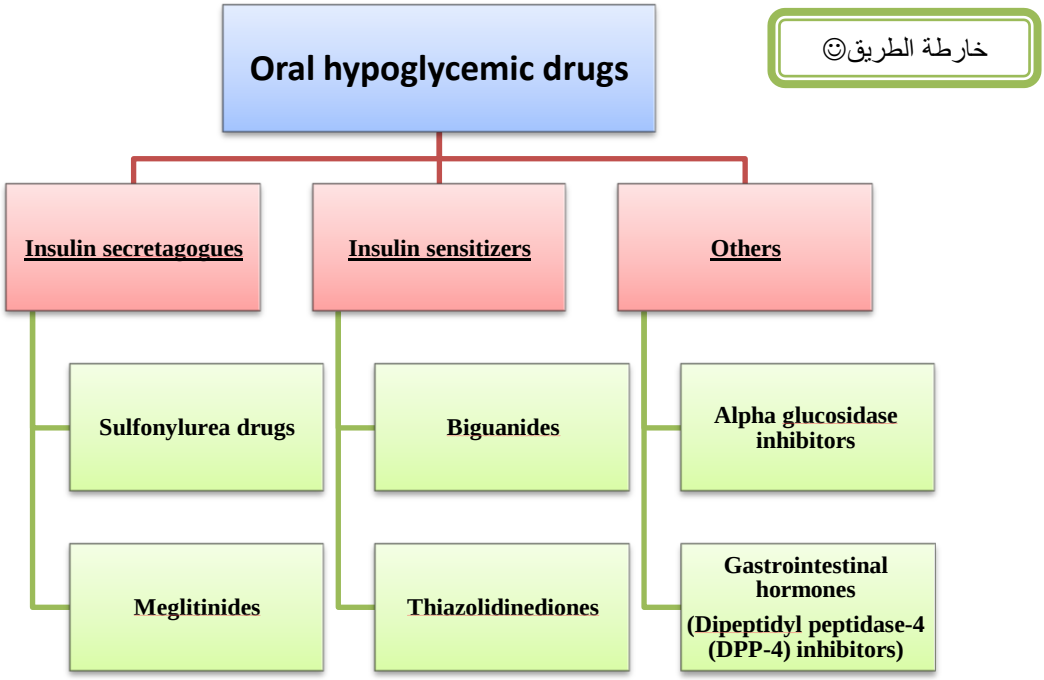
- type 1 IDDM→ is due to absolute deficient of insulin b\c all beta-cell are destructed.

-The only treatment for type 1 is → **injection of insulin**

-In type 2 → partial secretion of insulin b\c of partial functioning beta-cell BUT the amount of insulin isn't enough OR there is resistance in peripheral tissue

- Rx →**oral hypoglycemic drugs**

SO we cannot treat type 1 by using oral hypoglycemic B/c theses drugs need functional beta cell to produce their action! However sometimes we use insulin in T2DM when there is exhausted Beta-cells ((No more endogenous insulin secretion)).



This Classification is according to MOA:

1- Insulin secretagogues :oral hypoglycemic drugs have the capacity to stimulate beta cell to stimulate insulin secretion

2- Insulin sensitizers: don't have the ability to stimulate beta cell→don't cause insulin secretion BUT work by reducing the insulin resistance in the peripheral tissue!

1st Insulin secretagogues:

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

Include: A) Sulfonylureas **B)** Meglitinides

A) Sulfonylureas :

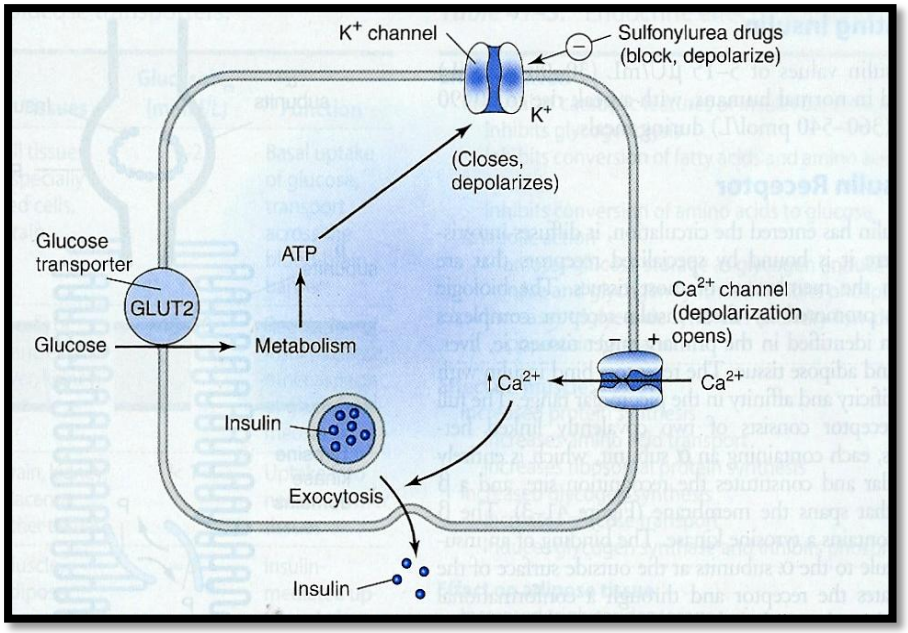
Mechanism of action of sulfonylureas:

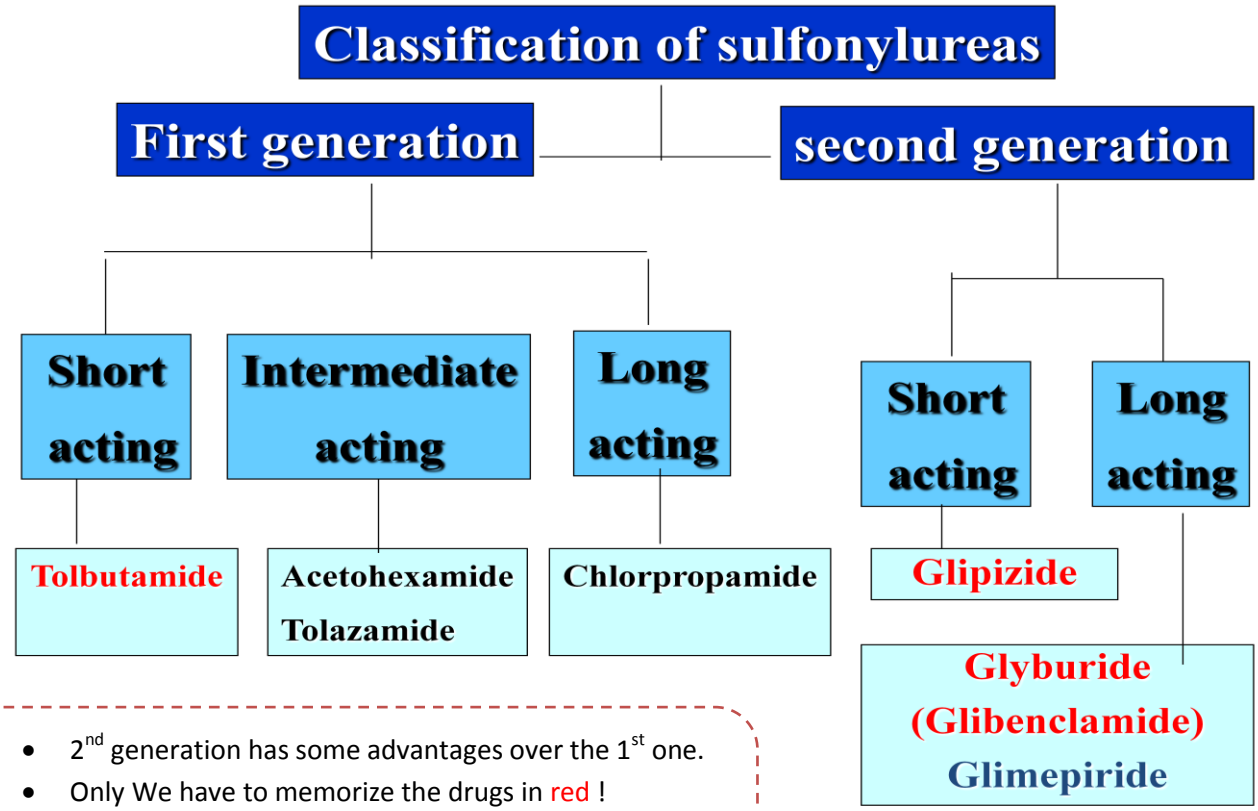
- ✓ Stimulate insulin release from functioning B cells by blocking of ATP-sensitive K channels which causes depolarization and opening of voltage- dependent calcium channels, which causes an increase in intracellular calcium in the beta cells, which stimulates insulin release.
- ✓ Reduction of serum glucagon concentration
- ✓ Increase tissue sensitivity to insulin.

Mechanisms of Insulin Release

MOA:

Hyperglycemia→uptake of glucose by the cell via GLUT2→metabolite and librates ATP→ATP block the K channel (preventing efflux)→depolarization→ opening of Ca (increase inracellular Ca "↑influx) →exocytosis → secretion of insulin





- 2nd generation has some advantages over the 1st one.
- Only We have to memorize the drugs in red !
- Glibenclamide"USA" \Glyburide"UK" : memorize the 2 names !!!

Pharmacokinetics of sulfonylureas:

- Orally, well absorbed from GIT.
- Reach peak concentration after 2-4 hr.
- All are highly bound to plasma proteins.
- Duration of action is variable(short, intermediate & long).
- Second generation has longer duration than first generation.
- Metabolized in liver
- excreted in urine (elderly and renal disease)
- Cross placenta, stimulate fetal β-cells to release insulin

→ fetal hypoglycemia at birth.

-Long acting drugs in old pts. Or having renal or hepatic diseases→ expanded duration b\c there is no or impaired excretion → hypoglycemia

-not used in diabetic pregnant women (remember we use insulin for them So All oral Hypoglycemic drug not given to pregnant women)

First generation sulfonylureas

	Tolbutamid short-acting	Acetohexamide intermediate-acting	Tolazamide intermediate-acting	Chlorpropamide long- acting
Absorption	Well	Well	Slow	Well
Metabolism	Yes	Yes	Yes	Yes
Metabolites	Inactive	Active	Active	Inactive
Half-life	4 - 5 hrs	6 – 8 hrs	7 hrs	24 – 40 hrs
Duration of action	Short (6 – 8 hrs) Used 2,3 times per day	Intermediate (12 – 20 hrs)	Intermediate (12 – 18 hrs)	Long (20 – 60 hrs) Avoided in old pts. b\c it lead to severe hypoglycemia.
Excretion	Urine	Urine	Urine	Urine

The Table is not for memorization

They will not ask about it in the exam ☺

Tolbutamide:

safe for old diabetic patients or pts with renal impairment.

Risk comparing tolbutamide to other drugs that belong to 1st generation group is lower b\c of short duration of action

Second generation sulfonylureas **Glipizide - glyburide (Glibenclamide) **

Advantages over 1st generation:

- More potent than first generation (single dose)
- Have longer duration of action.
- Less frequency of administration
- Have fewer adverse effects
- Have fewer drug interactions

	Glipizide *short-intermediate *	Glibenclamide (Glyburide)	Glimepiride
Absorption	Well	Well	Well
Metabolism	Yes	Yes	Yes
Metabolites	Inactive	Inactive	Inactive
Half-life	2 – 4 hrs	Less than 3 hrs	5 - 9 hrs
Duration of	10 – 16 hrs	12 – 24 hrs	12 – 24 hrs
action	short	long	long
Doses	Divided doses 30 min before meals	Single dose	Single dose
Excretion	Urine	Urine	Urine

The Table is not for memorization

They will not ask about it in the exam ☺

Unwanted Effects:

1. Hyperinsulinemia & Hypoglycemia imp!:

- Less in tolbutamide.
- More in old age, hepatic or renal diseases.

2. Weight gain imp! due to increase in appetite

3. GIT upset. not the main thing =)

4- Also there could be allergic reaction to Sulfa as ADRs

- ADRs more with long duration

-Insulin could cause hypoglycemia & weigh gain b\c it has anabolic effect.

CONTRAINDICATIONS:

- ✓ Hepatic impairment or renal insufficiency (risk lead to hypoglycemia)
- ✓ Pregnancy & lactation
- ✓ Type I diabetes
- ✓ Not given to ketoacidosis pts b\c KA is an emergency condition that needs rapid Rx.

B) Meglitinides * Repaglinide *:

- rapidly acting insulin secretagogues > so No need to stay long time after taking the drug to start eating☺

Mechanism of Action: As the MOA of sulfonylureas. =)

Stimulate insulin release from functioning β cells via blocking ATP-sensitive K-channels resulting in calcium influx and insulin exocytosis.

Pharmacokinetics of meglitinides

- ✓ Orally, well absorbed.
- ✓ Very fast onset of action, peak 1 h.
- ✓ short duration of action (4 h).
- ✓ Metabolized in liver and excreted in bile.
- ✓ Taken just before each meal (3 times/day) >> If patient skip one meal he has to skip the medication with it, otherwise he will have hypoglycemia.

Uses of Meglitinides

- Type II diabetes:

monotherapy or combined with metformin (*better than monotherapy*).

- Patients allergic to sulfur or sulfonylureas

metformin is an insuline sensitizer when we give it with Meglitinides that mean we work in 2 ways

نلعب عالحبلين يعني ...(=

Adverse effects of Meglitinides As ADRs of sulfonylureas. =)

- Hypoglycemia.
- Weight gain.

2nd Insulin sensitizers

Are drugs which increase the sensitivity of target organs to insulin.

Include : **A)** Biguanides **B)** Thiazolidinediones

A)Biguanides * Metformin*:

Mechanism of action of metformin

- ✓ Does not require functioning *B* cells.
- ✓ Does not stimulate insulin release.
- ✓ Increases peripheral glucose utilization (tissue glycolysis).
- ✓ Inhibits hepatic gluconeogenesis.
- ✓ Impairs glucose absorption from GIT.
- ✓ Reduces plasma glucagon level.
- ✓ Anti-Hyperlipidemia action ..Imp!! (b/c most of diabetic patients have also Hyperlipidemia)
    - ↓LDL &VLDL.
    - ↑ HDL

Pharmacokinetics of metformin

- ✓ orally.
- ✓ NOT bound to serum protein So no drug-drug interaction.
- ✓ NOT metabolized.
- ✓ t ½ 3 hours.short
- ✓ Excreted unchanged in urine

Uses of metformin

- ✓ Type II diabetes particular, in overweight and obese people (with insulin resistance).imp
- ✓ Monotherapy or in combination.
- ✓ Can be used to treat PCOS & infertility

Advantages: imp

- No risk of hyperinsulinemia or hypoglycemia or weight gain (anorexia). Because it does not stimulate insulin release

Adverse effects of metformin

- **GIT disturbances**: nausea, vomiting, diarrhea ***The most imp***
- **Lactic acidosis**: in patients with renal, liver, pulmonary or cardiac diseases.**imp**
- Long term use interferes with vitamin B_{12} absorption.
- Metallic taste in the mouth

What cause lactic acidosis ?

1- ↑glucose utilize >> glycolysis >↑ lactate production

2- no gluconeogenesis which one of the substance used in this process is lactates>> ↑ lactate in blood

this side effect is rare except in patients with renal, liver, pulmonary or cardiac diseases b/c of the accumulation of lactate > lactic acidosis

Contraindications of metformin

- Pregnancy.
- Renal disease.
- Liver disease.
- Alcoholism.

It may cause lactic acidosis

- Conditions predisposing to hypoxia as cardiopulmonary dysfunction

B)Thiazolidinediones (glitazones) **Pioglitazone (Actos)**

Mechanism of action:

✓ Acts by binding to PPAR-γ.
✓ Increase glucose uptake and utilization in muscle and adipose tissue.
✓ Increase sensitivity of target tissues to insulin.

Pharmacokinetics of pioglitazone

✓ 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 of pioglitazone

✓ Type II diabetes with insulin resistance.
✓ Used either alone or combined with sulfonylurea, biguanides or insulin.
✓ No risk of hypoglycemia when used alone b/c it does not cause insulin release .

Adverse effects of pioglitazone:

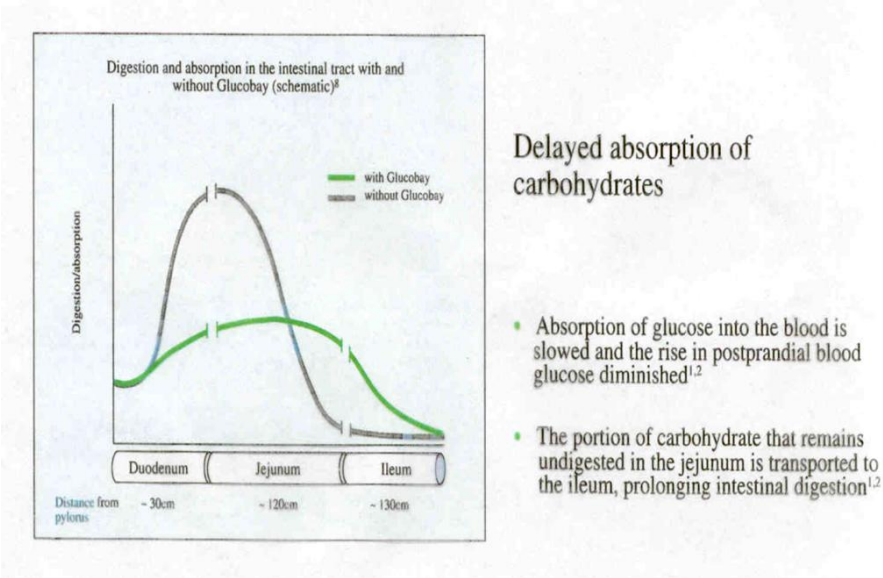
✓ Hepatotoxicity ?? (liver function tests for 1st year of therapy).
✓ Fluid retention (Edema). So it is contraindicated in patients with congestive heart failure.
✓ Precipitate congestive heart failure
✓ Mild weight gain caused by edema.

3rd Others

A)α-Glucosidase inhibitors *Acarbose*" act on GIT"

MOA:

- ✓ Reversible inhibitors of intestinal α-glucosidases in intestinal brush border that are responsible for degradation of oligosaccharides to monosaccharides (carbohydrate digestion).
- ✓ decrease carbohydrate digestion and glucose absorption in small intestine.
- ✓ Decrease postprandial hyperglycemia.
- ✓ Taken just before meals(The Meal which eaten by the patient should contain carbohydrates, if pt. skip one meal ,should skip one dose .
- ✓ No hypoglycemia if used alone (not with secretagogues drug)



Notes : α-glucosidases are enzymes involved in breaking down complex carbohydrates such as starch and glycogen break down bound in (trisaccharides), (disaccharides)and (oligosaccharide)

Kinetics:

- ✓ Given orally, poorly absorbed b/c their action mainly on GIt & should stay in it☺ So main side effect related to Git and there is no systemic effect
- ✓ Metabolized by intestinal bacteria.
- ✓ Excreted in stool and urine.

Uses :

- ✓ are effective alone in the earliest stages of impaired glucose tolerance. " in border line not diagnose by diabetics"
- ✓ Type II diabetics (combined with sulfonylurea).

Adverse effects:

- ✓ GIT: Flatulence, diarrhea, abdominal pain

B)Dipeptidyl peptidase-4 (DPP- 4) inhibitors *Sitagliptin*

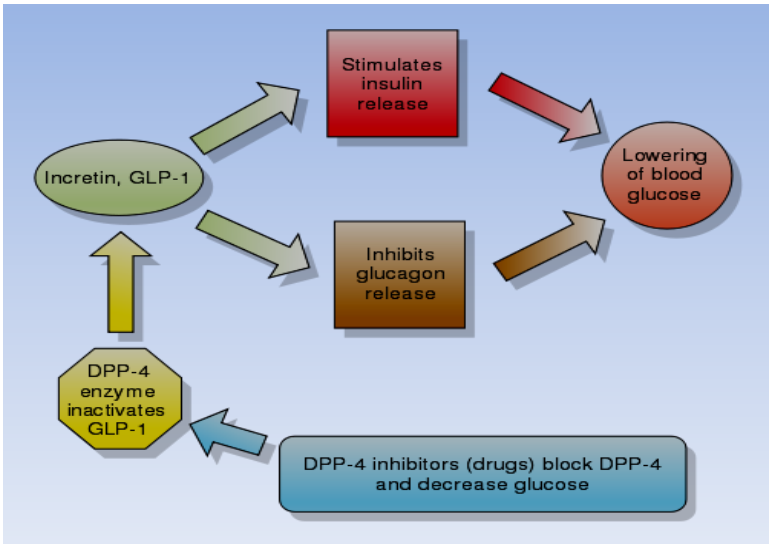
Dipeptidyl peptidase-4 : enzyme that involve in degradation of **incretins *"gastrointestinal hormones"***

Kinetics:

- ✓ Orally
- ✓ Given once daily
- ✓ half life 8-14 h
- ✓ Dose is reduced in pts with renal impairment.

Mechanism of action of sitagliptin *(DPP- 4) inhibitors*:

Inhibits DPP-4 enzyme and increases in incretins secretion (gastrointestinal hormones secreted in response to food). This results in an increase in insulin secretion & decrease in glucagon secretion.



Clinical uses:

- ✓ Type 2 DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs.

Adverse effects

- ✓ Nausea, abdominal pain, diarrhea.
- ✓ Nasopharyngitis

SUMMARY

Class	Mechanism	Site of action	Main advantages	Main side effects
Sulfonylureas Tolbutamide Glipizide Glibenclamide (glyburide)	Stimulating insulin production by inhibiting the KATP channel	Pancreatic beta cells	- Effective Inexpensive	- Hypoglycemia - Weight gain
Meglitinides repaglinide	Stimulates insulin secretion	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	Decreases insulin resistance	Fat, muscle		-Hepatoxicity -Edema
α-Glucosidase inhibitors Acarbose	Inhibits α-glucosidase	GI tract	Low risk	GI symptoms, flatulence
DPP-4 inhibitor Sitagliptin	Increase secretin	GI tract		