Summaries for endocrine pharma lectures

« لو أن الناس كلما استصعبوا أمرًا تركوه؛ ما قام للناس دنيا ولا دين! »

عمر بن عبدالعزيز

L1,2 | Summary-1

1- Thioamides

Drug	Propylthiouracil (PTU)	Methimazole & Carbimazole
MOA	- Inhibit synthesis of thyroid hormones by inhibiting the peroxidase enzyme that catalyzes the iodination of tyrosine residues. - PTU: blocks the conversion of T4 to T3 in the peripheral tissues.	
P.K	- Rapidly absorbed. - Accumulate in thyroid. - Cross the placenta.	
	- 80-90% protein binding. - Short $T_{1\2}$ - Cross the placenta. - Less secreted in breast milk → Recommended in pregnancy & breast feeding.	- Most of the drug is free. - Slower excretion (48h) - Concentrated in thyroid. - Secreted in breast milk → not recommended in pregnancy & breast feeding.
ADRs	Skin reactions, Arthralgia, Polyarthritis, GIT effects, Agranulocytosis.	
	Immunoallergic hepatitis, ANCA + vasculitis.	Abnormal sense of taste or smell.

2- IODINE (Lugol's solution, potassium iodide)

Drug	- Organic iodides as: iopanoic acid or ipodate. - Potassium iodide.
MOA	- Inhibit thyroid hormone synthesis & release. - Block the peripheral conversion of T4 to T3. - The effect is not sustained (produce a temporary remission of symptoms)
Uses	- Prior to thyroid surgery to decrease vascularity & size of the gland. - Following radio-active iodine therapy - Thyrotoxicosis
C.I	- Should not be used as a single therapy - Should not be used in pregnancy. - May produce iodism (Rare, as iodine is not much used now) - Iodism Symptoms: Skin rash, hypersalivation, oral ulcers , metallic taste, bad breath.

3- Radioactive iodine (RAI)

Drug	- ^{131}I isotope (therapeutic effect due to emission of β rays)* *Accumulates in the thyroid gland and destroys parenchymal cells, producing a long-term decrease in thyroid hormone levels
P.K	- Clinical improvement may take 2-3 months. - Cross placenta & excreted in breast milk. - Available as a solution or in capsules.
Uses	- Hyperthyroidism mainly in old patients (above 40). - Graves' disease. - Patients with toxic nodular goiter. - As a diagnostic.
Disadvantages	- High incidence of delayed hypothyroidism. - Large doses have cytotoxic actions (necrosis of the follicular cells followed by fibrosis). - May cause genetic damage. - May cause leukemia & neoplasia.

4- Adrenoceptor blocking agents

Drug	Propranolol, Atenolol, Metoprolol	C.I	Asthmatic patients → in case of Propranolol.
MOA	Adjunctive therapy to relief the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness.		

L1,2 | Summary-2

Thyrotoxicosis during pregnancy

- Better to start therapy before pregnancy with:
  - ^{131}I or subtotal thyroidectomy to avoid acute exacerbation during pregnancy.
- During pregnancy:
  - **Radioiodine** is contraindicated.

* **Propylthiouracil** is the **drug of choice during pregnancy**.

Management of hyperthyroidism due to Graves' disease

Sever	Mild-moderate
- Definitive therapy with radioiodine preferred in adults. - Normalization of thyroid function with anti-thyroid drugs before surgery in elderly patients and those with heart disease.	- Child, pregnant, or lactating women: start methimazole, 5–30 mg/day, (PTU preferred in pregnant women). - If treated then it relapsed → definitive radiodine therapy in adults

Anti-Hypothyrodism

Drug	Levothyroxine (T_4)
P.K	- A synthetic form of the thyroxine (T4), is the drug of choice for replacement therapy. - Stable and has a long half life (7 days) → given once daily. - Absorption is increased when hormone is given on empty stomach
Uses	- Hypothyroidism of almost all etiology.
ADRs	Over dose: - Child: Restlessness, insomnia, accelerated bone maturation. - Adult: arrhythmias, tremor, heat intolerance.
C.I	Old pts & pts w\ cardiac problems: treatment is started with reduced dosage.

	Liothyronine (T3)	Liotrix
P.K	- More potent & rapid action than levothyroxine. - Short $T_{1\2}$ → not recommended for routine replacement therapy.	- Combination of synthetic T4 & T3 in ration 4:1. - The major limitation to this product are high cost & lack of therapeutic rationale.
C.I	- Should be avoided in cardiac pts.	

Hypothyrodism with:

Myxedema coma	Pregnancy
- Life threatening hypothyrodism. - The treatment of choice is **loading dose of levothyroxin I.V** 300-400µg initially followed by 50µg daily. - I.V liothyronine for **rapid** response but it may provoke **cardiotoxicity**. - I.V hydrocortisone → may be used in case of adrenal & pituitary insufficiency.	○ In pregnant hypothyroid patient 20-30% increase in thyroxine is required because of: 1. Elevated maternal thyroxine binding globulin (**TBG**) induced by **estrogen**. 2. Early development of **fetal brain** which depends on **maternal thyroxine**.

L3 | Summary-1

	1- BISPHOSPHONATES Are compounds that have 2 phosphonate (PO3) groups.	2- RANKL INHIBITORS
Drug	❖ **Non- Nitrogenous:** ○ Etidronte, Clodronate , Tildronate ❖ **Nitrogenous*:** → currently used ○ Alendronate P.O, Ibandronate I.V, Risedronate P.O, Zoledronate I.V (the strongest)	Denosumab
MOA	○ Are structurally similar to pyrophosphate, ○ They preferentially "stick" to calcium ➔ concentrate in bones, bound to hydroxapatite, decreasing its solubility and making it more resistant to osteoclastic activity. ○ Inhibit osteoclast function → prevent bone resorption. 3rd generation "**Zoledronate**" the most potent osteoclast inhibitor. ○ Block steps in cholesterol synthetic pathway in osteoclast that act as signaling molecules responsible osteoclastic hydrolytic & phagocytic activity →(stop function→apoptosis)	1- binds to RANKL "expressed by osteoblast" → block RANKL from interacting with RANK "expressed on preosteoclasts" → inhibit osteoclastogenesis 2- it binds to mature osteoclast promote its apoptosis. Net effect : prevent bone resorption
P.K	○ poorly absorbed (must be given on an empty stomach / or infused IV.) ○ t1/2 1 hr. ○ half of absorbed drug accumulates in bones , remainder →excreted unchanged in urine ○ in bone it's retained for months , depending on bone turnover	-
Uses	○ osteoporosis , 2ndry to menopause , glucocorticoids ○ Paget's disease ○ Malignancy - associated hypercalcemia	-
Dose	○ Once weekly, or on two consecutive days each month. ○ Should be taken in upright position (to avoid esophagitis). ○ Separate 4 hrs before giving Ca, Mg, Al containing drugs	-
ADRs	1- GIT irritation, nausea , vomiting , gastritis , ulceration "avoided by large amount of water" 2- Gastro-esophageal reflux + ulceration "avoided if given on empty stomach while in upright position for 30 min." 3- flu like manifestation upon IV infusion. 4- osteonecrosis of the jaw "in dental implant or extraction is already planned, delay bisphosphonate therapy for a few months until healing of the jaw is complete" 5- Atrial fibrillation > women with **alendronate & zoledronate**	○ Infections : urinary & respiratory ○ Eczema & skin rash ○ Constipation ○ Cataract ○ Joint pain
C.I	○ decreased renal function. ○ peptic ulcer / esophageal reflux	in patients with hypocalcemia. (correct ca & vit D levels before starting **denosumab**)

L3 | Summary-2

3- STRONTIUM

Sr2+ : is a divalent cation, resembling Ca2+ in atomic & ionic properties.
It is orally active as distrontium

MOA	possess " dual action " resulting in a rebalance of bone turnover in favor of bone formation. ● **On Osteoblast**: it acts as agonist on Ca Sensing Receptor (CaSR) enhances differentiation of preoteoblast to osteoblast→ ↑bone formation. It stimulate the expression of OPG > increase ↑ RANKL binding > -ve of osteo-clustogenesis > ↓ bone resorption. ● On Osteoclast; Acts as agonist on Ca Sensing Receptor [CaSP] suppress differentiation of > preoteoclast to osteoclast → ↑ osteoclast apoptosis → ↓ bone resorption
P.K	○ Orally with a modest bioavailability 25% ○ Binds partially to plasma proteins and strongly to bones. ○ t ½ 60 hrs. ○ Excreted mainly by the kidney
Uses	○ Osteoporosis, 2ndry to menopause, glucocorticoid. ○ Malignancy, associated hypercalcaemia
interaction	Food specially containing milk + its products - **Antacids** - Oral **tetracycline & quinolones** chelate it "2 hour space for precaution"
ADRs	GIT irritation; nausea, vomiting, headache, eczema "resolve in 1st 3 months''
C.I	In severe renal disease - In hypersensitivity to it - In increased risk of venous thromboembolism - In phenylketonuria

Raloxifene

1st selective estrogen Receptor modulator (SERM) for prevention and treatment of osteoporosis

Mechanism

Antiestrogens that exhibits partial agonistic action; acting as an agonist in bone & an antagonist in some female sex organs

Advantages

- Increase bone density (2%) & fracture risk (30%)
- No stimulation of breast or endometrial tissue
- No need for progestin in women with uterus
- Decrease LDL
- Good for women with risk of uterine and breast cancer.
- Lower risk of thromboembolism compared to estrogen

Disadvantages

May increase hot flushes - No effect on HDL

Estrogen and androgen

essential for normal bone remodeling
Estrogen in females - Androgen in males

Mechanism

- Increase osteoclast apoptosis & inhibit osteobalst apoptosis.
- Decrease No. & depth of resorption cavities.
- Increase release of growth factors from osteoblasts.
- Decrease release of inflammatory cytokines causing resorption

ADRs

- For HRT (estrogen):

vaginal bleeding,
risk of breast cancer
venous thromboembolism.

L4 | Summary

Drug	Parathyroid hormone PTH		
characteristic	○ Relaced by parathyroid gland Low plasma Ca^{++} Section is inversely related to Ca^{++}		
Effect	○ Intermittent ↑ osteoblast number & function →↑ bone formation →↑ bone mass & strength Continuous: ↑osteoclast →bone resorption→↑ serum Ca^{++}		
Uses	○ Treatment of sever osteoporosis Resistant cases failed to respond to other medications		
Drug	**Teriparatide**	**Vitamin D**	**Calcitonin**
characteristic	-PTH analogue. -Anti-osteoporosis drugs. -Give once daily by subcutaneous injection.	-Vitamin D is a steroid hormone that is intimately involved in the regulation of plasma Ca^{++} levels. -In biological activities VitD2=VitD3.	-Synthesized by Para follicular cells of thyroid gland. - ↓in plasma Ca^{++}. -Routes of administration: S.C, Nasal spray or solution -It has lower efficacy compared to other drugs
Effects	-Once daily: Stimulation of osteoblast over osteoclast activity → New bone formation. -Continues bone resorption stimulated more then bone formation → Detrimental to the skeleton.	-↑Bone resorption -↑Ca^{++} absorption from intestine, ↑renal Ca^{++} reabsorption &↓ production of PTH. -All lead to ↑ plasma Ca^{++} concentration.	- Inhibiting osteoclast activity → inhibiting bone resorption - ↓ reabsorption of Ca^{++} & PO_4 by kidney →↑ excretion
Indications	-Postmenopausal osteoporosis. -Patients how have risk to get fracture. -Patients not responding to other drugs.	-Rickets. -Osteomalacia. -Osteoporosis. -Psoriasis. -Cancer prevention for prostate & colorectal.	-Hypercalcemia in case of short term treatment of hypercalcemia of malignancy, Paget's disease -Osteoprosis as alternative to other drugs
ADRs	-Carcinogenic effect (osteosarcoma). -Diarrhea, heart burn, nausea. -Headache, leg cramps, orthostatic hypotension. -↑ serum Ca ++ which may → kidney stones.	-	Nausea, nasal irritation Local inflammation at sit flushing of face & hand
C.I	-People how have risk for osteosarcoma like: Paget's disease & radiation treatment involving bone. - Not recommended for children	-	-

L5 | Summary ☺

corticosteroid Agonist

groups	Glucocorticoids	Mineralocorticoids
Mech. of action	1. Corticosteroid is present in the blood bound to the corticosteroid binding globulin(CBG) and enters the cell as the free molecule. 2. The intracellular receptor is bound to the stabilizing proteins, including heat shock protein 90(Hsp90) and several others(X). When the complex binds a molecule of steroid, the Hsp90 and associated molecules are released.(When the drug is 3. bound with the receptor the stable protein is detached from the receptor) 4. The Steroid – receptor complex enters the nucleus as a dimer, binds to the glucocorticoid response element(GRE) on the gene, and regulates gene transcription by **RNA polymerase2** and associated transcription factors. 5. The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response	
P.D	• Metabolic effects • Catabolic effects • Immunosuppressive effects • Anti – inflammatory effects	-

Drugs	Cortisol	Aldosterone	Fludrocortisone
Characteristic	○ The major natural glucocorticoid is cortisol(hydrocortisone). ○ The physiologic secretion of cortisol is regulated by adrenocorticotropic (ACTH) and varies during the day(circadian rhythm). ○ The peak occurs in the morning and the trough occurs about midnight (The drugs will be more beneficial if we use in the morning)	The Major natural mineralocorticoid in human. • Regulation: by ACTH and by the renin-angiotensin system and is very important in the regulation of blood volume and blood pressure. Aldosterone has short half life. little glucocorticoid activity.	Is a mineralocorticoid favored for replacement therapy after adrenalectomy and in other conditions in which mineralocorticoid therapy is needed **long duration of action** significant glucocorticoid activity
P.K & P.D	❖ **P.K & P.D for cortisols:** ○ Given **orally** ,cortisol is well absorbed from GIT ○ Cortisol in the plasma is 95% bound to CBG ○ It is metabolized by the liver and has **short duration of action** compared with the synthetic congeners. ○ It diffuses poorly across normal skin and mucous membranes ○ The cortisol molecule also has a small but significant salt – retaining (mineralocorticoid) effect. This is an important cause of hypertension in patients with cortisol secreting adrenal tumor or a pituitary ACTH secreting tumor (cushing's syndrome).		

Synthetic Glucocorticoids

Prednisone and its active metabolite: (prednisolone, dexamethasone, triamcinolone).	Beclomethasone and Budsonide
○ Longer half life ○ Longer duration of action ○ Reduce salt retaining effect ○ Better penetration of lipid barriers for ○ Topical activity.	○ Have been developed for use in **Asthma** and other condition in which good surface activity on mucous membrane or skin is needed and systemic effects are to be avoided ○ These drugs rapidly penetrate the airway mucosa. ○ **Very short half lives** after they enter the blood, so that systemic effects and toxicity are greatly reduced.

Corticosteroid Antagonists

	Receptor Antagonists		Synthetic inhibitors	
Drugs	Spironolactone eplerenone	Mifepristone	ketoconazole	
Mech. of action	Antagonize aldosterone at its receptor. Spironolactone is a K^+-sparing diuretic.	competitive inhibitor of: • glucocorticoid receptors • progesterone receptors	**It inhibits the cytochrome p450** enzymes necessary for the synthesis of <u>all steroids</u>	
USES	So use it in conditions when we want less Aldosterone e.g.: hypertension, edema functioning adrenal adenoma involving zona glomerulosa.	useful in the treatment of Cushing's syndrome	• **Adrenal cancer**, when surgical therapy is impractical or unsuccessful because of metastasis.	
			Adrenocortical cancer (steroid producing tumor) in conjunction with other drugs.	Used in a no. of conditions in which reduced steroid level are desirable: Adrenal carcinoma, Hirsutism, Breast cancer, Prostate cancer.

L6 | Summary-1

Insulin

Sources	• **Beef Insulin** :Differs from human insulin by 3 amino acids (antigenic). • **Porcine** Insulin:Differs by one amino acid (antigenic) • **Human Insulin analogues :**Prepared by recombinant DNA techniques. **Less immunogenic**. Modifications of amino acid sequence of human insulin can change pharmacokinetics.
Routs of administration of exogenous insulin	Can not be given orally (why ?) Insulin syringes (s.c., arms, abdomen, thighs). Portable pin injector (pre-filled). Continuous S.C. infusion (insulin pump).More convenient ,Eliminate multiple daily injection ,Programmed to deliver basal rate of insulin. I.V (in a hyperglycemic emergency)
Insulin degradation	Basal level of endogenous insulin is 5-15 µU/ml. Half life of circulating insulin is 3-5 min. 60% liver & 40% kidney (**endogenous insulin**) 60% kidney & 40% liver (**exogenous insulin**)

Types of insulin preparations

Differs in pharmacokinetic properties mainly : 1) Rate of absorption (Onset of action).
2) Duration of action.
Variation is due to: 1) Change of amino acid sequence. 2) Size and composition of insulin crystals in preparations.

Preparation	A- Ultra-Short acting insulin Lispro, aspart, glulisine	B- Short-acting (regular) insulins e.g. Humulin R, Novolin R
Physical characteristics	Clear solution at neutral pH	Clear solution at neutral pH
Chemistry	Monomeric analogue	Hexameric analogue
Route & time of administration	S.C. 5 min (no more than 15 min) before meal I.V. in emergency (e.g. diabetic ketoacidosis)	S.C. 30 – 45 min before meal I.V. in emergency (e.g. diabetic ketoacidosis)
Onset of action	**Fast 5 – 15 min (S.C)**	**rapid 30 – 45 min (S.C)**
Peak level	30 – 90 min	2 – 4 hr
Duration	**3 – 5 hr Shorter**	**6 – 8 hr longer**
Usual administration	2 – 3 times/daypostprandial hyperglycemia & emergency diabetic ketoacidosis	2 – 3 times / day postprandial hyperglycemia & emergency diabetic ketoacidosis
	Advantages of Insulin Lispro vs Regular Insulin : Rapid onset of action (due to rapid absorption) Reduced risk of postprandial hypoglycemia and hyperinsulinemia (due to shorter duration of action, no more than 3-4 hrs regardless of dose).	

L6 | Summary-2

Types of insulin preparations cont.

Preparation	C- Intermediate acting insulins		D- Long acting insulins Insulin glargine (lantus), Insulin detemir (Levemir)
	Isophane (NPH) insulin	Lente insulin (Humulin L, Novolin L)	
Physical characteristics	**Turbid** suspension at neutral pH	**Turbid** suspension at neutral pH	Insulin glargine (lantus) : **Clear** solution BUT forms precipitate (hexamer) at injection site. absorbed less rapidly than NPH & Lente insulin.
chemistry	Insulin mixtures NPH/regular insulin 75/25 , 70/30 , 50/50 (NPL= NPH / lispro) (NPA= NPH / aspart) NPL & NPA have the same duration as NPH Have two peaks	Mixture of: 30% semilente insulin (amorphous precipitate of zinc insulin in acetate buffer) 70% ultralente insulin (poorly soluble crystal of zinc insulin)	-
ROA	Given S.C. only **not intravenously**	Given S.C., **not intravenously**	Given s.c., **not intravenously** Once daily
Onset of action	**1-2 h.**	**(1-3 h) Delayed**	**Slow onset of action 2 h.**
Peak level		Peak serum level 4-8 h	after 4-5 h
Duration	13-18 h.	13-20 h	Prolonged duration of action (24 h)
Usual administration	Can not be used in ketoacidosis or emergency	not used in diabetic ketoacidosis or emergency.	- Produce broad plasma concentration plateau l(**low continuous insulin leve**). **Glargine** must be used in regimens with **rapid** or **short** acting insulins **- Should not** be mixed with other insulins in **the same syringe**
	Lente and NPH insulins are equivalent in activity		
	Advantages over intermediate-acting insulins: ▪ Constant circulating insulin over 24 hr with no peak (**peakless profile**). ▪ Produce flat prolonged hypoglycemic effect. ▪ Safer than NPH & Lente insulins ▪ (reduced risk of **nocturnal hypoglycemia**).		

Insulin Dosing considerations:

- Blood glucose monitoring is required in all patients receiving insulin
- Rotate injection sites within the same region.
- Insulin should be stored in refrigerator and warm up to room temp before use.

Complications of Insulin Therapy:

Hypoglycemia, Hypersensitivity reactions, Lipodystrophy at injection site, Weight gain (due to anabolic effects of insulin), Insulin resistance, Hypokalemia.

To sum up: Insulin analogues are used to treat **type I diabetes**.
Fast acting insulins (**lispro, aspart**), given s.c. or i,.v., produce fast action, used to mimic postprandial insulin.
Short acting insulin (**Regular insulin**), given s.c. or i.v. produce rapid action, used to mimic postprandial insulin.
Intermediate acting insulin (**lente, Isophane**) produce slower action, than regular insulin, given s.c. not i.v.
Long acting insulins (**glargine, detemir**) produce constant circulating insulin over 24 hr with no peak (peakless profile), s.c. not i.v.

L7 | Summary

Treatment of diabetic ketoacidosis

First correction of dehydration	○ Fluid therapy :Infusion of isotonic saline (0.9% sodium chloride) to Restore blood volume and perfusion of tissues.
2ed correction of hyperglycaemia	○ Regular insulin (short acting) :should be administered by means of continuous intravenous infusion in small doses through an infusion pump it stops lipolysis and promotes degradation of ketone bodies .
3ed correction of Electrolyte deficits	○ Potassium therapy : potassium is added to infusion fluid to correct the serum potassium concentration.
4th correction of Ketoacidosis	○ Bicarbonate therapy : for metabolic acidosis should be used only if the arterial pH < 7.0 after 1 hour of hydration. ○ (should be administered every 2 hours until the pH is at least 7.0)

Treatment of Hypoglycaemia

Conscious patient	Unconscious patient
○ **Sugar containing beverage or food (30 g orally)**	○ **Glucagon (1 mg S.C. or I.M)** ○ **20-50 ml of 50% glucose solution I.V. infusion(risk of possible phlebitis)**

L8,9 | Summary-1

A- Insulin Secretagogues
(increase the amount of insulin secreted by the pancreas)

Class

1- Sulfonylureas

MOA

- 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.
- ↑ Hyperglycemia → Blockade of ATP dependent K+ channels → Opening of voltage-dependent Ca++channels → ↑ intracellular calcium in the beta cells → ↑ Insulin release.

P.K.

- 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.
- Metabolized in liver
- Excreted in urine (elderly and renal disease)
- Cross placenta, stimulate fetal β-cells to release insulin → fetal hypoglycemia at birth.

First generation			Second generation	
Tolbutamide (shrt acting)	**Acetohexamide** **Tolazamide** (intermediate acting)	**Chlorpropamide** (long acting)	**Glipizide** (short acting)	**glibenclamide** (**Glyburide**) **Glimepiride** (long acting)

- 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**

ADRs

- **Hyperinsulinemia** & **Hypoglycemia**:
  - More common in long acting sulfonylureas. particularly chlorpropamide, glyburide, and glimepiride)
  - More in **old age, hepatic or renal diseases.**
  - Less in tolbutamide.
- Weight gain due to increase in appetite unless the diabetic diet and exercise program are followed.

Drug

2- Meglitinides Repaglinide, Nateglinide

MOA

- Repaglinide are rapidly acting insulin secretagogues
- Insulin secretagogue.
- Mechanism of action is identical to sulfonylureas.

P.K

- **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) the dose should be skipped if the meal is missed.

Indications

- Type II diabetes (monotherapy or in combination with other oral hypoglycemic drugs)
- As alternative to sulfonylureas in **patients allergic to sulfur**.

ADRs

- **Less incidence than sulfonylureas**
- Hypoglycemia.
- Weight gain.

L8,9 | Summary-2

B- Insulin sensitizers

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

Drug	Biguanides e.g: **Metformin**	Thiazolidinediones (glitazones) e.g: **Pioglitazone**
MOA	- Increases glucose utilization by peripheral tissues (tissue glycolysis) - Reduces insulin resistance. - Inhibits hepatic gluconeogenesis. - Reduce LDL and VLDL & Increase HDL.	- Activate peroxisome proliferator-activated receptor - (PPAR-γ). - Increase glucose uptake and utilization in muscle and adipose tissue. - Increase sensitivity of target tissues to insulin.
P.K	- orally. - NOT bound to serum protein. - NOT metabolized. - t ½ 3 hours. - Excreted unchanged in urine	- 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
Indications	- In patients with type 2 diabetes who are obese because it promotes modest weight reduction (first-line therapy). - Type II diabetes as monotherapy or in combination.	- Type II diabetes with insulin resistance. - Used either alone or combined with sulfonylurea, biguanides or insulin. - No risk of hypoglycemia when used alone
ADRs	- No risk of hypoglycemia - **No weight gain** - has prominent lipid-lowering activity - Lactic acidosis - GIT disturbances: **Metallic taste** in the mouth, nausea, vomiting, diarrhea - **Interference with vitamin B12 absorption** (long term use).	- Hepatotoxicity (liver function tests for 1st year of therapy). - Fluid retention (Edema). - Congestive heart failure - Mild weight gain. - Failure of estrogen-containing oral contraceptives
C.I	- Renal disease. - Liver disease. - Alcoholism. - Cardiopulmonary dysfunction. - Pregnancy.	

C- Others

Glucosidase inhibitors

drug	Acarbose	Miglitol
MOA	- Reversible **inhibitors of intestinal-glucosidases** in intestinal brush border that are responsible for carbohydrate digestion. - Decrease carbohydrate digestion and glucose absorption in small intestine (lower postprandial glucose level).	
P.K	**Acarbose**: - Given orally, **poorly absorbed**. - Metabolized by intestinal bacteria. - Excreted in stool and urine.	
ADRs (Both)	- **GIT side effects:** Flatulence, diarrhea, abdominal pain, bloating.	
Uses	- Effective alone in the **earliest stages** of impaired glucose tolerance - **Not** recommended alone as therapy for **moderate to severe hyperglycemia** - Most useful in combination with other oral hypoglycemic drugs or with insulin.	
C.I	- irritable bowel syndrome - Inflammatory bowel disorders - Intestinal obstruction.	

L8,9 | Summary -3

Incretins mimetics

- 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.
- Increase insulin secretion & decrease in glucagon secretion (regulate blood glucose).

Drug	GLP-1 agonists Dulaglutide
P.K	- Is glucagon-like peptide-1 (GLP-1) agonist. - **Given S.C**. once a week.
Uses	- patients with type 2 diabetes who are **not** controlled with oral medication
ADRs	- **Nausea & vomiting** (most common). - Abdominal pain, decreased appetite & fatigue.

Dipeptidyl peptidase-4 inhibitor (DPP- 4 inhibitors)

Drug	Sitagliptin, Vildagliptin
MOA	- Inhibit DPP-4 enzyme thus increase incretin hormone (GLP-1).
P.K	- Orally - Given once daily
Uses	- Type II DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs.
ADRs	- Nausea, abdominal pain, diarrhea - **Nasopharngitis**

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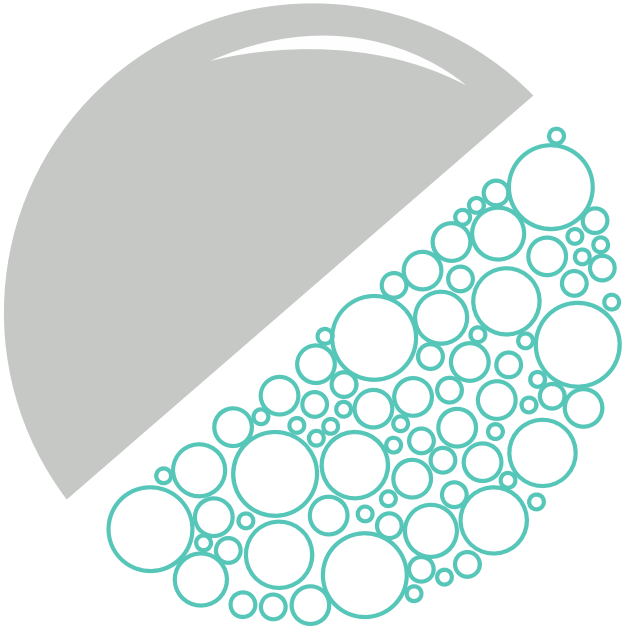

Pharmacology 435

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