SUMMARY OF CHAPTER NO. 08, 09, 12, 17 & 20 OF COMPREHENSIVE PHARMACY REVIEW 7TH EDITION

8. ORGANIC CHEMISTRY AND BIOCHEMISTRY

Organic chemistry

Functional groups affect hydrophilicity, lipophilicity, reactivity, shelf life, stability, biotransformation, metabolism.

Alkanes

Also called paraffins, saturated hydrocarbons.

General formula: R-CH2-CH3. Lipid soluble.

Common reactions: halogenation, combustion.

Chemically inert to air, heat, light, acids, bases. Stable in vivo.

Alkenes

Also called olefins, unsaturated hydrocarbons.

General formula: R-CH=CH2. Lipid soluble.

Common reactions: addition of hydrogen or halogen, hydration (to form glycols), oxidation (to form peroxides).

Volatile alkenes and peroxides may explode in presence of O2 and spark

Stable in vivo. Hydration, peroxidation, reduction may occur.

Aromatic hydrocarbons

Based on benzene. Exhibit multicenter bonding. Lipid soluble.

Common reactions: halogenation, alkylation, nitration, sulfonation.

Chemically stable.

In vivo: hydroxylation, diol formation.

Alkyl halides

Halogenated hydrocarbons. General formula: R-CH2-X.

Lipid soluble. ↑ degree of halogenation → ↑ Solubility.

Common reactions: dehyro-halogenation, nucleophilic substitution.

Stable on the shelf. Not readily metabolized in vivo.

Alcohols

Contains OH group. May be primary (R-CH2-OH), secondary (R1/R2-CH-OH), or tertiary (R1/R2/R3-C-OH).

Alcohols are lipid soluble.

Low molecular weight alcohols are water soluble. ↑ hydrocarbon chain length → ↓ water solubility.

Common reactions: oxidation, esterification.

Oxidation: primary alcohol → aldehyde → acid.

Secondary alcohol → ketone. Tertiary alcohol → not oxidized.

Stable on shelf. In vivo: oxidation, sulfation, glucuronidation.

Phenols

Aromatic compounds containing OH groups directly connected to aromatic ring. Monophenols → one OH. Catechols → two OH.

Phenol (carbolic acid): water soluble. ↑ ring substitution → ↓ water solubility. Most phenols are lipid soluble.

Common reactions: with strong bases to form phenoxide ion, esterification with acids, oxidation to form colored quinones.

On the shelf: oxidation with air or ferric ions.

In vivo: sulfation, glucuronidation, aromatic hydroxylation, o-methylation.

Ethers

General formula: R-O-R.

Lipid soluble. Partially water soluble. ↑ hydrocarbon chain → ↓ water solubility.

Common reaction: oxidation to form peroxides (may explode).

In vivo: o-dealkylation. Stability ↑ with size of alkyl group.

Aldehydes

General formula: R-CHO (contains a carbonyl group C=O).

Lipid soluble. Low molecular weight aldehytes are also water soluble.

Common reactions: oxidation (to acids, in vivo and in vitro) and acetal formation.

Ketones

General formula: R-CO-R (contains a carbonyl group C=O).

Lipid soluble. Low molecular weight ketones are also water soluble.

Nonreactive and very stable on the shelf.

In vivo: some oxidation or reduction.

Amines

Contain an amino group (-NH2). Primary (R-NH2), secondary (R1/R2-NH), tertiary (R1/R2/R3-N), quaternary (R1/R2/R3/R4-N+ X-).

Lipid soluble. Low molecular weight amines □ water solubility. ↑ branching → ↓ water solubility (primary amines and most soluble). Quaternary amines (ionic) and amine salts are water soluble.

Common reactions: oxidation (air oxidation on shelf), salt formation with acids. Aromatic amines are ↓ basic → ↓ reactive with acids.

In vivo: glucuronidatin, sulfation, methylation. Primary →oxidative deaminatin. Secondary → acetylation. Secondary / Tertiary → dealkylation.

Carboxylic acids

General formula: R-COOH (Carboxyl group –COOH).

Lipid soluble. Low molecular weight acid and Na/K salts → water soluble.

Common reactions: salt formation with bases, esterification, decarboxylation.

Very stable on shelf. In vivo: conjugation (with glucuronic acid, glycine, glutamine), beta oxidation.

Esters

General formula (R-COOR).

Lipid soluble. Low molecular weight esters are slightly water soluble.

Common reaction: hydrolysis to form carboxylic acid and alcohol (in vivo by esterases / in vitro).

Amides

General formula: R-CONH2 or R-CONR1/R2 (lactam form).

Lipid soluble. Low molecular weight amides are slightly water soluble.

No common reactions. Very stable on shelf.

In vivo: enzymatic hydrolysis by amidases in the liver.

BIOCHEMISTRY

Amino acid and proteins

Monomeric units of protein (peptide bonds). Formula: NH2-CH-R/-COOH.

Proteins are made of 20 AA, differ in R side chain (alpha (C)).

Protein hydrolysis to AAs by acids, bases, enzymes.

AA ionize (depending on pH) to zwitterions structure (NH3+-CH-COO-/R) → ↓ water solubility, ↑ melting point.

Levels of protein structure: primary, secondary (alpha/beta), Tertiarry, Quaternary.

Carbohydrates

Polyhydroxy aldehydes or ketones

Monosaccharides: simple single unit sugars, e.g., glucose, fructose.

Oligosaccharides: short chains of monosaccharides joined covalently, e.g. sucrose (has to convert into glucose, fructose before GI absorption), maltose (hydrolyzed by maltase into 2x glucose), lactose (milk sugar, has to convert into galactose, glucose before GI absorption).

Polysaccharides: long chains of monosaccharides, e.g., cellulose, glycogen.

Pyrimidines and purines

Bases → bond with ribose → nucleosides → bond with phosphoric acid → nucleotides → building blocks of nucleic acid.

Exhibit tautomerism (isomerism): can be keto or enol

Pyrimidines bases: cytosine, uracil, thymine.

Purine bases: adenine, guanine

DNA bases: thymine, cytosine, adenine, guanine

RNA bases: uracil, cytosine, adenine, guanine.

Biopolymers

Enzymes

Linked amino acid chains (proteins) → catalysts for biological reactions. They reactions' ↓ activation energy but do not change reaction equilibrium point, are used up or changed in the reaction. May require cofactors or coenzymes.

Cofactor: inorganic (metal ion) or nonprotein organic molecule.

Prosthetic group: cofactor firmly bound to apoenzyme (protein portion of a complex enzyme).

Coenzymes: organic cofactor that is not firmly bound but actively involved in catalysis. **Holoenzyme:** complete catalytically active enzyme system.

Lyases: removes functional group (deaminase, decarboxylase).

Ligases: bind two molecules (e.g. DNA ligase → 2 nucleotides).

Isomerases: change D→L, cis→trans, vice versa.

Polysaccharides

Also called **glycans.** Long chain polymers of carbohydrates.

Homopolysaccharides: Contains one type of monomeric units.

Starch → plant's reserve food, two glucose polymers (linear water soluble amylose, and branched water insoluble amylopectin), enzymatic hydrolysis → maltose (glucose disaccharide).

Glycogen → branched D-glucose chain, polysaccharide storage in animal cells (liver, muscles).

Cellulose → water soluble, in plant cell wall, linear D-glucose chain, can't be digested (hydrolyzed) by humans.

Heteropolysaccharides: contains two or more monomeric units.

Heparin → acid mucopolysaccharide with sulfate derivatives, contains glucosamine, in lung tissue, used to prevent clotting.

Hyaluronic acid → in bacterial cell wall, virteous humor, synovial fluid, contains glucosamine.

Nucleic acids

Linear polymers of **nucleotides** → pyrimidine and purine bases linked to ribose or deoxyribose sugars (**nucleosides**) and bound to phosphate groups.

Phosphodiester bonds: join successive DNA / RNA nucleotides.

DNA: compared to RNA it lacks an OH group and contains T rather than U. (D→T, R→U).

DNA: two complementary alpha helical strands coiled to form double helix. Hydrogen bonding between specific base pairs hold the strands together. **Hydrophobic bases** are on the inside of the helix. **Hydrophilic** deoxyribose phosphate on the outside.

Backbone: alternating phosphate and pentose units with a purine or pyrimidine attached to each.

Strong acids associated with cellular cations and basic proteins (histones, protamines).

rRNA (ribosomal): in ribosomes.

mRNA (messenger): the template for protein synthesis → specifies the polypeptide amino acid sequence.

tRNA (transfer): carries activated amino acids to ribosomes for incorporation to the growing polypeptide chain.

Biochemical metabolism

Factors affecting metabolism: substrate concentration, enzymes, allosteric (regulatory) enzymes, hormones, compartmentation.

Catabolism: degradation reactions that release energy for useful work (e.g. mechanical, osmotic, biosynthetic).

Anabolism: biosynthetic (build-up) reactions that consumer energy to form new biochemical compounds (metabolites).

Amphibolic pathways: may be used for anabolic or catabolic purposes. Example: **Krebs cycle,** it breaks down metabolites to release 90% of the organism's energy, but it also uses metabolites for form compounds such as AA.

Bioenergetics

Substrate level phosphorylation: forms one unit of ATP per unit of metabolite, no oxygen required.

Oxidative phosphorylation: forms 2 or more ATP per unit of metabolite. Uses oxidoreductase enzymes (e.g. dehydrogenases) using cofactors NAD (nicotinamide A dinucleotide) or FAD (flavin). Energy released from the reaction is used to form ATP in the mitochondria.

Carbohydrate metabolism

Catabolism: releases energy from carbohydrates.

Glycogenolysis: breakdown of glycogen into glucose phosphate in the liver, skeletal muscles → controlled by glucagon and epinephrine.

Glycolysis: breakdown of sugar phosphates (e.g. glucose, fructose, glycerol) into pyruvate (aerobically) or lactate (anaerobically) to produce energy (ATP)

Anabolism: consumes energy to build complex from simple molecules

Glycogenesis: formation of glycogen in the liver and muscles from glucose in diet → controlled by insulin.

Gluconeogenesis: formation of glucose from noncarbohydrate sources (e.g. lactate, pyruvate).

Krebs cycle

Location: in the mitochondria. Absent in RBCs (no mitochondria)

Catabolism: converts pyruvate (glycolysis), acetyl CoA (fatty acid degradation) and amino acids → into CO2 and water with release of energy. Oxygen dependent (aerobic).

Anabolism: forms amino acids (aspartate, glutamate) and heme ring from metabolites.

Electron transport: accept electrons and hydrogen from oxidation of Krebs cycle metabolites and couples the energy released to make ATP.

Lipid metabolism

Catabolism

Triglycerides stores in fat cells (adipocytes) are hydrolyzed by hormone-sensitive lipases into three fatty acids and glycerol

Fatty acids: broken down by beta oxidation to acetyl CoA → to Krebs cycle →breaks down to CO2, water and energy release.

Ketogenesis: very rapid break down of fatty acids leading to formation of ketone bodies (as in DM).

Glycerol: enters glycolysis → oxidized to pyruvate → to Krebs cycle → CO2 and water.

Steroids: may be converted to bile acids, vitamin D, hormones.

Anabolism

Fatty acids: formed in the cytoplasm. Unsaturation occurs I the mitochondria or endoplasmic reticulum. **Essential fatty acids:** linoleic acid (can not be synthesized, diet is only sources).

Terpenes: derived from acetyl CoA. Include: cholesterol, steroids, fat soluble vitamins (ADEK), bile acids.

Sphingolipids: forms a ceramide backbone with fatty acids. Joins with other compounds to form cerebrosides, sphingomyelin

Phosphatidyl compounds: i.e. phosphatidyl choline (lecithin), ethanolamine.

Nitrogen metabolism

Catabolism

Amino acids: amino group is removed by transaminase. Carbon skeleton is broken down to acetyl CoA or citric acid derivatives oxidized to CO2 and water for energy. Glycogenic amino acids form glucose as needed by guconeogenesis.

Purines: 90% is salvaged, 10% degrade to uric acid using xanthine oxidase.

Pyrimidines: breaks down to B-alanine, ammonia, CO2

Anabolism

Amino acids: from citric acid cycle intermediates.

Essential AA: TIM (threonine, isoleucine, methionine), HALL (histidine, arginine, lysine, leucine), PVT (phenylalanine, valine, tryptophan) → **PVT TIM HALL**

Purines / Pyrimidines: from aspartate, carbamoyl phosphate, CO2, other AA.

Nitrogen excretion

Excess nitrogen is toxic must be eliminated, mainly as urea.

Urea synthesis: in the liver using the **Krebs-Henseleit pathway.** Amino acid → AA transferases (transaminases) + pyridoxine (vitamin B6) as coenzyme → Ammonia → + glutamate → glutamine → + CO2 → carbamoyl phosphate → urea cycle → urea.

Uric acid synthesis: most purines are salvages. Remaining purines are excreted as uric acid.

9. MICROBIOLOGY

Taxonomy and nomenclature

Taxonomy

Classification or ordering into groups based on degree of relatedness.

Bacteria are named using the Linnaean or binomial system (*genus species = homo sapiens = human)*

Morphology

Cultural morphology

Based on size, shape and texture or colonies grown inj axenic (pure) cultures

Each colony originates from a Colony Forming Unit (CFU) consisting of a single cell or group of adherent cells

Microscopic morphology

Based on size, shape and arrangement of bacterial cells

Stains

Bacteria are small and transparent → must be stained to be examined by light microscopy

Simple

Single dye colors the cells (e.g. gentian violet, safranin)

Gram

Gram-positive *= purple*

Gram-negative = *pink*

Acid-fast

Stains only cells that have an outer layer of a waxy lipid (acid-fast) not those lacking that layer (non acid-fast)

Spore

Heat is used to facilitate the dye entering the spore

Capsule

Two dyes stain the cell and backgrounds allowing the visualization of the unstained capsular material

Bacterial cell shape and arrangement

Cocci (spherical)

-Chains (streptococci) -Pairs / diplococci (streptococcus pneumoniae)

-Clusters (staphylocci) -Packets

Bacilli Cylindrical rod-shaped (pseudomonads, Escherichia)

Coccobacilli (combination of small rods or flattened cocci)

Spirochetes (helical like a corkscrew)

Fusobacteria (tapered ends and slightly curved)

Filamentous (organisms are branching)

Vibrios (comma shaped)

Pleomorphic (exist in varied forms)

Other parameters

Presence or spores, capsules or slime layers

Mobility or type of flagella

Monotrichous = single flagella at either pole

Amphitrichous = flagellum at both poles

Lophotrichous = flagella at either or both poles

Peritrichous = flagella distributed evenly all around

Structure of the prokaryotic cell

Overview

Small and simple in design

Less complex inside, more complex outside

Lack a true nucleus, nuclear membrane or intracytoplasmic membraneous organelles (e.g., endoplasmic reticulum)

Cytoplasm is immobile (no endo or exocytosis)

Multiply asexually by binary fission (no mitosis)

Protein synthesis mediated by 70s not 80s ribosomes

Genetic material□single supercoiled circular strand of DNA **(nucleoid)**

12. PRINCIPLES OF PHARMACODYNAMIC / MEDICINAL CHEMISTRY

Effects of drugs

Drug action is the results of interaction between drug molecules and cellular components (receptors) → modulate ongoing cellular processes → alteration of function.

Drug receptor: any macromolecular component

Physiological receptors: receptors for endogenous ligands. Example: adrenergic receptors for catecholamines.

Agonist: drugs that resemble the effects of endogenous molecules. Example: bethanechol stimulates cholinergic receptors.

Pharmacologic antagonists: drugs that lack intrinsic activity and produce effects by ↓ action of endogenous molecules at receptors. **Competitive:** propranolol competes with catecholamines at beta receptors. **Noncompetitive:** MAO irreversible inhibitor tranylcypromine.

Partial antagonist: inhibits endogenous ligand from binding to the receptor but has some intrinsic activity. Example: nalorphine on opiate receptors.

Physiological antagonism: drug acts independently at different receptor to produce opposing action. Example: epinephrine and acetylcholine.

Neutralizing antagonism: two drugs bind to each other to form inactive compound. Example: digoxin-binding antibody sequesters digoxin.

Mechanisms of drug action

Cell surface receptors: can be proteins, glycoproteins or nucleic acids. Can be located at the cell surface, cytoplasm, or inside the nucleus. Receptor binding is very specific. Interactions: van der Waals, ionic, hydrogen, covalent → influence duration and reversibility of drug action. Interaction depends on chemical structure of drug and receptor.

Signal transduction by cell-surface receptors: drug receptor binding triggers signal through second messenger or effector in the cycoplasm. Example: isoproterenol binds beta receptor (coupled to adenylate cyclase via stimulatory G protein) →↑ cAMP. Second messengers may cause change in protein synthesis.

Signaling mediated by intracellular receptors: drugs bind to soluble DNA-binding protein cytoplasmic receptors → regulate gene transcription. Examples: thyroid hormone, steroid hormones, vitamin D, retinoids.

Target cell desensitization / hypersensitization: cellular protective mechanisms exist to maintain homeostasis and prevent overstimulation / understimulation of target cells. **Down regulation:** occur due to continuous prolonged drug exposure → ↓ receptor #. **Desensitization:** is the result of down regulation. Effect of subsequent drug exposure is ↓. Example: chronic albuterol use → down regulation of beta receptors → tolerance. **Heterogenous desensitization:** nonspecific desensitization by altering components of the signaling pathway. **Hyperactivity/hypersensitivity:** due to long term exposure to antagonists followed by abrupt cessation → new receptor synthesis → upregulation.

Pharmacologic effects not mediated by receptors: Colligative drug effects lack requirement for specific structures. Examples: volatile general anesthetics are lipophilic → interact with cell membrane lipid bilayer → ↓ excitability. Cathartics (mg sulfate, sorbitol) → ↑ osmolarity of intestinal fluids. **Antimetabolites:** structural analogs of endogenous compounds → incorporated into cellular components, examples: methotrexate, 5-fluorouracil, cytarabine. **Antacids:** such as Al hydroxide, Ca carbonate, Mg hydroxide act by ionic interaction to ↓ gastric acidity

Concentration-effect relationship

↑ dose → ↑ concentration at site of action → ↑ effect → up to a ceiling.

Quantal dose-response curve: # of patients exhibiting a defined response by specific drug dose. Bell shaped.

Graded dose-response curve: magnitude of drug effect vs. drug dose.

Efficacy is measured by the maximum effect.

Potency compared different molar doses of different drugs needed to produce the same effect.

Log dose-response curve: drug effect vs. log dose. Used to compare efficacy and potency of different drugs with same mechanism of action (same slope). **Efficacy;** determined by the height of the curve (Emax). **Potency**: compared using ED50 (dose producing 50% of Emax). **Competitive antagonist:** parallel shift to the right, same Emax is achieve but at ↑ dose. **Noncompetitive antagonist:** nonparallel shift to the right, lower Emax (action cannot overcome if more agonist is present).

Enhancement of drug effect

Addition: two different drugs with same effect → cumulative effect. Example: trimethoprim and sulfamethoxazole inhibit two different steps in folic acid synthesis → ↓↓ bacterial growth.

Synergism: two different drug with same effect → effect is ↑ than cumulative sum. Example: penicillin and gentamicin against pseudomonas.

Potentiation: one drug with no effect alone will ↑ effect of another active drug. Example: carbidopa (inactive dopa analog) ↓ degradation of levodopa.

Selectivity of drug action

Therapeutic index: TD50/ED50 (median toxic dose / median effective dose).

Margin of safety: minimum toxic dose for 0.1% of population (T_D 0.1) / minimum effective dose for 99.9% of population (E_D99.9). More practical

Drug sources and major classes

Natural products

Alkaloids (x-ine): plant-derived nitrogen containing compounds. Alkaline. Examples: morphine (opium poppy), atropine (belladonna), colchicine (autumn crocus, neutral).

Peptides / polypeptides: polymers of amino acids. From humans or animals. Smaller than proteins. No oral activity, short half life. Example: somatostatin, glucagon.

Steroids: from humans or animal. Estradiol, testosterone, hydrocortisone.

Hormones: chemicals formed in one organ and carried in the blood to another. Mostly steroids or proteins. Made synthetically, by recombinant DNA (insulin) or from animals (thyroid, conjugated estrogens).

Glycosides: sugar moiety bound to non-sugar (aglycone) moiety by glycosidic bond. From plant (digitoxin) or microbial (streptomycin, doxorubicin).

Vitamins: Water soluble: B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B12 (cyanocobalamin), C (ascorbic acid), folic acid, pantothenic acid, H (biotic).

Lipid soluble: A (retinol), D (ergocalciferol), E (alpha-tocopherol), K (phytonadione).

Polysaccharides: polymers of sugar from animals or humans (heparin).

Antibiotics: penicillin, tetracycline, doxorubicin.

Synthetic products

Drugs synthesized from organic compounds. May have chemical structure resembling active natural products (hydroxymorphone → morphine, ampicillin → penicillin).

Peptidomimetics: molecules with no peptide bonds, molecular weight < 700, activity similar to original peptide (e.g. losartan).

Drug action and physiochemical properties

Drugs must enter and be transported by body fluids. Drugs must pass membrane barriers, escape ↑ distribution to site of loss, penetrate to active site, be removed from active site, metabolized to a form easily excreted.

Drug polarity: relative measure of lipid and water solubility. Measured in **Partition Coefficient:** ratio of solubility in organic solvent to solubility in aqueous solvent (log value).

Water solubility: depends on ionic character and hydrogen ion bonding. Nitrogen and oxygen containing functional groups → ↑ water solubility. Required for GI dissolution, parenteral solutions, ophthalmic solutions, good urine concentration.

Lipid solubility: ↑ by nonionizable hydrocarbon chains and ring systems. Required for penetrating GI lipid barrier, penetrating BBB, IM depot injectables.

Ionization constant (Ka): indicates the relative strength of acids and bases. Expressed in negative log **(pKa).**

Strong acids: HCl, H2SO4, HNO3 (nitric), HC|O4 (perchloric), HBr, HIO3 (iodic).

Strong bases: NaOH, KOH, MgOH2, CaOH2, BaOH2, quaternary ammonium hydroxides.

Weak acids: organic acids containing carboxylic (-COOH), phenolic (Ar-OH), sulfonic (-**SO2**H), sulfonamide (-**SO2**NH-R), imide (-**CO**-NH-**CO**-), beta carbonyl (-**CO**-CHR-**CO**-) groups.

Weak bases: organic bases containing amino groups (1ry –NH2, 2ry -NHR, 3ry –NR2) and saturated heterocyclic nitrogen. Aromatic or unsaturated heterocyclic nitrogen are very weak bases → do not form salts.

Le Chatelier's priniciple governs ionization (weak acid at ↓ pH → ↓ ionization → cross lipid membranes).

Rule of nines: |pH-pKa|=1 → 90:10 (1 nine), |pH-pKa|=2 → 99:1 (2 nines).

Salts: virtually all salts are strong electrolytes. **Inorganic salts:** made by combining drugs with inorganic acids or bases (HCl, NaOH). Salt form has ↑ water solubility □ ↑ dissolution. **Organic salts:** made by combining acidic and basic organic molecules →↑ lipid solubility → depot injections (e.g. penicillin procaine).

Amphoteric salts: contain acidic and basic functional groups → form internal salts or zwitterions → solubility problems.

Neutralization reaction: e.g., occur when an acidic solution of an organic salt is mixed with a basic solution. The nonionized organic acid or base will ppt → IV drug incompatibility.

Drugs whose cation ends with **–onium** or **–inium** and anoic is Cl, Br, I, nitrate, sulfate (e.g. benzalkonium chloride, cetylpyridinium chloride) are quaternary ammonium salts → neural solution in water.

Structure and pharmacologic activity

Drug structure specificity

Structurally non-specific drugs: drug interaction with cell membrane depends more on the drug's physical properties than on its chemical structure. Interaction usually depends on cell membrane's lipid nature and drug's lipid attraction. Examples: general anesthetics, some hypnotics, some bactericidal agents.

Structurally specific drugs: pharmacologic activity depends on drug binding to specific endogenous receptors.

Drug receptor binding

Receptor site theories: Lock-key theory: over-simplification that assumes a complete complementary relationship between drug and receptor. **Induced fit theory:** also assumes a complete complementary relationship between drug and receptor but provides for mutual conformational changes between drug and receptor, it can explain phenomenon of allosteric inhibition. **Occupational theory of response:** further postulates that intensity of pharmacologic response is proportional to number of occupied receptors.

Receptor site binding: ability of a drug to bind to specific receptor is mostly determined by its chemical structure not physical properties. Chemical reactivity influences its bonding ability and exactness of fit to the receptor. **Drug interaction** is similar to fitting a jigsaw puzzle pieces, only drugs of similar shape and chemical structure can bind and producer response. Usually only a portion of the drug molecule is involved in receptor binding. **Pharmacophore:** functional group that is critical for receptor interaction. Drugs with similar pharmacophores may have similar qualitative but not quantitative activity. **Agonist:** good receptor fit → ↑ affinity → ↑ response. **Antagonist:** drug with some binding but no pharmacophore → no response but it blocks other drugs from binding.

Stereochemistry

Types of stereoisomers: optical, geometric, conformational.

Optical isomers: contains at least one chiral (asymmetric) carbon (four different substitutes).

Enantiomers: optical isomers that are mirror image of each other, identical physical and chemical properties, potentially different potency, receptor fit, activity, metabolism, etc. One enantiomer rotate the plane of polarized light clockwise (dextro, D, +), the other counter clockwise (Levo, L, -).

Example: dextrorphanol → narcotic analgesic and antitussive, levorphanl → only antitussive. **Racemic mixture:** equal mixgture of D and L enantiomers, optically inactive.

Diastereomers: stereoisomers which are neither mirror image, nor superimposable. Drug must have a minimum of 2 chiral centers. Different physicochemical properties (solubility, volatility, melting point).

Epimers: special type of diastereomers, compounds are identical in all aspects except stereochemistry around one chiral center. Epimerization is important for drug degradation and inactivation.

Geometric (cis-trans) isomers: occurs due to restricted rotation around a chemical bond (double bond, rigid ring system). Cis-trans are not mirror images, have different physicochemical and pharmacologic properties, because functional groups can be separated by different distances → not equal fit to receptors. If functional groups are pharmacophores → different biologic activity. Example: cis-diethylstilbestrol has 7% estrogenic activity of trans-diethylstilbestrol.

Conformational isomers (rotamers, conformers): non-superimposable molecule orientations due to atoms rotation around single bonds. Common for most drugs, allows drugs to bind to multiple receptors.

Bioisosteres: molecules containing groups that are spatially and electronically equivalent, same physicochemical properties.

Isosteric replacement of functional groups → alter metabolism → Δ potency, SE, activity, duration of action (e.g. procainamide, an amide, has longer duration of action than procaine, an ester).

Isosteric analogs: may act as antagonists (e.g. alloxanthine is a xanthine oxidase inhibitor, compared to its isostere, xanthine, the enzyme substrate).

Mechanisms of drug action

Interaction with receptors

Agonists: have both affinity and intrinsic activity with the receptor.

Partial agonists: interact with same receptors but with similar affinity but lower intrinsic activity → ↓ response.

Pharmacologic antagonists: bind to the same receptor as the agonist but with no intrinsic activity. Can be reversible, irreversible, competitive, noncompetitive (like enzyme inhibitors).

Chemical antagonists: two compounds react → inactivation of both. Example: heparin (acidic polysaccharide) with protamine (basic protein), chelating agents as metal poisoning antidotes (EDTA for calcium / lead, penicillamine for copper, dimercaprol for mercury / gold / arsenic).

Functional / physical antagonists: produce antagonistic physiologic actions by binding at separate receptors. Example: acetylcholine, NorEpinephrine.

Interaction with enzymes

Activation

Due to ↑ enzyme protein synthesis.

Examples: barbiturates, antiepileptics (phenytoin), rifampin, antihistamines, griseofulvin, oral contraceptives.

Mechanism: by allosteric binding or coezymes such as vitamins (esp vitamin B complex), cofactors (Na, Mg, Ca, Zn, Fe).

Inhibition

Due to interaction with the apoenzyme, coenzyme or enzyme.

Reversible inhibition: results from non-covalent interaction. Equilibrium exists between bound and free drug.

Irreversible inhibition: results from covalent stable interaction.

Competitive inhibition: occurs when there is a mutually exclusive binding of the substrate and inhibitor.

Noncompetitive inhibition: occurs when the drug binds to an allosteric site on the enzyme.

Interaction with DNA/RNA

Inhibition of nucleotide biosynthesis: caused by folate, purine, pyrimidine antimetabolites.

Folic acid analogs: e.g. methotrexate, trimetrexate, ↓ dihydrofolate reductase → ↓ purine, thymidylate.

Purine analogs: e.g. 6-mercaptopurine, thioguanine, act as antagonists in the purine bases synthesis.

Pyrimidine analog: e.g. 5-fluorouracil, ↓ thymidine synthase.

Inhibition of RNA/DNA biosynthesis: due to interference with nucleic acid synthesis. Use mainly as antineoplastic agents (Cancer chapter).

Inhibition of protein synthesis

Tetracyclines: ↓ tRNA binding to ribosomes and block release of completed peptides from ribosomes.

Erythromycin, chloramphenicol: bind to ribosomes, ↓ peptidyl transferase, ↓ formation of peptide bond, ↓ peptide chain formation

Aminoglycosides: binding to ribosomes → formation of abnormal protein, ↓ addition of AAs to peptide chain, misreading of mRNA tempelate → incorporation of incorrect AAs in peptide chain.

Interaction with cell membranes

Digitalis glycosides: ↓ cell membrane Na-K pump → ↓ K influx, ↓ Na outflow.

Quinidine: prolong polarized and depolarized states of membrane potential in myocardial membranes.

Local anesthetics: interfere with membrane permeability to Na-K → block impulse conduction in nerve cell membranes.

Polyene antifungals: e.g. nystatin, amphotericin B, alter membrane permeability.

Antibiotics: e.g. polymyxin B, colistin, alter membrane permeability

Acetylcholine: ↑ membrane permeability to cations.

Proton pump inhibitors: ↓ H+/K+ pump in parietal cell membranes □ ↓ efflux of protons to the stomach.

Nonspecific action

Form monomolecular layer over entire areas of cells. Large dose is given. Examples: volatile general anesthetic gases (ether, nitrous oxide), some depressants (ethanol, chloral hydrate), antiseptics (phenol, rubbing alcohol).

17. DRUG METABOLISM AND INTERACTIONS

Drug metabolism

Definition: drug metabolism (or biotransformation) is the biochemical changes drugs an foreign chemicals (xenobiotics) undergo in the body leading to formation of metabolites.

Inactive metabolites: examples: hydrolysis of procaine to p-aminobenzoic acid, oxidation of 6-mercaptopurine to 6-mercapturic acid.

Metabolites with similar activity: examples: codeine is demethylated to morphine (↑ activity), acetohexamide is reduced to l-hydroxyhexamide (↑ activity), imipramine demethylated to desipramine (same activity).

Metabolites with altered activity: retinoic acid (vitamin A) is isomerized to anti-cancer agent isoretinoic acid, antidepressant iproniazid is dealkylated to anti-TB isoniazid.

Bioactivated metabolites (prodrugs): enalapril hydrolyzed to enalaprilat, suldinac is reduce to the active sulfide, levodopa is decarboxylated to dopamine.

Biotransformation pathways

Phase I reactions

Polar functional groups are introduced to the molecule, or unmasked by oxidation, reduction, hydrolysis.

Oxidation:

Most common reaction. Mostly in the liver. Catalyzed by cytochrome P450.

Cytochrome P450: oxidases, bound to smooth endoplasmic reticulum, require NADH, exist in multiple isoforms (CYP11Ax, CYP17By, etc) → large # of substrates. Involved in metabolism or bile acids, steroids, xenobiotics / drugs.

Oxidized drug → ↑ polarity / water solubility → ↓ tubular reabsorption → ↑ urine excretion.

Reduction

Same goal as oxidation (↑ polarity by reductases).

GI bacterial flora → azo and nitro reduction reactions.

Enzymatic hydrolysis

Addition of water across a bond → ↑ polar metabolites.

Esterase: present in the plasma and tissues, nonspecific, hydrolyzes esters to alcohol and acid, responsible for activation of many prodrugs. Example: procaine.

Amidase: hydrolyze amides into amines and acid (deamidation) in the liver. Example: procainamide.

Phase II reactions

Functional groups of the original drug or a phase I metabolite are masked by a conjugation reaction → ↑↑ polar metabolites → ↑ excretion, no crossing of cell membranes (pharmacologically inactive, no toxicity).

Conjugation reactions: combine parent drug (or metabolite) with certain natural endogenous constituents (glucuronic acid, glutamine, glycine, sulfate, glutathione). Requires high energy molecule and an enzyme.

High energy molecule: consist of coenzyme bound to endogenous substrate, parent drug, or metabolite.

Enzyme: called transferases, found in the liver and catalyze the reaction.

Glucuronidation: most common conjugation pathway due to large supply of glucuronic acid (high energy form reacts using glucuronyl transferase).

Common with OH group (form ethers) and COOH group (form esters). Reaction adds 3-OH groups and 1-COOH group → ↑↑ hydrophilicity.

Glucuronides with ↑ MWt → bile excretion → to intestines → intestinal beta-glucuronidase hydrolyze the conjugate → reabsorption.

Sulfate conjugation: using sulfo-transferase.

Amino acid conjugation: reaction of glycine or glutamine with aliphatic or aromatic acids to form amides using N-acyltransferase.

Glutathione conjugation: very critical for preventing toxicity from harmful electrophilic agents (halides, epoxides). Glutathione (tripeptide) + electrophile + glutathione S-transferase → mercapturic acid.

Methylation: of oxygen- nitrogen- or sulfer-containing drugs → less polar but inactive metabolites. Example: COMT methylates catecholamines such as epinephrine.

Acetylation: → less polar metabolites with N-acetyl-transferase. Metabolites (e.g. of sulfonamides) may accumulate in the kidney → crystalluria / tissue damage.

Factors influencing metabolism

Species differences

Qualitative differences: occur mainly in Phase II reactions. Determines the actual metabolic pathway. It can result from a genetic deficiency of a particular enzyme or difference in a particular endogenous substrate.

Quantitative differences: occur mainly in phase I reactions. Due to difference in the enzyme level, presence of species specific isozymes, amount of endogenous inhibitor or inducer, extent of competing reactions.

Physiologic / disease state

Due to pathologic factors that alter liver function.

Congestive heart failure: ↓ output→ ↓ hepatic blood flow → ↓ metabolism

Δ albumin production → fraction of bound drug.

Genetic variations

Acetylation rate: depends on the amount of N-acetyl-transferase, which depends on genetic factors.

Fast acetylators → ↑ hepatotoxicity from isoniazid.

Slow acetylators → ↑ other isoniazid SE.

PM Phenotype: ↓ metabolism of B-blockers, antiarrhythmics, opioids, antidepressants.

Drug dosage

↑ dose → may saturated metabolic enzymes. As the saturation approaches 100% → change from first to zero-order metabolism.

When metabolic pathway is saturated > possible alternative pathways. Example: therapeutic APAP doses → glucuronic / sulfate conjugation, toxic doses → conjugation is saturated → N-hydroxylation → liver toxicity

Nutritional status

Conjugation agent levels (sulfate, glutathione) is dependent on nutrition

↓ protein diet → ↓ glycine, ↓ oxidative drug metabolism capacity.

Diet ↓ in essential fatty acids (linoleic acid) → ↓ synthesis of certain enzymes → ↓ metabolism of hexobarbital.

Diet ↓ in minerals (Ca, Mg, Zn) → ↓ metabolism. ↓ Fe → ↑ metabolism.

Diet ↓ in vitamins (A, B, C, E): ↓ C → ↓ oxidation. ↓ E → ↓ dealkylation, hydroxylation.

Age

Metabolic enzyme systems are not fully developed at birth → ↓ doses in infants / children to avoid SE, especially for glucuronide conjugation.

Older children → liver develops faster than ↑ in body weight → ↓ efficacy.

Elderly → ↓ metabolizing enzymes → ↓ elimination → ↑ Cp → ↑ SE

Gender

Due to Δ androgen, estrogen, adrenocorticoid activity → Δ CYP450 isozymes.

Example: oxidative metabolism is faster in men.

Administration route

Oral: first-pass effect → ↑ oral dose

IV: by pass first-pass effect → ↓↓ dose compared to oral dose.

Sublingual / rectal: also bypass first-pass effect. Variable absorption from rectal administration.

Chemical structure

Presence of certain functional groups influences drug's metabolic pathway (route, extent, degree of metabolism).

Circadian rhythm

Nocturnal Cp of theophylline, diazepam are ↓ than diurnal Cp.

Extra-hepatic metabolism

Plasma: contains esterases (hydrolyze esters). Simple esters (procaine, succinyl choline) are rapidly hydrolyzed in the blood. Esterases can also activate prodrugs.

Intestinal mucosa: microsomal oxidation, conjugation (glucuronide, sulfate) first pass effect of lipid soluble drugs during absorption.

Intestinal bacterial flora: secrete metabolizing enzymes.

Ulcerative colitis → ↑ flora. Diarrhea, antibiotics → ↓ flora. Flora secrete beta glucuronidase → hydrolyze polar glururonide conjugates of bile → reabsorption of free nonpolar bile acids → eneterohepatic circulation. Flora convert vitamin K to active form, and cyclamate (sweetener) to cyclohexylamine (carcinogen). Flora produce

azoreductase → converts sulfasalazine to 5-aminosalicylic acid (anti-inflammatory) and sulfapyridine (antibacterial).

Stomach acidity: degradation of penicillin G, carbenicillin, erythromycin, tetracycline, peptides / proteins (insulin).

Nasal mucosa: ↑ CYP450 activity and metabolism on nasal decongestants, anesthetics, nicotine, cocaine.

Lung: first pass metabolism of IV, IM, transdermal, SC drugs but to ↓ degree than the liver. Also, second pass metabolism for drugs leaving the liver.

Placenta: if drug is lipid soluble enough to get to circulation → pass through the placenta too. Placenta is not a physical or metabolic barrier to xenobiotics. Very little metabolism occurs. Smoking induce certain enzymes in pregnant women ↑ carcinogens from polycyclic HC.

Fetus: depends on fetal age, ↓↓ glucuronic acid conjugation.

Chloramphenical → ↓ glucuronidation → **gray baby syndrome**. ↓ bilirubin glucuronide → neonatal hyperbilirubinemia.

Strategies to manage metabolism

Pharmaceutical

Sublingual tablets: deliver drugs directly to systemic circulation, bypassing hepatic first pass metabolism. Example: nitroglycerin.

Transdermal products: continuous drug supply for long period of time. Example: nitroglycerin.

IM depots: continuous drug supply for long period of time. Example: highly lipid soluble esters of esradiol (benzoate) and testosterone (enanthate) slow absorption and activation by hydrolysis.

Enteric coated tablets: protect acid sensitive drugs. Examples: omeprazole, erythromycin, methenamine.

Nasal administration: for lung delivery of peptides (e.g. calcitonin salmon) which has no oral bioavailability. Lung contains protease inhibitors → peptide stability.

Pharmacologic

Levodopa (L-dopa): amino acid precursor of dopamine (for Parkinson's). Unlike dopamine, it can penetrate BBB and reach CNS to be decarboxylated to dopamine.

Carbidopa: DOPA decarboxylase inhibitor that does not cross BBB → ↓ peripheral activation and SE.

Beta-lactam AB: use clavulanic acid (a beta-lactamase inhibitor).

Ifosfamide: alkylating agent → in vivo metabolic activation → nitrogen mustard.

Acrolein is a byproduct of metabolic activation react with nucleophiles on renal proteins → hemorrhagic cystitis. Combine ifosfamide. with **mesna** (neutralizes acrolein in the kidney).

Chemical

Testosterone: not orally active due to rapid oxidation of 17-OH group.

Methyl-testosterone: 17alpha-methyl group → ↓ potent but no rapid first pass metabolic deactivation → used orally. Same for estradiol analogs.

Tolbutamide: oxidation of para-methyl group → rapid deactivation.

Chlorpropamide: non-metabolizable para-chloro group → long t1/2.

Isoproterenol: potent beta agonist for asthma. Rapid metabolism by COMT (catechol) → poor oral activity.

Metaproterenol: not metabolized by COMT → orally active, long t1/2.

Octreotide: synthetic octa-peptide → ↓ severe diarrhea in tumors, SC. It mimics action of somatostatin (14-AA peptide, short t1/2, only IV infusion) but resistant to hydrolysis, proteolysis.

Prodrugs

Require in vivo biotransformation (phase I) to produce activity

The following are potential advantages for prodrugs:

↑ **water solubility**

Useful for ophthalmic and parenteral formulations

Example: sodium succinate esters, sodium phosphate esters to make water-soluble steroid prodrugs

↑ **lipid solubility**

↑ **duration of action:** estradiol lipid-soluble esters (benzoate, valerate, cypionate) →prolonged activity (IM of esters in oil).

↑ **oral absorption:** by converting carboxylic acid groups to esters → converted back to active acids by plasma esterases. Example: lipophilic orally absorbed enalapril → very potent orally inactive enalaprilat.

↑ **topical absorption:** of steroids by masking hydroxyl groups as esters or acetonides → ↓ polar → ↑ dermal permeability. Examples: triamcinolone acetonide, betamethosone valerate, diflorasone diacetete.

↑ **palatability:** sulfisoxazole acetyl (ester, ↓ water solubility, ok taste for children) → sulfisoxazole (bitter)

↓ **GI irritation**

NSAIDs → ulceration by direct irritant effect of acidic molecules and ↓ of gastro-protective PG. Sulindac, nabumetone → prodrugs with ↓ GI effect

Site specificity

Methyldopa: structurally similar to L-dopa → transported to CNS → metabolized to active alpha-methyldopamine → central alpha-2 agonist

Omeprazole: activated at acidic pH < 1 →inhibition of H+/K+ATPase.

Formaldehyde: effective urinary tract antiseptic. Orally □ ↑ toxicity. Methenamine → non-toxic prodrug → hydrolyzes to formaldehyde and ammonium ions in acidic urine (pH<5.5). Use enteric coating to prevent activation in the stomach.

Olsalazine: polar dimer of 5-aminosalisalyic acid →poor oral absorption. In large intestine → colonic bacteria cleave azo bond → free active.

Diethylstilbestrol: synthetic estrogen for prostate cancer → feminizing SE. Diethylstilbestrol diphosphate (ester prodrug) → activated by acid phosphatase in prostate tumor cells → ↑ local action, ↓ systemic SE.

↑ **shelf-life**

Cefamandole: 2nd generation cephalosporin, unstable in solid dosage forms. Cefamandole nafate: stable formic acid ester → hydrolyzed by plasma esterases.

Cyclophosphamide: stable prodrug → in vivo oxidation + nonenzymatic decomposition → active phosphoramide mustard.

Drug interactions

Types of interactions: drug-drug, drug-food, drug-chemical, drug-laboratory.

Precipitant: drug, food or chemical causing the interaction.

Object: drug affected by the interaction.

Epinephrine, erythromycin → decompose in IV alkaline pH → do not mix with aminophylline (alkaline).

PK interactions

Due to Δ in absorption, distribution (protein / tissue binding), elimination (excretion / metabolism).

Absorption

Epinephrine (vasoconstrictor) → ↓ percutaneous absorption of lidocaine (local anesthetic).

CHF → ↓ GI blood flow → ↓ drug absorption

MAO inhibitors + foods w/ tyramine→↓ metabolism→ hypertensive crisis

Antibiotics (erythromycin) → ↓ intestinal flora → ↓ digoxin microbial deactivation → ↑ bioavailability.

Antacids / H2 antagonists → ↑ GI pH → ↓ ketoconazole dissolution

Δ intestinal motility (anticholinergics → ↓, laxatives → ↑) → Δ absorption

Cholestyramine / kaolin → digoxin adsorption → ↓ bioavailability

Complexation by divalent cations → ↓ tetracycline bioavailability

Distribution

Due to Δ in plasma protein binding / displacement or tissue / cellular interactions.

Valproic acid displaces **phenytoin** and ↓ its liver metabolism → ↑↑ phenytoin.

Quinidine displaces **digoxin** and ↓ digoxin clearance → ↑↑ digoxin.

Elimination / clearance

Due to Δ in kidney or liver clearance (enzyme induction / inhibition, enzyme substrate competition, Δ blood flow) .

Grapefruit juice is a powerful inhibitor of CYP3A4.

Enzyme inducers: tobacco (polycyclic aromatic HC), barbiturates, rifampin, carbamazepine, phenytoin, omeprazole, troglitazone.

Enzyme inhibitors: cimetidine, ketoconazole, ciprofloxacin, erythromycin, ritonavir / nelfinavir, clopidrogel.

Food-drug interactions

Δ drug absorption. Example: Complexation of tetracycline + calcium

Delayed/ ↓ absorption: NSAIDs, APAP, antibiotics, ethanol.

↑ absorption: griseoflulvin, metoprolol, phenytoin, propoxyphene

Chemical-drug interactions

Smoking (enzyme induction) → ↑ clearance of theophylline, BZD, TCA

Alcohol: acute use → ↓ metabolism, chronic use □ ↑ metabolism.

PD interactions

Antagonistic, additive or synergistic effect.

Similar action → excessive or toxic response.

Example: alcohol + antihistamine → both CNS depressants, promethazine + antihistamine → both anticholinergic.

Thiazide diuretic → deplete potassium → ↑ sensitivity to digoxin, deplete sodium → ↑ lithium toxicity, anticoagulant + aspirin → ↑ risk of bleeding.

Significance and management of interactions

Potential drug interactions

Multiple-drug therapy: including Rx and OTC. ↑ → ↑ potential.

Multiple prescribers: different prescribers are not aware of history

Patient compliance: example: tetracycline not on empty stomach.

Patient risk factors: elderly at ↑ risk (Δ body composition, GI transit, drug absorption, distribution, ↓ protein binding, ↓ drug clearance). Patients with diseases (DB, AIDS, etc) and atopic (hyper-responsive) patients are at ↑ risk.

Clinical significance

Not all interactions are dangerous. Interacting drugs can be prescribed under supervision with monitoring. Example: cimetidine with antacids → do not take both at the same time

Some interactions are good → ↑ efficacy, ↓ SE.

Examples: trimethoprim + sulfamethoxazole (↑ efficacy in UTI), amoxicillin + clavulanate potassium (beta lactamase inhibitor → ↑ spectrum), hydrochlorothiazide + enalapril (balance potassium), penicillin + probenicid (↓ tubular secretion, ↑ t1/2), saquinavir + food (↑ absorption).

Likelihood: established, probable, suspected, possible, unlikely

Consider dose side and duration, interaction onset / severity.

Management of drug interactions

Review patient profile: drug history and risk factors

Avoid complex therapeutic regimens

Determine probability of a significant interaction

Suggest alternatives: APAP not aspirin for headache with warfarin

Monitor SE. Monitor prothrombin time if warfarin is given with sulfonamides (may be prolonged).

Re-evaluate profile when changing therapy. Example: if d/c a thiazide diuretic → d/c potassium supplement also.

20. DRUG INFORMATION RESOURCES

(FOR IMPORTANT MCQs)

Drug Information Resources

Primary (Journals)

Benefits: most current source, learn from case studies, new developments, ↑ communications with professionals / consumers, CE credits, prepare for board certification exams.

Limitations: information is not always 100% accurate.

Secondary (abstracts / indexes)

Benefits: enable quick and selective screening of primary literature for specific information. May have enough info to answer the question.

Limitations: only finite number of journal reviewed, lag time between article publication and citation in the index, usually good only to locate the original article (no full answers),

contain only interpretations / description of the study which may be misleading (not whole story).

Tertiary (textbooks)

Benefits: easy and convenient access to large number of topics, include background information on drugs / diseases, validity and accuracy of information can be verified by using references.

Limitations: may take years to publish information may be outdated, chapter author may not have done a thorough literature search, author may have misrepresented the original article.

Considerations: author, publisher, edition, year of publication, scope, presence of bibliography.

Internet

Benefits: expanded searching capabilities, most useful for company specific information, issues currently in the news, alterative medicine, government information.

Limitations: may not be peer reviewed or edited, not always reliable (evaluate source).

Strategies for evaluating information requests

Talk with the inquirer

Determine reason for inquiry: news-related question, medical condition

Clarify drug ID / availability: correct name spelling, generic vs. brand, manufacturer, country, Rx vs. OTC, under investigation drug, dosage form, purpose for use.

Identify / assess product / resource availability

US drugs: American Drug Index, Drug Facts and Comparisons, Drug Topics Red Book, PDR, Martindale the Extra Pharmacopoeia, American Hospital Formulary Service

Foreign drugs: Martindale the Extra Pharmacopoeia, Index Nominum, US Adopted Names, USP Dictionary of Drug Names.

Investigational drugs: Martindale the Extra Pharmacopoeia, Drug Facts and Comparisons, Unlisted Drugs, NDA Pipeline.

Orphan drugs: for rare disease affected < 200,000 people → cost of development is unlikely to be offset by sales → FDA offers assistance and financial incentives to

encourage development. Drug Facts and Comparisons, National Information Center for Orphan Drugs and Rare Diseases (NICODARD).

Unknown drugs: are drugs on hand but are not identified → identify by physical characteristics or chemical analysis. Sources: PDR, Facts and Comparisons, Drug Topics Red Book, Ident-A-Drug Handbook, Lexi-Comp, manufacturer, lab.

Unapproved (off-label) uses: Drug Facts and Comparisons, Martindale the Extra Pharmacopoeia, Index Medicus, Drugdex, USP DI, AHFS

Drug interactions: Drug Interactions Facts, Evaluations of Drug Interactions, Hansten's Drug Interactions Analysis and Management.

Drug stability / compatibility: Trissel's Handbook of Injectable Drugs, Trissel's Stability of Compounded Formulations, King's Guide to Parenteral Admixtures.