

SECTION 9: Drugs Acting on Kidney

42. Diuretics

1. Overview & Relevant Physiology:

- Diuretics are drugs that increase urine output by inhibiting sodium reabsorption in different segments of the nephron. They promote the elimination of salt and water and are used to manage conditions like hypertension, heart failure, and edema.

Key Physiological Points:

- Sodium reabsorption occurs in various segments of the nephron: proximal tubule (65%), loop of Henle (20%), distal convoluted tubule (10%), and collecting duct (5%).
- The kidney regulates body fluid volume, electrolyte balance, and pH through filtration and selective reabsorption and secretion.

2. Classes of Diuretics:

a. Thiazide Diuretics:

- Mechanism: Inhibit Na^+/Cl^- co-transporter in the distal convoluted tubule, reducing sodium reabsorption.
- Clinical Uses: First-line therapy for hypertension, edema due to CHF or nephrotic syndrome, calcium nephrolithiasis.
- Examples: Hydrochlorothiazide, Chlorthalidone.
- Adverse Effects: Hypokalemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypocalciuria, metabolic alkalosis.
- Monitoring Parameters: Electrolytes, particularly potassium; blood pressure.

b. Loop Diuretics:

- Mechanism: Inhibit the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ transporter in the thick ascending limb of the loop of Henle, causing a marked increase in sodium and water excretion.
- Clinical Uses: Acute pulmonary edema, chronic heart failure, hypercalcemia, renal failure, ascites.
- Examples: Furosemide, Bumetanide, Torsemide.

- Adverse Effects: Hypokalemia, hypocalcemia, ototoxicity, volume depletion, nephrotoxicity (especially with NSAIDs).
- Monitoring Parameters: Serum electrolytes, renal function, hearing tests if needed.

c. Potassium-Sparing Diuretics:

- Mechanism: Inhibit aldosterone in the distal nephron (e.g., Spironolactone) or directly block Na^+ channels (e.g., Amiloride).
- Clinical Uses: Heart failure, cirrhotic ascites, hyperaldosteronism, co-administration with loop or thiazide diuretics to counter hypokalemia.
- Examples: Spironolactone, Amiloride, Eplerenone.
- Adverse Effects: Hyperkalemia, gynecomastia (with spironolactone), metabolic acidosis.
- Monitoring Parameters: Potassium, renal function.

d. Carbonic Anhydrase Inhibitors:

- Mechanism: Inhibit carbonic anhydrase in the proximal tubule, leading to increased bicarbonate excretion.
- Clinical Uses: Glaucoma, altitude sickness, metabolic alkalosis.
- Examples: Acetazolamide, Methazolamide.
- Adverse Effects: Metabolic acidosis, hypokalemia, nephrolithiasis, paresthesias.
- Monitoring Parameters: Serum bicarbonate, electrolytes.

e. Osmotic Diuretics:

- Mechanism: Increase osmotic pressure in the glomerular filtrate, inhibiting reabsorption of water and solutes.
- Clinical Uses: Cerebral edema, acute glaucoma, oliguric renal failure.
- Examples: Mannitol.
- Adverse Effects: Dehydration, electrolyte imbalance, risk of acute kidney injury.
- Monitoring Parameters: Serum electrolytes, fluid status.

43. Antidiuretics

1. Overview:

- Antidiuretic drugs reduce urine output by promoting water reabsorption in the kidney, primarily through the action of vasopressin (ADH) analogs. These drugs are mainly used in diabetes insipidus and conditions requiring increased water retention.

2. Classes of Antidiuretics:

a. Vasopressin (ADH) and Desmopressin (DDAVP):

- Mechanism: Vasopressin acts on V2 receptors in the collecting ducts of the nephron to increase water permeability, leading to water reabsorption. Desmopressin is a selective V2 receptor agonist with minimal V1 receptor effects (less vasoconstriction).
- Clinical Uses: Central diabetes insipidus, nocturnal enuresis, hemophilia A (increases factor VIII), von Willebrand disease.
- Examples: Vasopressin, Desmopressin.
- Adverse Effects: Hyponatremia (water intoxication), vasoconstriction (with vasopressin), headache.
- Monitoring Parameters: Serum sodium, fluid intake/output.

SECTION 10: Drugs Affecting Blood and Blood Formation**44. Haematinics and Erythropoietin****1. Haematinics:**

- Haematinics are agents that promote hemoglobin formation by increasing the availability of key components, particularly iron, folic acid, and vitamin B12.

a. Iron Preparations:

- Mechanism: Iron is a critical component of hemoglobin. It is absorbed in the duodenum and jejunum and transported via transferrin. Stored in the liver as ferritin.
- Clinical Uses: Iron-deficiency anemia, chronic blood loss, pregnancy.
- Examples: Ferrous sulfate, Ferric carboxymaltose, Iron sucrose.
- Adverse Effects: GI upset, constipation, black stools, iron toxicity (in overdose).
- Monitoring Parameters: Hemoglobin, ferritin, transferrin saturation.

b. Folic Acid:

- Mechanism: Essential for DNA synthesis. Folic acid deficiency leads to megaloblastic anemia due to impaired DNA synthesis in erythroid precursors.
- Clinical Uses: Megaloblastic anemia, prevention of neural tube defects in pregnancy.
- Adverse Effects: Rare.
- Monitoring Parameters: CBC, serum folate levels.

c. Vitamin B12 (Cyanocobalamin):

- Mechanism: Required for DNA synthesis and neurologic function. Deficiency leads to megaloblastic anemia and neurological symptoms.
- Clinical Uses: Pernicious anemia, vitamin B12 deficiency.
- Adverse Effects: Rare, can cause anaphylaxis in parenteral forms.
- Monitoring Parameters: CBC, serum B12 levels.

2. Erythropoietin:

- Mechanism: Stimulates erythroid progenitor cells in the bone marrow to produce red blood cells. Erythropoietin production is primarily regulated by oxygen levels in the kidneys.
- Clinical Uses: Anemia of chronic kidney disease, chemotherapy-induced anemia.
- Examples: Epoetin alfa, Darbepoetin alfa.
- Adverse Effects: Hypertension, thromboembolism, pure red cell aplasia (rare).
- Monitoring Parameters: Hemoglobin, blood pressure, iron status (adequate iron levels are necessary for efficacy).

45. Drugs Affecting Coagulation, Bleeding, and Thrombosis

1. Anticoagulants:

a. Heparin and LMWH (Low Molecular Weight Heparin):

- Mechanism: Heparin activates antithrombin III, which inhibits thrombin and factor Xa. LMWHs preferentially inhibit factor Xa.
- Clinical Uses: Prevention/treatment of DVT, pulmonary embolism, acute coronary syndrome.
- Examples: Unfractionated Heparin, Enoxaparin.
- Adverse Effects: Bleeding, heparin-induced thrombocytopenia (HIT), osteoporosis (long-term use).
- Monitoring Parameters: aPTT (for heparin), anti-Xa levels, platelets.

b. Warfarin:

- Mechanism: Inhibits vitamin K epoxide reductase, decreasing synthesis of factors II, VII, IX, and X.
- Clinical Uses: Long-term anticoagulation in atrial fibrillation, mechanical heart valves.
- Adverse Effects: Bleeding, teratogenicity, skin necrosis.
- Monitoring Parameters: INR (target 2-3 in most cases).

c. Direct Oral Anticoagulants (DOACs):

- Mechanism: Directly inhibit thrombin (Dabigatran) or factor Xa (Rivaroxaban, Apixaban).
- Clinical Uses: Stroke prevention in atrial fibrillation, treatment of DVT/PE.
- Adverse Effects: Bleeding, GI disturbance.
- Monitoring Parameters: Renal function, no routine monitoring for efficacy.

2. Antiplatelets:

a. Aspirin:

- Mechanism: Irreversibly inhibits COX-1, reducing thromboxane A2 synthesis and platelet aggregation.
- Clinical Uses: Prevention of MI, stroke.
- Adverse Effects: GI bleeding, allergy, Reye's syndrome in children.
- Monitoring Parameters: Platelet function, clinical signs of bleeding.

b. Clopidogrel (ADP Receptor Inhibitor):

- Mechanism: Irreversibly inhibits the P2Y12 receptor on platelets, preventing ADP-mediated activation of the GPIIb/IIIa complex, which is crucial for platelet aggregation.
- Clinical Uses: Prevention of stroke, MI, especially after stenting or acute coronary syndrome.
- Adverse Effects: Bleeding, thrombocytopenia, TTP (rare).
- Monitoring Parameters: Platelet count, signs of bleeding.

c. Glycoprotein IIb/IIIa Inhibitors:

- Mechanism: Block the final common pathway for platelet aggregation by inhibiting the GPIIb/IIIa receptor on platelets.
- Clinical Uses: Acute coronary syndrome, during percutaneous coronary interventions (PCI).
- Examples: Abciximab, Eptifibatide.
- Adverse Effects: Bleeding, thrombocytopenia.
- Monitoring Parameters: Platelet count, bleeding time, clinical monitoring for bleeding.

3. Fibrinolytics (Thrombolytics):

- Mechanism: Convert plasminogen to plasmin, which degrades fibrin and dissolves thrombi.
- Clinical Uses: Acute ischemic stroke (within 4.5 hours), STEMI, massive pulmonary embolism.

- Examples: Alteplase (tPA), Streptokinase, Urokinase.
- Adverse Effects: Severe bleeding, intracranial hemorrhage, allergy (especially with streptokinase).
- Monitoring Parameters: PT, aPTT, signs of bleeding.

4. Antifibrinolytics:

- Mechanism: Inhibit plasminogen activation, thus preventing fibrinolysis and stabilizing blood clots.
- Clinical Uses: Control of excessive bleeding during surgery, trauma, or menorrhagia.
- Examples: Tranexamic acid, Aminocaproic acid.
- Adverse Effects: Thrombosis, hypersensitivity reactions.
- Monitoring Parameters: Signs of thrombosis, clot stability.

46. Hypolipidaemic Drugs

1. Overview:

- Hypolipidaemic drugs lower lipid levels in the blood, mainly cholesterol and triglycerides, to reduce the risk of cardiovascular disease. The key lipid parameters affected are LDL-C (low-density lipoprotein cholesterol), HDL-C (high-density lipoprotein cholesterol), and triglycerides.

2. Classes of Hypolipidemic Drugs:

a. HMG-CoA Reductase Inhibitors (Statins):

- Mechanism: Inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, leading to upregulation of LDL receptors on hepatocytes and enhanced clearance of LDL from the blood.
- Clinical Uses: First-line therapy for hypercholesterolemia, prevention of cardiovascular disease (CVD).
- Examples: Atorvastatin, Simvastatin, Rosuvastatin.
- Adverse Effects: Myopathy, rhabdomyolysis (rare), hepatotoxicity, new-onset diabetes (in some cases).
- Monitoring Parameters: Lipid profile, liver enzymes (AST/ALT), creatine kinase (CK) if muscle pain occurs.

b. Fibrates:

- Mechanism: Activate peroxisome proliferator-activated receptor-alpha (PPAR- α), increasing lipoprotein lipase activity, leading to enhanced clearance of triglyceride-rich lipoproteins.
- Clinical Uses: Hypertriglyceridemia, particularly when associated with risk of pancreatitis.
- Examples: Fenofibrate, Gemfibrozil.
- Adverse Effects: Gallstones, myopathy (especially when combined with statins), hepatotoxicity.
- Monitoring Parameters: Lipid profile, liver function tests, CK if combined with statins.

c. Niacin (Vitamin B3):

- Mechanism: Inhibits hormone-sensitive lipase in adipose tissue, reducing the release of free fatty acids, and lowers VLDL and LDL production while increasing HDL.
- Clinical Uses: Hyperlipidemia, particularly in patients with low HDL.
- Adverse Effects: Flushing (can be mitigated with aspirin), hyperglycemia, hyperuricemia (gout), hepatotoxicity.
- Monitoring Parameters: Lipid profile, blood glucose, liver function tests, uric acid levels.

d. Bile Acid Sequestrants:

- Mechanism: Bind bile acids in the intestine, preventing their reabsorption. This forces the liver to use more cholesterol to produce bile acids, thereby lowering blood LDL cholesterol.
- Clinical Uses: Hypercholesterolemia, especially in patients who cannot tolerate statins.
- Examples: Cholestyramine, Colestipol, Colesevelam.
- Adverse Effects: GI disturbances (bloating, constipation), malabsorption of fat-soluble vitamins (A, D, E, K).
- Monitoring Parameters: Lipid profile, GI tolerance.

e. Cholesterol Absorption Inhibitors:

- Mechanism: Inhibit the absorption of cholesterol at the brush border of the small intestine.
- Clinical Uses: Hypercholesterolemia, usually in combination with statins.
- Example: Ezetimibe.
- Adverse Effects: Mild GI disturbances, allergic reactions (rare).
- Monitoring Parameters: Lipid profile.

f. PCSK9 Inhibitors:

- Mechanism: Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9), which increases the number of LDL receptors available to clear LDL from the blood.
- Clinical Uses: Familial hypercholesterolemia, patients who need additional LDL-lowering despite statins and ezetimibe.
- Examples: Alirocumab, Evolocumab.
- Adverse Effects: Injection site reactions, upper respiratory tract infections.
- Monitoring Parameters: Lipid profile, signs of allergic reactions.