MED 443
King Saud University

PHARMACOLOGY TEAM 443

List of drugs

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EDITING FILE

L1: Growth hormone & Drugs used in pituitary Adenoma

GH Deficiency: *GH Agonists*

Drug	Sermorelin	Somatropin	Somatrem	Mecasermin
Overview	**Synthetic** growth hormone releasing hormone **(GHRH)**	**Recombinant** (Genetically engineered) **human GH.** **Somatropin:** A 191-amino acid peptide, **identical** to the native form of hGH.		**Recombinant IGF-1,** administered S.C.
Uses	Used if a patient possesses **defective hypothalamic release of GHRH** BUT **normally** functioning anterior pituitary somatotrophs.	• Documented Growth failure in pediatric patients associated with **GH deficiency** and **Turner syndrome** (to increase height in girls by 10-15 cm). • Idiopathic short stature. • Wasting of muscles in patients with AIDS. • Short bowel syndrome in patients who are also receiving specialized nutritional support.		Used for children with **severe IGF1 deficiency** due to mutations in the GH receptor (**Laron dwarfism)** or development of neutralizing antibodies against GH.
ADRs	-	• **Leukemia** • Rapid growth of melanocytic lesions • Hypothyroidism • Insulin resistance, • Arthralgia. • ↑ in cytochrome P450 activity.		The common ADR is **Hypoglycemia** (Insulin like action)**:** **avoided** by consumption of meal **20 min** before or after the administration of drug.

GH overproduction: *GH Antagonists*

Drug	Octreotide	Lanreotide	Pegvisomant
Overview	**Somatostatin analogues**		**GH receptor antagonist**
MOA	**Octreotide:** • **Inhibit GH secretion.** • Partially inhibits GH-induced IGF-1 generation. • Reduce GHRH release.		**Pegvisomant:** A long-acting derivative of a mutant GH that is able to cross-link GH receptors but is incapable of inducing the conformational changes required for receptor activation.
P.K.	• Synthetic long-lasting peptide • 45 times **more potent** • Suppress GH levels for 6–12 h. • Given every 4 weeks., S.C / I.M	Given I.M	• Given S.C. • Check IGF-1 level every 4-6 weeks. • Monitoring GH **not** useful. Because it doesn't affect GH secretion from pituitary • Dose 10-40 mg/d
use	**Treatment of acromegaly**		
ADRs	• Significant GI disturbances. • **Cardiac conduction abnormalities**	• **Gallstones.**	-

Drug	Dopamine agonists
Overview	• (only high doses) can be used as primary and adjuvant treatment but their response rate is low. (Not used unless other drugs are contraindicated)

Note: Best in lowering GH? IM Octreotide. Best in lowering IGF? Pegvisomant. Cabergoline is more effective than bromocriptine

L1: Growth hormone & Drugs used in pituitary Adenoma

Prolactinomas: D2 receptor Agonists

Drug	**Bromocriptine** 2-bromo-α- ergocryptine mesylate	**Cabergoline**	**Pergolide Mesylate**
Source	**Ergot derivatives** (#CNS: vasoconstrictors used for treatment of migraine)		Long-acting **ergot derivatives**
use	**In case of ★ Prolactinoma (pituitary adenoma with excess release of prolactin) the initial therapy is generally dopamine agonists.**		
M.O.A.	Selective activation of D2 receptors located on lactotroph cell surface (PRL-producing cells) → decrease adenylate cyclase activity → decreasing in cAMP level → **inhibition of prolactin (PRL) synthesis & release.**		
P.K.	• The absorption rate from the GI tract is 25-30%. • Given orally. • Very high **first-pass effect**, • Excreted via the **biliary route** into the feces. • **start low dose** at 2.5 mg day at night before increasing to 2.5 – 10 mg per day in divided doses. • Take with food to reduce side effects.	• **more expensive**. • given once or twice a week with a starting dose of 0.25 mg 2 x week.	-
	Titrate (Adjust the dose) based on prolactin levels & tolerability		
Actions	• More effective in inhibiting prolactin release than inhibiting GH release • Inhibiting prolactin secretion **without the uterotonic, vasospastic** properties of other ergots. • **Safe in pregnancy.**	• **more effective** than bromocriptine for **tumor shrinkage** • **Well tolerated (less side effects at regular doses) but not safe in pregnancy.**	• dopaminergic properties • strong **vasospasm and uterotonic**
ADRs	-		# during pregnancy
	GI intolerance, postural hypotension, constipation, nasal stuffiness, dizziness - avoided by beginning with low dose therapy		

L2&3: Drugs used in hyperthyroidism & hypothyroidism

Hyperthyroidism treatment

1. Thioamides (Antithyroid Drugs)

Drugs	**Propylthiouracil (PTU)** administered every 6 - 8 hrs.	**Methimazole / Carbimazole** administered every 8 hrs *Carbimazole: Prodrug* → converted to methimazole (active metabolite)
M.O.A.	• Inhibit thyroid hormones synthesis by **inhibiting peroxidase** enzyme that catalyzes the **iodination of tyrosine** residues. • **Propylthiouracil (but not Methimazole) Blocks the conversion of T_4 to T_3** in peripheral tissues.	
P.K. PB: protein binding	• Rapid absorption, accumulates in thyroid, crosses placenta	
	• **t1/2:** 1.5 hrs (short). | **PB :** 80 - 90%. • **Excretion:** kidney within 24 hrs.	• **t1/2:** 6 hrs (long) | **PB :** mostly free. • **Excretion:** slow in urine in 48 hrs.
Pregnancy & Breast feeding	• **Pregnancy [Drug of choice]:** highly **protein bound**→ crossing placenta is less readily. • **Breast feeding**: less secreted in breast milk→ recommended.	• **Pregnancy:** not recommended. • **Breast feeding:** secreted → not recommended.
ADRs	• **Skin reactions:** urticarial or macular reactions • **Arthralgia** • **Agranulocytosis:** Graves' disease patients | within 90 days of treatment.	• **GIT:** gastric distress + nausea • Polyarthritis (antithyroid **arthritis**)
	• Immunoallergic **hepatitis:** PTU • ANCA-positive vasculitis (Rare)	**Only Methimazole:** • **Abnormal sense of taste or smell** (Rare)

2. Iodides: (Lugol's Solution | Potassium Iodide)

Drugs	**Organic Iodides** (Iopanoic acid, Ipodate)	**Potassium Iodide**
M.O.A.	• **Inhibit thyroid hormone synthesis and release**. • Block the peripheral conversion of **T_4 to T_3**. "like PTU" • The effect is **not sustained** (***temporary*** *remission of symptoms*). • **Decreases the blood flow** to the thyroid (↓ Vascularity)	
Uses	• **Prior to thyroid surgery:** ↓ **vascularity** & **size** of gland.	• Thyrotoxicosis
Precautions	• Not used as a **single therapy** + **pregnancy** • **Iodism** [***skin rash - hypersalivation - oral ulcers - metallic taste - bad breath***]: iodine is not much used now → rare.	

3-Radioactive Iodine (RAI)

Drug	**Radioactive Iodine** (**Clinical improvement:** 2 - 3 months, t1/2=5d)	
M.O.A.	• **^{131}I isotope:** therapeutic effect due to emission of β rays. • **Accumulates** in the thyroid → **destroys parenchymal cells** →long-term ↓ in thyroid hormone levels.	
Uses	• Hyperthyroidism mainly in **old patients** (above 40). • Patients with **toxic nodular goiter**.	• **Graves'** disease. • **Diagnostic**.
#	• **Pregnancy:** crosses placenta.	
Disadvantages	• **Delayed hypothyroidism** (high incidence). • **Cytotoxic** actions: necrosis of follicular cells → fibrosis (large doses).	• **Genetic** damage. • Leukemia & **neoplasia**.

L2&3: Drugs used in hyperthyroidism & hypothyroidism

4- Adrenoceptor Blocking Agents (Beta Blockers)

Drug	Propranolol	Atenolol	Metoprolol
M.O.A.	• Beta Blockers.		
Uses	• **Adjunctive** *symptomatic* **therapy** to **relief adrenergic symptoms** of hyperthyroidism [**tremor** - **palpitation** - heat intolerance - **nervousness** - tachycardia].		
#	• **Asthmatic patients.**	"Atenolol & Metoprolol **can** be used in asthmatics"	

Hyperthyroidism: Treatment in Pregnancy

Overview	- Better to start therapy **before pregnancy** with ^{131}**I** or subtotal **thyroidectomy** to avoid acute exacerbation during pregnancy **- Drug of Choice: Propylthiouracil (PTU)** **- Contraindication: radioiodine (RAI)** Pregnancy→ PTU

Hypothyroidism Treatment

Levothyroxine (T_4) L-thyroxine/eltroxin

M.O.A.	★ Synthetic form of **thyroxine** (T_4).
P.K.	• Stable, **Half-life:** 7 days (long) • **Administration:** once daily. Oral **(0.025 - 0.3 mg tablets)** | Parenteral **(200 - 500 µg)**. • **Dose: 12.5 – 25 µg/day** for two weeks and then increased every two weeks. • **Absorption:** increased when hormone is given on empty stomach. • **Restore normal levels:** within **2-3 weeks**.
Uses	• **[Drug of choice] for replacement therapy**. Especially in CVD patients instead of Liothyronine • Hypothyroidism regardless of etiology: Congenital - Hashimoto thyroiditis - **Pregnancy**.
ADRs *Overdose* *"symptoms of Hyper"*	**Children:** • Restlessness • Insomnia • Accelerated bone maturation **Adults:** • Cardiac arrhythmias (atrial fibrillation) • Tremor / Restlessness • Headache • Tachycardia • Change in appetite • Heat intolerance • **Weight loss** • Muscle pain
Precautions	• Start with reduced dosage in old patients & patients with cardiac problems.

Liothyronine (T_3)

P.K.	• More **potent** (3-4 times). • **Rapid onset of action** compared to levothyroxine. • **Half-life: short** → not recommended for routine replacement therapy (require multiple daily dose) • **Administration: multiple daily doses. Oral (5 - 50µg tablets)** | Parenteral **(10 µg/ml).**
#	• **Cardiac patients** "any misdosing may cause serious problems (CVS symptoms of hyperthyroidism)"

Liotrix

M.O.A.	• Combination of **synthetic T_4 & T_3** in a ratio 4:1 that attempt to mimic the natural hormonal secretion.
limitations	• **High cost,** Lack of therapeutic rationale because 35% of T_4 is peripherally converted to T_3.

Drug	Levothyroxine (T_4)	Liothyronine (T_3)
Comparison	↓ potent than liothyronine, ↑ T1/2 → ↓ daily doses + ↑ protein binding	↑ potent than levothyroxine, ↓ T1/2 → ↑ daily doses + ↓protein binding

L4&5: Treatment of osteoporosis

Important

1A. Antiresorptive: Bisphosphonates

	Nitrogenous (Less potent)	Non-Nitrogenous (Stronger)
Drugs	• Alendronate (oral) • Ibandronate (oral) • Risedronate (oral) • Zoledronate (I.V.)	• Etidronate • Clodronate • Tiludronate
M.O.A	• Structurally **similar to pyrophosphate** and work by: 1. Preferentially "stick" to calcium → concentrate in bones, bound to hydroxyapatite, decreasing its solubility and making it more resistant to osteoclastic activity. 2. Prevent bone resorption by Inhibiting osteoclast function.	
P.K.	• **Zoledronate** (3rd generation) : has the **highest potency** for osteoclast inhibition **used for Emergencies -given IV-** • Poorly absorbed (<10%), **food impair absorption** more → must be given on an empty stomach / infused IV • T1/2 = 1 hr • 1/2 of absorbed drug **accumulates** in bones, remainder is excreted unchanged in urine • **In bones it is retained for months, depending on bone turnover.**	
Uses	• **Osteoporosis**; secondary to **menopause or glucocorticoids**..etc • Paget's Disease: • **Malignancy-associated hypercalcemia**	**C.I** • Decreased renal function • Peptic Ulcer • Esophageal reflux • Alendronate & Zoledronate in CVD Patients
Doses	• Once weekly or on two consecutive days each month • **Should be taken in upright position** with large amount of water **to prevent esophagitis** • Should be given 4 hrs before having any Ca, Mg, Al containing drugs. (chelating agent) **Note: Calcium and Vit D supplementation, should be given after a gap from ingestion of bisphosphonates because**	
ADRs	• **GIT irritation**; nausea, vomiting, gastritis , **ulceration** → to avoid give large amount of water • Gastroesophageal reflux ± ulcerations → to avoid give on empty stomach • Flu like manifestations (fever, chills) upon IV infusion • **Osteonecrosis** of the mandible bone of jaw upon long use with IV infusion preparation usually after dental surgical procedures. • If a **dental implant** or extraction is already planned, delay bisphosphonate therapy for a few months **until healing** of the jaw is complete • **Atrial fibrillation → women with alendronate & zoledronate**	

Important

1B. Antiresorptive: RANKL inhibitors

Denosumab

It is a fully humanized MOA that **mimics the activity of osteoprotegerin (OPG)**

M.O.A.	- Binds with high affinity to RANKL, mimicking the effect of OPG → **Blocks RANKL from interacting with RANK receptor** expressed on preosteoclast → ↓ osteoclastogenesis → no mature osteoclasts - Binds also to mature osteoclasts → increase their apoptosis **Net effect → decreasing bone resorption**
P.K.	Administered subcutaneously every 6 months
Uses	Extremely expensive and reserved **for patients who cannot tolerate or respond to bisphosphonate**
ADRs	• Infections: urinary & respiratory • Eczema & skin rash • Pancreatitis

Female slide

1C. Dual effect: Antiresorptive + Bone Anabolic Agents

Strontium

M.O.A.	• resembling Ca^2 - ↑bone formation - ↓ bone resorption
C.I	• **Phenylketonuria** • Increased risk of venous thromboembolism Don't give it to immobile Patients.
Interactions	• Precaution: 2 hrs spacing ○ Food specially containing milk ± its products

L4&5: Treatment of osteoporosis

2A. Hormonal Therapy: Sex Hormones

Drugs	MOA	Uses	ADRs
Estrogen	• Estrogen in females and Androgens in males are essential for normal bone remodeling: ○ ↑ osteoclast apoptosis and Inhibit osteoblast apoptosis (protective effect on the bones) ○ ↑ release of growth factors from osteoblasts ○ ↓ number and depth of resorption cavities ○ ↓ release of inflammatory cytokines causing resorption	• **Hysterectomy (Removal of uterus)** : use estrogen only • If **uterus is present**: Estrogen + **Progestin** to protect the uterus • Hormonal Replacement therapy **(HRT)**: menopausal symptoms • **SERMs**: Menopause/Elderly	HRT (estrogen): - Vaginal bleeding - Risk for breast cancer - Venous thromboembolism
Androgen		Elderly men	

Important

2B. Hormonal Therapy: Selective Estrogen Receptor Modulators (SERMs)

Drug	MOA	Uses	Advantages	ADRs
Raloxifene	• Anti-Estrogens that exhibits partial agonistic action • Agonist in bones and Antagonist in some female sex organs	1st SERM for prevention and treatment of osteoporosis **(especially postmenopausal)**	• ↑ bone density by (2%) and ↓ fracture risk by (30%) • No need for **progestin** in women with a uterus. • **No stimulation of breasts nor endometrial tissue.** • **Good for women with a risk of breast and uterine cancer.** • Lower risk for thromboembolism compared to estrogen. • ↓ LDL	-May ↑ hot flushes -No effect on HDL

Parathyroid Hormone

MOA	Uses	ADRs
• Bone: Mobilization of Ca^{2+} and PO_4^{3-} from bone. In response to hypocalcemia, • Kidney: ↑ Ca^{2+} reabsorption ↓*excretion* & ↑ formation of calcitriol *which is the active form of vitamin D* • GIT: ↑ absorption of Ca^{2+}	• Treatment of severe osteoporosis. • Resistant cases failed to response to other medications ★★The effect depends on the way of administration/Exposure: • Daily, Intermittent administration of PTH, for 1 to 2 hours/day leads to a net stimulation of bone formation. Mechanism: ↑ Osteoblast function/number→ Bone formation→ Bone mass/strength • Continuous exposure to elevated PTH leads to bone resorption and risk of fracture. Mechanism: ↑ Osteoclast → ↑ Bone resorption → ↑ Serum Ca^{2+}	-

PTH analog

Drug	MOA	Uses	ADRs	C.I
Teriparatide	Depend upon the pattern of systemic exposure: **- Once daily administration → stimulation of osteoblastic activity** over osteoclastic activity. - By contrast, **Continuous administration** → bone resorption may be stimulated more than bone formation.	• Should not be used routinely due to **carcinogenic effects** • Use in **severe osteoporosis** or patients **not responding** to other drugs. • Good for postmenopausal osteoporosis.	• **Carcinogenic effect (osteosarcoma)** • Diarrhea, heartburn, nausea. • Headache, leg cramps. • Hypotension when standing • Elevated serum calcium can occur in some cases leading to **kidney stones**.	people with increased risk for bone tumors (*osteosarcoma*) including: • **Paget's disease** • People who had **radiation treatment** involving bones • **children**

L4&5: Treatment of osteoporosis

Vitamin D

MOA	steroid hormone that is intimately involved in the regulation of plasma calcium levels. The overall effect of vitamin D is to ↑ **plasma Ca^{2+} concentrations**, which is done by: • **Bone:** Increases bone resorption & activation of osteoblast cells.Although it causes resorption, the net effect is activation of osteoblasts • **Kidney:** Increased reabsorption of Ca^{2+} & PO_4. • **GIT:** Increased absorption of Ca^{2+} from the intestine. • Decreases the production of PTH by the **parathyroid glands**

Calcitonin

MOA	Uses	ADRs
• **Bone:** Decreases bone resorption by **inhibiting osteoclast activity**. • **Kidney:** Decreases reabsorption of Ca^{2+} & PO_4, thus increasing their excretion. • No effect on the GIT	**it has lower efficacy compared to other drugs)** • **Hypercalcemia** (short-term treatment of hypercalcemia of malignancy). • **Paget's disease.** • Osteoporosis	• Nausea • Local inflammation (at site of Injection) If given SC • Flushing of face & hands • Nasal irritation If given as nasal spray

L6: Corticosteroids

Agonist		Antagonists	
Glucocorticoids	**Mineralocorticoid**	**Synthesis inhibitors**	**Receptor antagonists**
Natural: cortisol/hydrocortisone	**Natural**: Aldosterone	Ketoconazole	**Glucocorticoid receptors** -Mifepristone
Synthetic: Prednisone Dexamethasone / Budesonide Beclomethasone ➔ compared to cortisol: • Longert1/2 & duration of action • Reduce salt retaining effect • Better penetration of lipid barriers for topical activity.	**Synthetic** Fludrocortisone (**has the highest mineralocorticoid action)**		**Mineralocorticoid receptors** -Spironolactone

Corticosteroids Agonists

Classes	Natural Glucocorticoids	Synthetic Glucocorticoids		Mineralocorticoids
Drug	**Cortisol (hydrocortisone)**	**Prednisone Dexamethasone**	**Budesenoide Beclomethasone**	**Aldosterone Fludrocortisone**
MOA	1. Steroid in the blood is bound to corticosteroid binding globulin (CBG) → enters the cell as a free molecule 2. activates the intracellular receptor that is bound to the stabilizing proteins (Hsp90) + several others (X) →, Hsp90 + (X) are released. 3. The steroid–receptor complex enters the nucleus, binds to the (Glucocorticoid or Mineralocorticoids) response-element 4. on the gene, and regulates gene transcription by RNA polymerase 2 5. The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings the hormone response.			
Uses	**Adrenal Disorder**: 1. **Addison's disease** 2. Acute adrenal insufficiency 3. Congenital adrenal hyperplasia **Non-adrenal Disorder:** 1. Allergic reactions & Infections 2. Collagen vascular disorder & Hematologic disorders 3. Organ transplants 4. GI disorders (**IBD**) 5. Neurologic disorders **Dexamethasone for cerebral edema** 6. Pulmonary / Renal / Thyroid diseases 7. Miscellaneous (**hypercalcemia & mountain sickness**)		**Asthma**	-**Aldosterone**: Salt-retaining hormone regulates blood volume & pressure -**Fludrocortisone:** Replacement therapy after adrenalectomy
ADRs	**Only natural**: Hypertension **Toxicity**: -**Cushing's syndrome.** - Subcapsular Cataract - Peptic ulcer -Diabetes Mellitus. -Osteoporosis -Impaired wound healing			

Corticosteroids Antagonists

Classes	Receptor Antagonists		Synthetic Inhibitors
Drug	**Spironolactone**	**Mifepristone**	**Ketoconazole**
MOA	**Mineralocorticoid antagonist & K-sparing diuretics**	Competitive inhibitor of glucocorticoids	1-Antifungal in low doses 2-Inhibits cytochrome p450 enzymes necessary for synthesis of all steroids
Uses	Primary aldosteronism (**Conn's syndrome)**	**Cushing syndrome**	**Adrenal cancer** Hirsutism Breast & prostate cancer

L7: Drugs used in DM type 1

Insulin

Routes of administrations of exogenous insulin	★ Can not be given orally 1. **All can be given S.C :** Insulin syringes, Pre-filled pen injector, Continuous S.C. infusion/Insulin pump 2. Intravenously IV -in a hyperglycemic emergency- **Only Glulisine | Aspart | Lispro | Regular Insulin** (ultra-short & short acting) 3. Inhaled aerosols, transdermal, intranasal **(Under Clinical Trials).**

Onset & Duration of Action

Ultra short acting Lispro Insulin , Aspart Insulin	**Short acting** Humulin (Regular insulin)	**Intermediate acting** insulin Isophane(NPH) | Lente	**acting Long** Insulin glargine
• Onset: very fast (5-15 min) • DOA: Short (3-5 hr)	• Onset:Fast (30-45 min) • DOA: Fast (6-8 hr)	• Onset: (1-2 hr) • DOA: (13-18 hr)	• Onset:Delayed (2 hr) • DOA: (24 hr)

Complications

1. **Hypoglycemia & Hypokalemia**
2. Hypersensitivity Reactions
3. **Weight gain** (Due to anabolic effects of insulin)
4. **Lipodystrophy** (a buildup of fatty tissue) at the injection sites.
5. Insulin resistance

Class	Ultra short acting insulin	Short acting insulin
Drugs	**Insulin Lispro, Insulin Aspart, Glulisine**	**Humulin (Regular insulin), Novolin R**
P.K	• **Clear solutions** at neutral pH. (IV) • Does not aggregate (monomeric analogue) • 3 times/day Mimic the prandial mealtime insulin release.	• Clear solutions at neutral pH Soluble crystalline zinc insulin. • Forms hexamers • it requires administration 1 h or more before a meal
Uses	• I.V in emergency diabetic ketoacidosis (DKA) • S.C to control postprandial hyperglycemia • Prefers for external insulin pump	• I.V in emergency diabetic ketoacidosis (DKA) • S.C to control postprandial hyperglycemia • Can be used in pregnancy
Class	**Intermediate acting insulin**	
Drugs	**Isophane (NPH) insulin**	**Lente insulin**
Overview	• NPH:Neutral Protamine Hagedorn insulin in phosphate buffer. • A combination of protamine & crystalline zinc insulin • **often combined with regular and rapid-acting**	Mixture of: • 30% semilente insulin (amorphous precipitate of zinc insulin in acetate buffer) • 70% ultralente insulin (poorly soluble crystal of zinc insulin)
P.K	• **Turbid suspension** at neutral pH ; **not I.V can't be used in ketoacidosis or emergency** • Given S.C. only	• **Turbid suspension** at neutral pH **not I.V can't be used in ketoacidosis or emergency** • Given S.C. only • Lente and NPH insulins are equivalent in activity
Class	**Long acting insulin**	
Drugs	**insulin Glargine(Lentus)**	**insulin Detemir**
P.K	• Clear solution **BUT forms precipitate (hexamer)** at injection site • Absorbed less rapidly than NPH & Lente insulin • Given S.C. only , **not IV** • **Should not be mixed with other insulins in the same syringe.** • **Given once** daily, used with rapid or short acting insulins	
Overview	• Produce broad plasma concentration plateau **(low continuous insulin level | peakless)** • Constant circulating insulin peak-less profile • Helps control basal glucose levels without producing hypoglycemia. • Reduced risk of nocturnal hypoglycemia →Safer than NPH & Lente insulins.	

L8: Management of diabetic ketoacidosis and hypoglycemia

Diabetic ketoacidosis

Insulin Deficiency: (acute emergency situation), which is mostly associated with **type I diabetes**

Symptoms: Ketotic Breath (Fruity acetone smell), Rapid & deep Respiration (Kussmaul–Kien respiration) , Classic features of hyperglycemia (Thirst & Polyuria.) , Tachycardia , NV , abdominal pain , Mental status changes (confusion, coma)

Diagnostic Criteria: Glucose > 250, pH<7.35, HCO3-<15 mmol/L, Ketonemia/Ketonuria.

Treatment stepwise	Specifications
Fluid therapy Rehydration	Corrects Dehydration → Restores blood volume & perfusion Method: **Isotonic Saline** (0.9% NaCl) OR Lactated Ringer Solution Infusion
Regular Insulin	Corrects Hyperglycemia → Stops lipolysis & promotes degradation of ketone bodies Method: Continuous I.V infusion in small doses **(Regular insulin)**
K^+ Therapy	Corrects Electrolyte deficits (serum K+ conc.) Method: K+ added to infusion (to prevent insulin therapy-produced hypokalemia)
$HCO3^-$ Therapy Only if pH<7 after 1 hr of hydration	Corrects Metabolic acidosis Method: Every 2 hrs until pH is at least 7

Hypoglycemia

Precautions

1. Monitoring of blood glucose level (blood sugar level should be checked routinely)
2. Patients should carry glucose tablets or hard candy to eat if blood sugar gets too low
3. Diabetic patient should wear a medical ID bracelet or carry a card
4. Patient should not skip meals or eat partial meals
5. Patient should eat extra carbohydrates if he will be active than usual

Treatment

Conscious patient	dextrose tablets, glucose gel, or any sugar-containing beverage or food may be given.
Unconscious patient	• Glucagon (1 mg S.C or I.M) • Emergency: 20-50 ml of 50% glucose solution I.V. infusion/bolus over 2–3 mins
other (male slides only)	Somatostatin (SST): (Longer-acting analogues such as octreotide and lanreotide) • are also useful for treatment of severe secretory diarrhea and carcinoid tumors. Given IM • Side effects: Gallbladder abnormalities (stones and biliary sludge) Diazoxide (antihypertensive, antidiuretic with potent hyperglycemic actions when given orally) • interacts with the KATP channel on the β cell membrane and either prevents its closing or prolongs the open time → inhibits insulin secretion • Adverse effects: Retention of Na+ /fluid, hyperuricemia, thrombocytopenia, and leukopenia • Uses: may be useful in children with neonatal hyperinsulinism.

Hyperosmolar Hyperglycemic Syndrome

Aggressive rehydration & restoration of glucose and electrolyte homeostasis + Low-dose insulin therapy may be required

L9&10 Drugs used in DM type 2

1) Insulin Release(Secretagogues)

A) Sulfonylurea

Drug	1st generation Short acting: **Tolbutamide**	1st generation Long acting: **Acetohexamide** **Tolazamide** **Chlorpropamide**	2nd generation Short acting: **Gliclazide** **Glipizide**	2nd generation Long acting: **Glyburide (glibenclamide)** **Glimepiride**
MOA	1- blocking of ATP-sensitive K channels which causes depolarization and 2- opening of voltage- dependent calcium channels, which causes 3- an increase in intracellular calcium in the β cells, which 4- stimulates insulin release.			
P.K	• Orally • Highly bound to plasma protein • Cross placenta → fetal hypoglycemia at birth (give insulin) • Second generation is more potent than first generation			
Uses	Treatment of Type 2 diabetes monotherapy or in combination with other antidiabetic drugs			
ADRs	1. Hyperinsulinemia & **Hypoglycemia**: 2. **Weight gain** due to increase in appetite 3. Allergic rashes can occur, and bone marrow toxicity	**C.I :** Pregnancy, sulfa allergy, renal disease, Liver disease		

B) Meglitinides

Drug	Repaglinide	Nateglinide
MOA	1-Rapidly acting insulin secretagogues. 2-Mechanism of action is identical to sulfonylureas	
P.K	• Orally • Taken just before each meal "used for controlling postprandial Glucose " • Shorter DOA & onset	
Uses	As alternative to sulfonylureas (SU) in patients **allergic** to them (SU).	
ADRs	Less incidence of **Hypoglycemia** , Weight Gain	

2) Insulin sensitizers

A) Biguanides

Drug	Metformin
MOA	• reduce intracellular ATP and activation of AMP-dependent kinase(AMPK) leading to reduced insulin resistance ↓ insulin resistance by ↑sensitivity of peripheral target organs to insulin • ↑ peripheral glucose utilization (tissue glycolysis) • ↓gluconeogenesis and absorption of glucose from GIT • Improve lipid profile:↓LDL,↓VLDL ,↑HDL • Stimulation of hepatic fatty acid oxidation
P.K	• Given orally! Not bound to serum protein Advantages: ★ **No risk of hypoglycemia.** ★ **No weight gain** •**Inexpensive**
Uses	★★**first-line therapy In patients with type 2 diabetes who are obese,** • Infertility in women with polycystic ovarian syndrome
ADRs	GIT disturbance: • Metallic taste, NVD • Malabsorption of Vitamin B12 • **Lactic acidosis:**in cardiopulmonary, renal and liver disease, alcoholism C.I: Pregnancy And who are at risk of lactic acidosis

L9&10 Drugs used in DM type 2

2) Insulin sensitizers

B) Thiazolidinediones (glitazones)

Drug	Pioglitazone	Rosiglitazone
MOA	• activating PPAR-γ: ↑ sensitivity of target tissues to insulin → ↑ glucose uptake and utilization in muscle and adipose tissue.	
P.K	• Orally (once daily dose) • Highly bound to plasma albumins (99%)	
Uses	• Type 2 diabetes with insulin resistance. • Used either alone or in combination with sulfonylurea, biguanides or insulin	
ADRs	• Hepatotoxicity • Fluid retention (Edema) • Congestive heart failure • Mild weight gain • DDI: Failure of estrogen-containing oral contraceptives	

3) α-Glucosidase inhibitors

Drug	Acarbose	Miglitol
MOA	• Reversible inhibitors of intestinal α-glucosidases in intestinal brush border cells that are responsible for carbohydrate digestion. • ↓ carbohydrate digestion and glucose absorption in small intestine (lower postprandial glucose level).	
P.K	• No hypoglycemia if used alone • Orally, not absorbed	
Uses	• Effective alone in the earliest stages of impaired glucose tolerance • Most useful in combination with other oral hypoglycemic drugs or with insulin.	
ADRs	• GIT: **Flatulence**, bloating, diarrhea, abdominal pain. Acarbose	
C.I	• Irritable bowel syndrome (IBS). • Inflammatory bowel disorders (IBD) • Intestinal obstruction.	

4) Glucose transporter inhibitor

Drug	Canagliflozin	Dapagliflozin	Empagliflozin
MOA	• The SGLT2 inhibitors act by promoting glucose excretion into the urine, thereby reducing the concentration of circulating glucose. The resulting glycosuria is associated with an osmotic diuresis and salt excretion.		
P.K	• Orally absorbed		
Uses	• Have potentially beneficial effect on weight,blood pressure,cardiovascular outcome Decrease fluid retention		
ADRs	• Urinary and genital tract infections • Polyuria and thirst • Itching in genital area (pruritus) • osmotic diuresis and constipation		

L9&10 Drugs used in DM type 2

5) D2-agonist

Drug	Bromocriptine
MOA	Lowers glucose through unknown mechanism inhibit the hypothalamus axis that increase glucagon which result in inhibition of glucagon release
ADRs	• Nausea and vomiting • Headache • Dizziness

6) Incretin mimetics & related drugs

A) Glucagon-like peptide-1 (GLP-1) agonists

Drug	Liraglutide	Dulaglutide	Exenatide	Semaglutide (First oral GLP-1)
MOA	• ↑ insulin secretion from β cells by stimulating GLP 1 receptor In β cells, the end result of these actions is increased insulin biosynthesis and exocytosis in a ★ glucose-dependent manner • ↓ glucagon secretion by inhibiting alpha cells of the pancreas			
P.K	• S.C			
Uses	-Victoza®: is the lower dose for diabetes. S.C once daily - **Saxenda®**: is the higher dose for obesity. S.C once daily - As a treatment for adults who are ★obese or overweight with at least one weight related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia).	–	- **Byetta®**: immediate-release given S.C. twice daily - **Bydureon®**: extended-release given once weekly	- Ozempic ®: (S.C once weekly): the injectable -Rybelsus ®(Orally once daily)
ADRs	• Nausea, vomiting and diarrhea (most common) • Hypoglycemia when combined with Sulfonylureas or insulin • Pancreatitis (rare).			

B) Gastric inhibitory polypeptide analogues

Drug	Tirzepatide (Mounjaro ®)
MOA	• It is dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist. • has a greater affinity to GIP receptors than to GLP-1 receptors
P.K	S.C once weekly
Uses	• aid in weight loss, reduce the risk of hypoglycaemia. • Contribute to cardiorenal protective effects. • Providing good glycemic control.
ADRs	Nausea, diarrhea and vomiting

L9&10 Drugs used in DM type 2

7) Dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitors)

Drug	Sitagliptin (Januvia®)
MOA	• Inhibit DPP-4 enzyme and leads to an increase in incretin hormones (GLP-1)level. • This results in an increase in insulin secretion & decrease in glucagon secretion. • Slows gastric emptying, decreases appetite.
P.K	Given orally/once daily.
Uses	Type 2 DM as an adjunct to diet & exercise as a monotherapy or In combination with other antidiabetic drugs.
ADRs	• Nausea, abdominal pain, diarrhea. • Nasopharyngitis. • Headache. • Pancreatitis, rare allergic reaction.

8) Amylin analogues

Drug	Pramlintide
MOA	• Pramlintide likely acts through the amylin receptor in specific regions of the hindbrain.
P.K	• Metabolism and clearance are primarily renal. • administered as a S.C. prior to meals
Uses	• types 1 and 2 diabetes as an adjunct inpatients who take insulin with meals.
ADRs	nausea and hypoglycemia especially with insulin.

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