Final Endocrine Pharmacology

Revision

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Lecture 3: Calcium & Vitamin D

Subclass	Drug	Indication	ADRs	Contraindications	Notes
PTH Analogue	**Teriparatide**	1- Postmenopausal Osteoporosis. 2- People have osteoporosis that have risk for fracture. 3- Severe Osteoporosis. 4- Patient with Osteoporosis not responding to other Drugs.	1-Carcinogenic Effects (Osteosarcoma). 2-Hypotension when standing (orthostatic Hypotension). 3-Kidney Stone.	Patient with risk for bone tumors (Osteosarcoma): 1- Paget's Disease. 2- Patient who had radiation treatment involving bone. 3- Not for Children.	Once Daily / S.C In thigh
Vit D	**Vit D Supplements**	1- Rickets. 2- Osteomalacia. 3- Osteoporosis. 4- Psoriasis. 5- Cancer Prevention (Prostate/Colorectal).	-	-	***Vitamin D2** is the prescription form of vitamin D & is also used as food additive (milk). ***Vitamin D3** is usually for vitamin D-fortified milk & foods & also available in drug combination products. *Vit D2 & D3 Have equal biological activities*
Calcitonin	**Calcitonin**	1- Osteoporosis (major indication; alternative to other drugs). 2- Hypercalcemia (short-term treatment of hypercalcemia of malignancy), 3-Paget's disease.	1-Nausea 2-Local inflammation at site of injection (S.C). 3-Flushing of face & hands 4-Nasal irritation (nasal spray).	Allergic People	*It has lower efficacy compared to other drugs. *Route of Administration: S.C, Nasal spray or solution (Calcitonin Salmon) has more affinity towards human calcitonin receptors

Lecture 4: Osteoporosis

Subclass	Drug	MOA	indication	ADRs	C.I	Notes
Bisphosphonates	**Alendronate Zoledronate Tildronate etc. (Suffix:dronate).** **Kinetics:* -Poorly absorbed, -given on an empty stomach- or infused IV. -Half of absorbed drug accumulates in bones. -In bone it is retained for months, depending on bone turnover.	1- bind to hydroxyapatite, decreasing its solubility and making it more resistant to osteoclastic activity. 2- Block steps in cholesterol Synthetic pathway in osteoclast.	1- Osteoporosis, secondary to menopause, glucocorticoids. 2- Paget's Disease 3 -Malignancy-associated hypercalcaemia	1-GIT irritation. 2-Gastro-esophageal reflux. 3-Flue like manifestations upon IV infusion 4-Osteo-necrosis of the jaw. 5-Atrial fibrillation > women with alendronate & zoledronate	Decreased renal function and Peptic ulcer / esophageal reflux	*Dosing:* 1-Once weekly, or on two consecutive days each month 2-Separate 4 hrs before giving Ca, Mg, Al containing drugs *Notes:* 1- When calcium and vit D supplementation given during bisphosphonate therapy *don't ingest it along with bisphosphonate* 2-Their relative potencies for osteoclast inhibition is the most with 3rd generation (zoledronate)
RANKL Inhibitors	**Denosumab**	mimics the activity of osteoprotegerin (OPG).	-	1- Infections; 2- Urinary & respiratory 3- Eczema & skin rash 4- Constipation 5- Cataract 6- Joint pains	In patients with Hypocalcemia, -must Correct Ca & Vit D levels-	Administration: Subcutaneous every 6 months
Strontium	**Strontium** **Kinetics:* -Orally with a modest bioavailability 25% Binds partially to plasma proteins and strongly to bones -t ½ 60 hrs -Excreted mainly by the kidney	On Osteoblast: 1-it acts as agonist on [CaSR] > enhances proliferation of osteoblast > ↑ bone formation 2-It stimulates the expression of OPG > ↓ bone resorption. On Osteoclast: Acts as agonist on [CaSP] > suppress differentiation of osteoclast >↑ osteoclast apoptosis and ↓ bone resorption	1-Osteoporosis, secondary to menopause, glucocorticoids.. 2-Malignancy-associated hypercalcaemia	1- GIT irritation. 2- Headache 3- Eczema (All resolve in 1st 3 months)	1- Severe renal disease. 2- Hypersensitivity. 3- Increased risk of venous thromboembolism 4-Phenylketonuria	*Interaction: 1- Food specially containing milk+ its products 2- Antacids 3- Oral tetracycline & quinolones chelate it *Precaution of interactions: 2h spacing

Lecture 4: Osteoporosis cont.

Subclass	Drug	MOA	indication	ADRs	Notes
Estrogens/ Androgens	**Estrogens/ Androgens**	1- ↑ osteoclast apoptosis 2- ↓ osteoblast apoptosis 3- ↓ No. & depth of resorption cavities 4-↑ release of growth factors from osteoblasts. 5- ↓ release of inflammatory cytokines.	1-Give Estrogens: If hysterectomy, + progestins if uterus present. 2-Give HRT: Menopausal Symptoms. 3-Give SERMs: Menopause / Elderly. 4-Androgens: Elderly men.	*HRT (estrogen): 1- Vaginal bleeding 2- Breast cancer. 3- Venous thromboembolism	-
SERMs	**Raloxifene**	Antiestrogens that exhibits partial agonistic action (acting as an agonist in bone & an antagonist in some female sex organs)	Prevention and treatment of osteoporosis	1- Hot flushes 2- No effect on HDL	Advantages: 1-↑ bone density & ↓ fracture risk. 2-No stimulation of breast or endometrial tissue. 3-No need for progestin in women with uterus 3- ↓ LDL 4-Good for women with risk of uterine and breast cancer. 5- ↓ r risk of thromboembolism compared to estrogen.

Lecture 5: Corticosteroids

Class	Subclass	Drug	Notes:	Indications	ADRs
Glucocorticosteroids Agonists	**Natural**	**Cortisol (Hydrocortisone)**	*Well absorbed from GIT (Orally) *Short duration of action. *Diffuses poorly across normal skin and mucous membranes. *Important cause of cushing's.	*Adrenal Disorders: 1- Addison's disease. 2- Acute adrenal insufficiency. 3- Congenital hyperplasia. *Non-adrenal disorders: 1- Allergic reactions. 2- Collagen vascular disorders. 3- Organ transplant. 4- GI disorders. 5- Hematological disorders. 6- Infections 7- Neurological disorders. 8- Pulmonary disorders. 9- Thyroid disorders. 10- Renal disorders. 11- Miscellaneous (Please recall examples on each from the lecture)	1- Cushing's syndrome. 2- Increase growth of fine hair on face, thighs & trunk. 3-Myopathy, Muscle wasting. 4- Thinning of skin. 5- Diabetes mellitus. 6- Osteoporosis. 7- Aseptic necrosis of hip. 8- Impaired wound healing. 9- Pts should be on *high protein and potassium-enriched diet.* 10- Peptic ulcers 11- Acute psychosis, depression. 12- Subcapsular cataracts. 13- Growth suppression. 14- Hypertension. 15- Adrenal suppression.
	Synthetic	**Prednisone**	*Its active metabolite **prednisolone, dexamethasone,triamcinolone.** *Longer half life and duration of action. *Better penetration of lipid barriers for *topical activity.*		
		Beclomethasone Budsonide	*Used in asthma = rapidly penetrate the airway mucosa. *Short half lives after they enter the blood, so *less* systemic effects and toxicity.		
Mineralocorticosteroids Agonists	**Natural**	**Aldosterone**	*Shorter life time. *Little glucocorticoid activity.	-	-
	Synthetic	**Fludrocortisone**	*Longer duration of action. *Significant glucocorticoid activity.	1- Replacement therapy after *adrenalectomy*. 2- When mineralocorticoid therapy is needed.	-

Lecture 5: Corticosteroids cont.

Class	Subclass	Drug	MOA	Indications	Notes
Corticosteroids Antagonists	**Receptor Antagonists**	**Spironolactone Eplerenone**	Antagonists of aldosterone at its receptor.	-	-
		Mifepristone	Competitive inhibitor of *glucocorticoid & progesterone* receptors	Cushing's Syndrome.	-
	Synthesis Inhibitors	**Aminoglutethimide**	1-It blocks the conversion of cholesterol to pregnenolone. 2-Inhibits the synthesis of all hormonally active steroids.	Adrenal cancer, when surgical therapy is impractical or unsuccessful because of metastasis.	**Used mainly in:* Adrenocortical cancer.
		Ketoconazole (Anti-fungal)	It inhibits the cytochrome p450 enzymes necessary for the synthesis of all steroids.		**Used mainly in:* Adrenal carcinoma, Hirsutism, Breast cancer or Prostate cancer.
		Metyrapone	-		-

Lecture 6 : Use of Insulin in The Treatment of Diabetes Mellitus

Subclass	Drug	Onset of Action	Duration	Peaks	Route	Physical ch.	Chemistry	Indications	Notes
Ultra-short acting insulins	**Lispro** **Aspart** **Glulisine**	5-15 m	3-5 h	30-90 m	S.C. I.V.	Clear	Monomeres	*Postprandial hyperglycemia (S.C.) *Diabetic ketoacidosis (I.V.)	*They are mixed with other insulins but the preparation should be used *immediately*. *Preferred for external *insulin pump*.
Short-acting insulins (*Regular*)	**Humulin R** **Novolin R**	30-45 m	6-8 h	2-4 h	S.C. I.V.	Clear	Hexamers	*Postprandial hyperglycemia (S.C.) *Diabetic ketoacidosis (I.V.)	*Can be used in pregnancy
Intermediate acting insulins	**NPH**	1-2 h	13-18 h	5-7 h	S.C.	Turbid	Combination	*Combined with lispro, aspart or regular insulins.	***NOT** used in emergency ie: DKA
	Lente	1-3 h	13-20 h	4-8 h					
Long acting insulins	**Glargine** **Detemir**	2 h	24 h	Peakless	S.C.	Clear	Hexamers	*Produce plasma conc. Plateau (low continuous insulin level). *Used with rapid or short acting regimens.	*Should not be mixed with other insulins with the same syringe. *Reduce risk of nocturnal hypoglycemia.

Lecture 7: Diabetic Ketoacidosis

	Subclass	Drug	MOA	indication	Notes
Treatment of Hyperglycemia	**Fluid therapy**	**Isotonic saline** (0.9% sodium chloride)	Restore blood volume and perfusion of tissues.	Dehydration (secondary to DKA)	IV Infusion.
	Insulin	**Regular insulin**	Insulin stops lipolysis and promotes degradation of ketone bodies.	Hyperglycemia	
	Potassium therapy	**-**	-	Electrolyte deficits	Added to infusion fluid
	Bicarbonate therapy	**-**	-	Ketoacidosis. Metabolic acidosis.	Should be used only if the arterial pH < 7.0 after 1h of hydration. Administered every 2 hours until the pH is at least 7.0
Treatment of Hypoglycemia	**Sugar containing beverage or food**		-	Hypoglycemic conscious patient	
	Glucagon		-	Hypoglycemic unconscious patient	S.C. or I.M
	Glucose solution		-		I.V. infusion Risk of possible **phlebitis**

Lecture 8 & 9: Hypoglycemic Drugs

<table>
<tr><th>Subclass</th><th>Drug</th><th>Duration of action</th><th>MOA</th><th>indication</th><th>ADRs</th><th>Contraindications</th><th>Notes</th></tr>
<tr><td rowspan="4">Sulfonylurea 1st generation</td><td><u>Tolbut</u>amide</td><td>Short
6 – 8 hrs</td><td rowspan="8">Insulin secretagogues

Blocking of ATP-sensitive K channels → depolarization → opening of voltage-dependent calcium channels → increase in intracellular calcium in the beta cells → stimulate insulin release.</td><td>- Elderly diabetic.
- Diabetic with renal impairment.</td><td rowspan="5">- Weight gain.
- Hyperinsulinemia and Hypoglycemia (with long acting)</td><td>Pregnancy</td><td rowspan="3">- Orally, well absorbed.
- Highly bound to plasma proteins.
- Metabolized in liver
- Excreted in urine</td></tr>
<tr><td>Acetohexamide</td><td rowspan="2">12 – 20 h
Intermediate</td><td rowspan="3">DM</td><td rowspan="3">Elderly, renal disease (especially long acting).
Pregnancy</td></tr>
<tr><td>Tolazamide</td></tr>
<tr><td>Chlorpropamide</td><td>20 – 60 h</td></tr>
<tr><td rowspan="3">Sulfonylurea 2nd generation</td><td>Glipizide</td><td>10 – 16 h</td><td rowspan="3">- More potent.
- Longer duration of action.
- Less frequency of administration.
- Fewer drug interactions.
- Absorption reduced by food (Glipizide).</td></tr>
<tr><td>Glyburide</td><td rowspan="2">12 – 24 h
Long</td></tr>
<tr><td>Glimepiride</td></tr>
<tr><td>Meglitinides</td><td>Repaglinide</td><td>Short
4h</td><td>Type II diabetes (monotherapy or in combination)
Alternative to sulfonylureas in patients allergic to sulfur.</td><td>Less incidence than sulfonylureas:
- Hypoglycemia.
- Weight gain.</td><td></td><td>- <u>Very fast</u> onset of action (peak 1h).
- Excreted in bile.
- Taken just before each meal (3 times/day)
- Slfa free.</td></tr>
</table>

Lecture 8 & 9: Hypoglycemic Drugs Cont.

Subclass	Drug	MOA	Indication	ADRs	Contraindications	Notes
Biguanides	**Metformin**	-Tissue glycolysis. - Reduces insulin resistance. -Inhibits hepatic gluconeogenesis. - ↓LDL, ↑HDL.	- Obese T2DM (1st line) -T2DM (monotherapy or in combination)	-Metallic taste. **-Lactic acidosis.** -Interference with vitamin B12 absorption **(long term use).**	-Renal and liver disease. -Alcoholism. -Cardiopulmonary dysfunction. -Pregnancy	- Excreted unchanged in urine. -Taken with meals -Started at a low dose.
Thiazolidinediones	**Pioglitazone**	-Activate peroxisome proliferator-activated receptor γ (**PPARγ**). -Glucose utilization in **muscle and adipose tissue**. -Increase sensitivity of target tissues to insulin.	T2DM with **insulin resistance** (monotherapy or in combination).	-Hepatotoxicity (LFT). -Fluid retention (Edema). -CHF. -Mild weight **gain**. -Failure of estrogen-containing oral contraceptives.	-	-Once daily (persistent effect). -Half life 3-4 h. - Excreted in urine and bile. -No risk of hypoglycemia when used **alone.**
α Glucosidase inhibitors	**Acarbose** **Miglitol**	-Reversible inhibitors of **intestinal a-glucosidases** that are responsible for carbs digestion. - ↓ carbs digestion and glucose absorption in small intestine (lower postprandial glucose level).	- Alone in the **earliest stages** of impaired glucose tolerance. - In combination with other oral hypoglycemic drugs or with insulin.	-Flatulence. -Bloating. -Diarrhea. -Abdominal pain.	-Not used alone as therapy for moderate to severe hyperglycemia. -IBS. -IBD. -Intestinal obstruction.	-Excreted in feces. -No hypoglycemia if used **alone**.
Glucagon-like peptide-1 (GLP-1)	**Dulaglutide** **Exenatide**	↑ **Incretin** → ↑ insulin secretion & ↓glucagon secretion (regulate blood glucose).	-T2DM who are not controlled with oral medication.	- Decreased appetite and fatigue.	-	- Inactivated by dipeptidyl peptidase-4 (DPP-4). **- Given S.C, once a week.**
Dipeptidyl peptidase-4 (DPP-4) inhibitors	**Sitagliptin** **Vildagliptin**	- **Inhibit DPP-4 enzyme** (inhibit incretin breakdown) thus increase incretin hormone (GLP-1).	- Monotherapy in T2DM as an adjunct to diet & exercise. - Combination with other antidiabetic drugs.	-	-	-Orally. - Given once daily.