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Medicinal Chemistry studies tell About -

How Chemical Structure Influences Biological Activity

How Molecular & physicochemical properties of Drug molecule Influences the Drug pharmacokinetics & pharmacodynamic

Medicinal Chemistry is concerned all About to the Designing & Development of Drug which cover 3 stages -

Discovery — Choice of Therapeutic Target
Identification of Lead

Optimization of — Pharmacodynamics
Pharmacokinitics

Development stage — pre-clinical
-clinical studies

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History

History & Evolution of Medicinal Chemistry can be studied under four heads -

Drug of Antiquity
The Middle Age
The Nineteenth Century
The Twentieth Century

Drug of Antiquity

The oldest records of use of therapeutics plants and minerals were Derived from Ancient Civilization of the Chines, The Hindus.
* The Mayans of Central America and the Mediterranean peoples of Antiquity.

In Ancient Greek Apothecary Shops Could be found Herbs such as opium, Squill, Hyoscyamus and Viper toxic and Metallic Drug such as Copper, Zinc, ore, Iron, Sulphate.

The Middle Age

Paracelsus (1493) Swiss physician
Used Antimony and its salts the

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The Nineteenth Century

It is also Considered as Age of Innovation

Synthesis of Urea 1828, Acetic Acid in 1845 Kolbe, Methane in 1856 by Berthelot set the Age of organic chemistry.

The Isolation of Morphine by Sertürner in 1803 emetine from ipecacuanha by Pelletier in 1816

and purification of Caffeine, quinine & Colchicine Contributed to the increased use of pure substance as Therapeutic Agent

Pharmaceutical Industry come in to Existence at the end of 19th Century.

Medicinal Chemistry received formal recognition in Academic pharmacy in 1932

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The Twentieth Century

Domagk reported cure of gram +ve Bacterial Infection in man & Animal by Prontosil.

Discovery of Penicillin by Fleming in 1929

Further Development of various classes of Medicinal Agents like Analgesics, Anesthetics, steroids Hypnotics, anticonvulsants.

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Development in Medicinal Chemistry

Development in the field of Medicinal Chemistry opened the new areas of Research.

Genomics

Study of Human genes & Chromosomes

Combinatorial Chemistry

is a technique in which Large number of Different & Structurally Similar Compounds are produced rapidly and Submitted for pharmacological Assay.

High Throughout Screening

Use robotics

work,

quickly screen millions chemical to rapidly Identify Active compounds

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Summarized about Various physicochemical parameters that affect Drug Action.

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Physicochemical Properties In Relation to Biological Action

Physicochemical properties refers to How Functional gp present with in the Molecule its ;-

Acid Base properties, water Solubility
Partition Cofficient, Stereo-chemistry

and Ablity to interact with the Biological System

such as, Enzyme Active Sites & Receptor Sites

Solubility
Hydrogen Bonding
Ionization of Drug
Partition Cofficient

Complexation
Protein Binding
Bio-Iso-sterism
Stereo-Isomerism

Dipole Moment
Molar Refractivity
Electronic properties

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Solubility

It is defined as the Concentration of Solute in a Solvent at a given temperature.

Factors affecting
- Particle size
- Chemical Structure
- Surface area
- Crystal form

Only Dissolved Drug can pass to plasma membrane and Interact with Biological target to show Effect

Hydrogen Bonding

Hydrogen Bonding formed b/w

Nonbonding Electron pair of Heteroatom like N.O.S
Electron Deficient Hydrogen atoms of -OH, -NH, -SH

How Hydrogen Bonding affect the Solibility of the Drug.

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Intermolecular Hydrogen Bonding Increases the water solubility.

Intra-molecular Hydrogen Bonding Decreases water solubility

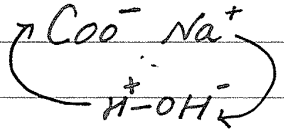
Ionization

Apart from Hydrogen Bonding
Another interaction Imp for solubility is ion Dipole interaction that can found in Organic Salts

Organic Salts Countains Cation & Anions

Cation interaction with -ve charged ion
Anion intract with +ve charged ion

Ex.



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Electronic properties

Calculation of Electronic properties of Molecules
Useful parameter for the Estimation of a Chemical reactivity of Drug Molecules with Biological Targets

Some Electronic properties are helpful in Identifying the drugs of high toxicity

Electronic properties Based on.
Molecular Size, Shape, Volume

Dipole Moment

By ION Dipole Intraction drug get dissolved and then Distributed in Body fluid.

It is a Imp parameter for Determining the Energy, Geometry, Intermolecular forces of Molecules

Dipole moment is a parameter used to study Drug receptor Intraction and QSAR

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Molar Refractivity MR

The MR is imp criterion to measure the steric fector.

It is usually designated as a simple M. of the volume occupied Either by an Individual Atoms or group of Atoms.

Molar Refractivity Increases with I Increase the Volume and / Molecular weight of Drug Molecule.

Partition Cofficient.

Partition Cofficient is the Equilibrium Constant of Drug

Ratio of Concentration of Drug $\frac{\text{lipid Phase}}{\text{water Phase}}$

Grater then one Substance more soluble in fat like Solvin
Less then one " " " " water

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Protein Binding

Protein Binding of a Drug is Defined as the Reversible Binding of Drug with protein in Body.

Protein that Binds to Drugs are
- Serum albumin
- Glycoprotein
- Lipoprotein
- α, β, γ globulins.

Protein Binding of Drug Affect the
- Distribution
- Elimination
- Pharmacological Effect of Drug

Bio-Isosterism

Bioisosterism are a functional groups or molecules that have - similar chemical & physical properties
Broadly produce similar Biological properties.

According to Burger Biososteres are compounds or groups that possess - Near equal molecular Shape & Volume
Approximately similar Distribution of Electron
Exhibit similar physical & chemical properties
Target similar Biological Target

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Bioisosterism is used.

Improving biological & physical properties of Drug
" potency of Drug
Enhancing Stability of Drug
Improving Bioavailability of Drug

Role of Isomers in Biological Activity of Drug.

For the Biological Activity Drug should fits into the target with proper spaital arrangement.

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Drug Metabolism

Overall Activity of a Drug, not only Depends on interaction with receptors but also on pharmacokinetic processes like Absorption, Distribution, protein binding, Biotransformation and Excretion of Drug

These processes and amount of Drug Administered Determines the Concentration of the Drug Build up at the Site of Action

A Drug Absorbed through (stomach or intestine) must pass through liver before it reaches the systemic circulation. In the liver Drug is Metabolized or Excreted into Bile

If the Drug Extensively metabolized in liver then Bioavailability of the Drug Decreases. This is called First pass metabolism

Drugs and metabolites which are Eliminated from Liver into the Bile, pass into the lumen of the GI tract. Here some of the drugs may be reabsorbed as such or after further metabolism.

This recycling of Drug is called Enterohepatic circulation.

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Drug Metabolism / Biotransformation.

Metabolism / Biotransformation is a process which terminates Drug effect or that results in loss of pharmacological Activity.

Enzymatic biotransformation converts xenobiotics (Drug and nonessential foreigen compounds) into polar, hydrophilic and ionized molecules which Eliminate through urine by Excretion

Xenobiotics; Drugs, plant toxins, food additives insecticides, environmental chemicals called Xenobiotics.

Drug —Biotransformation→ Toxic Metabolite
Inactive Metabolite
More Active Metabolites than parent Drug
Less Active " " " "

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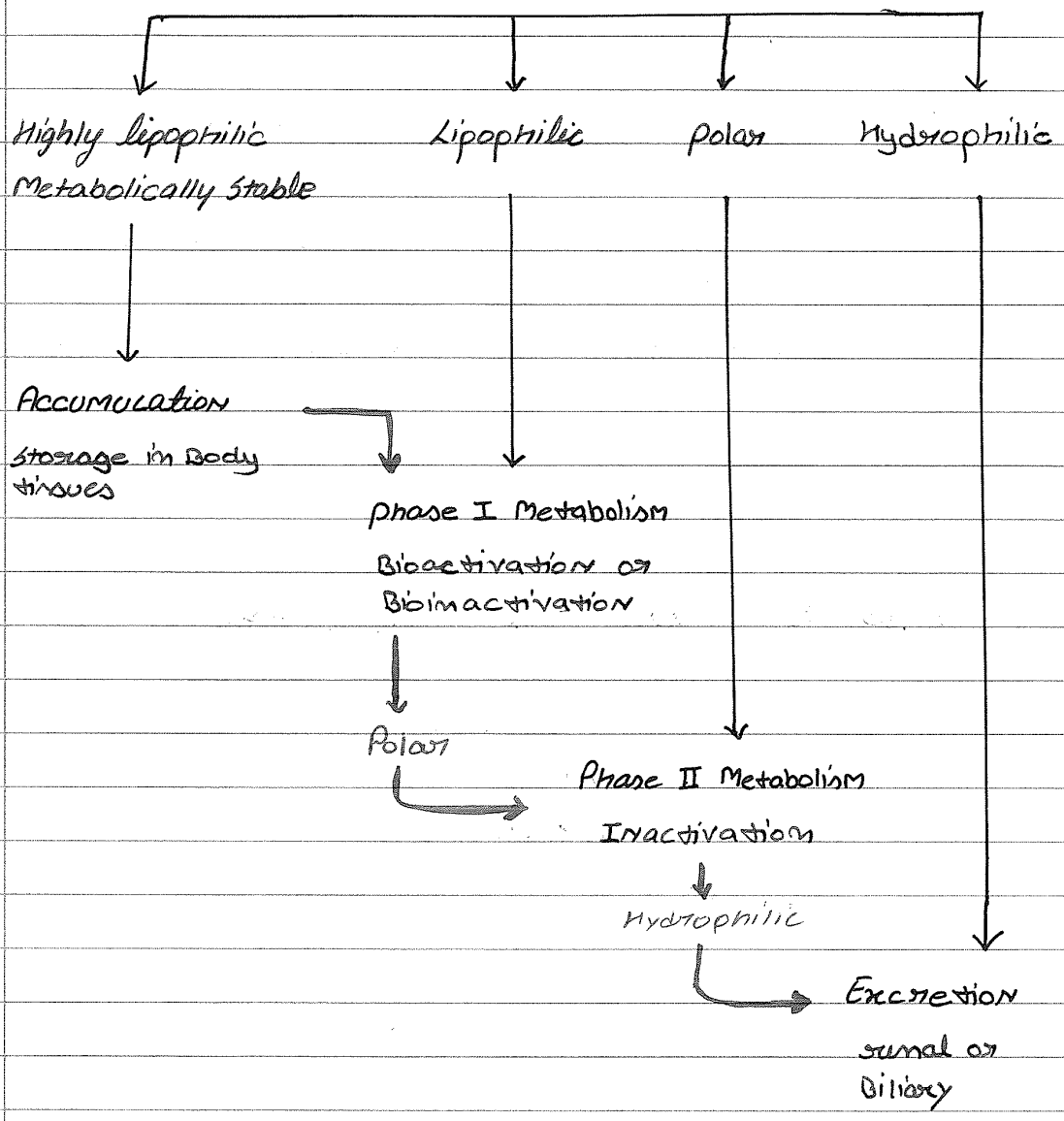
Biotransformation

Xenobiotics



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Phase 1, Metabolic Reactions

Converts the parent drug to a more polar metabolite by oxidation, reduction and hydrolysis.

As a result of phase I Reaction -

A new functional group is introduced

Or Existing functional group is modified

or functional group for phase II reaction is Exposed.

Types of Phase - 1 Reactions

1. Oxidation
2. Reduction
3. Hydrolysis

Reaction are non-synthetic in nature and in general produce a more water-soluble and less Active Metabolites.

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As most small molecule drugs are lipophilic in nature, Drug metabolism converts these Hydrophobic Compounds into more water soluble compounds that can be Excreted.

Typically, Oxidation is the most common phase 1 Reaction. The hepatic Cytochrome P450 system is the most Imp of the phase 1 Oxidation Systems.

Oxidative Biotransformation

Oxidative biotransformation is the most Common & Imp among phase I reaction.

This reaction required Both Molecules Oxygen & Reducing Agent.

The enzyme system carrying out oxidation called Oxidases or Monooxygenases.

Most Oxidation reactions are performed by isozymes Called Cytochrome P450.

Sequence of Events in Oxidation of Drug and Xenobiotics.

1. Formation of Enzyme - Substrate Complex by the Binding of Ferric CYP 450 to the substrate.

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2. Reduction of Enzyme substrate complex results in the formation of Ferrous CYP 450 - substrate Complex.

3. Reduction CYP 450 Ferrous CYP 450 - substrate complex binds to molecular oxygen to form Oxy - CYP 450 complex.

4. Oxy - CYP 450 complex undergo auto oxidation to a Ferric superoxide ANION.

5. Ferric superoxide ANION undergo reduction to give Peroxy - CYP 450 substrate Complex

6. Peroxy - CYP 450 substrate complex undergo Heterolytic cleavage to give Activated oxygen ($Fe^{5+}=O$) substrate complex.

7. Binding of Activated oxygen with substrate yield oxidized Drug and Ferric CYP 450 complex is regenerated.

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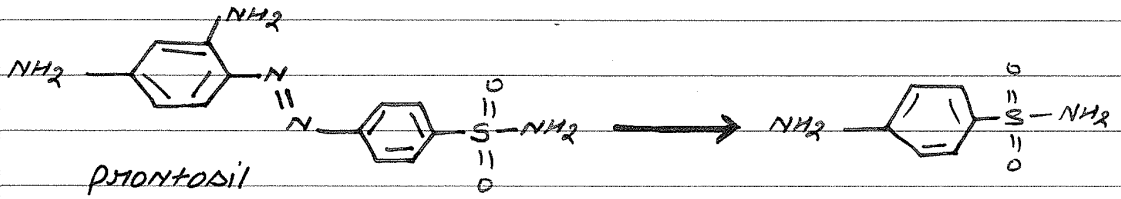
2 Reductive Biotransformation.

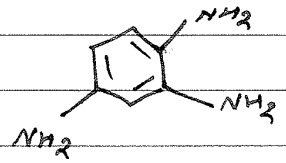
Liver microsomal enzymes catalyzes the reduction of azo and nitro compounds to primary amines

Azo Compounds like Prontosil & Sulfasalazine Converted to aromatic amine by azoreductase



Prontosil

Sulfanilamide



1,2,4 - Triaminobenzene

Reduction of ketone is an important metabolic pathway of Biotransformation.

Reduction is carried out by **ketone reductase**

Drug like naloxone, naltrexone, hydromorphone undergo reduction.

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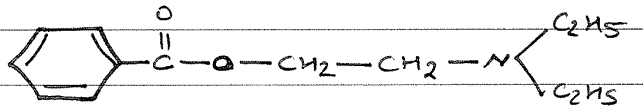
3. Hydrolytic Biotransformation.

Esters and amide xenobiotics are Hydrolyzed by Enzymes present in Blood, liver microsomes, kidney & other tissues.

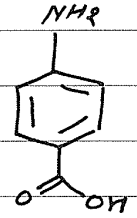
Esters and amides are Hydrolyzed rapidly by group of Enzymes Carboxyesterases.

Example of Carboxyestrases – cholinesterases, aryl Carboxyesterases, liver microsomal Carboxyesterase

Cholinesterase hydrolyses choline-like Esters, Procaine & Acetylsalicylic Acids.

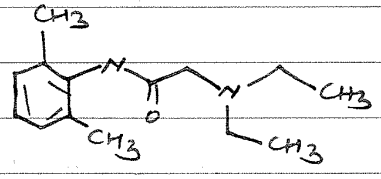


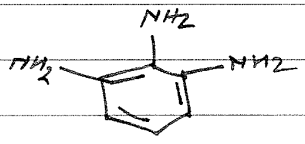
Procaine



Acetylsalicylic Acid

Amide Drugs such as Lignocaine Hydrolyzed Amine





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PHASE I Metabolic Biotransformation

May produce one, more changes in Drug Molecule

1. Decreased pharmacological Activity (Deactivation)
2. Increased Toxicity (Carcinogenesis, Cytotoxity)
3. Altered pharmacological Activity.

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Phase 2nd Metabolic Reactions

Phase II reactions results in Decrease in lipid solubility and increase in Hydrophilicity of Drug and metabolite from phase I reaction by adding hydrophilic ionic moiety to the substrate like glucuronic acid, sulphate or glycine.

Majority of phase II products Eliminated through Urine & Bile.

Types of Phase II Reactions.

1. Glucuronic Acid Conjugation
2. Sulphate Conjugation
3. Conjugation with Amino Acids
4. Acetylation
5. Methylation
6. Conjugation with glutathione.

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1. Glucuronic Acid Conjugation

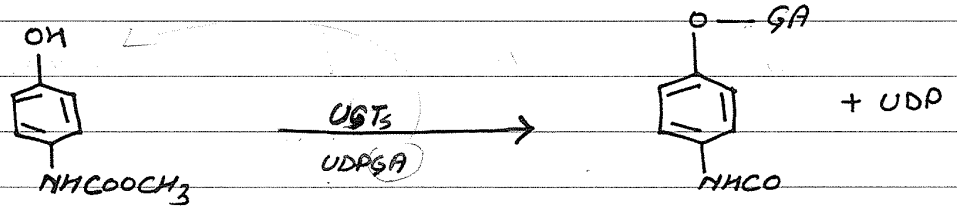
It is the most common and Imp of phase II Biotransformation. Glucuronic acid can forms Conjugates with Alcohols, phenols, esters, amines.

Enzyme – UDP – glucuronyl tranferase (Liver)

UDPGA transfers (glucuronic acid) moiety to xenobiotic in the presence of UDP – glucuronyl transferase Enzyme.

O-, N-, S-, Glucuronides

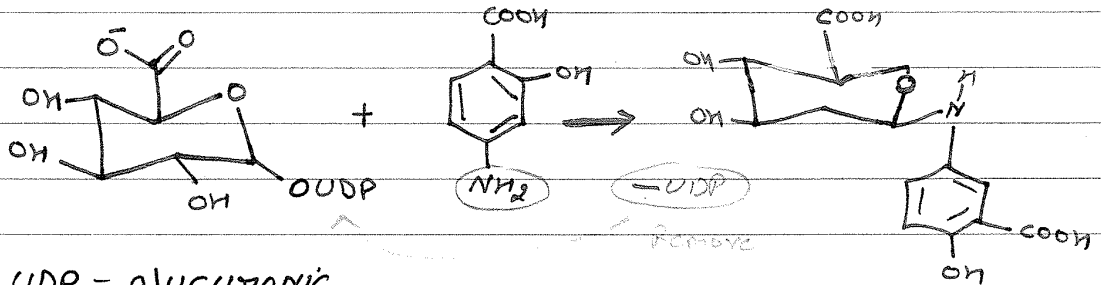
Glucuronides formed with alcohols & phenols called Ether (O-glucuronide)



Acetaminophen (Paracetamol)

Acetaminophen glucuronide.

para-Amino Salicylic acid Undergo (N-glucuronidation)



UDP – glucuronic

2. Sulphate Conjugation

It is imp reaction for the (Biotransformation of Steroid) hormones, bile acids, Catecholamine neurotransmitters. phenolic drugs and other xenobiotics.)

Sulphate Conjugation increases Hydrophilicity and Excretion of Drug.

Enzyme - Sulphotransferases.

A xenobiotic (substrate) is sulphated by the transfer of Active sulphate from (3'-phosphoadenosine-5 phosphosulphate) (PAPS).

SO_4^{2-} + ATP ⟶ 3-Phosphoadenosin-5' + ADP + PPi
Phosphosulphate

3. Conjugation with Amino Acids.

a) Carboxylic Acid xenobiotics undergo conjugation with Amino Acids.

b) Majorly Glycine and in some cases glutamine forms water Soluble ionic Conjugates with aromatic & aryl Aliphatic Carboxylic Acid

c) These amino acids conjugates are less toxic and Excreted readily to the Urine and bile.

d) Enzyme - Acyl Synthase

R-COOH + ATP + CoA $\xrightarrow[\text{Synthatase}]{\text{acyl}}$ R-CO-S-CoA + AMP
Xenobiotics

R-CO-S-CoA + R'NH₂ ⟶ R-CONH R' + CoASH

4 # Acetylation

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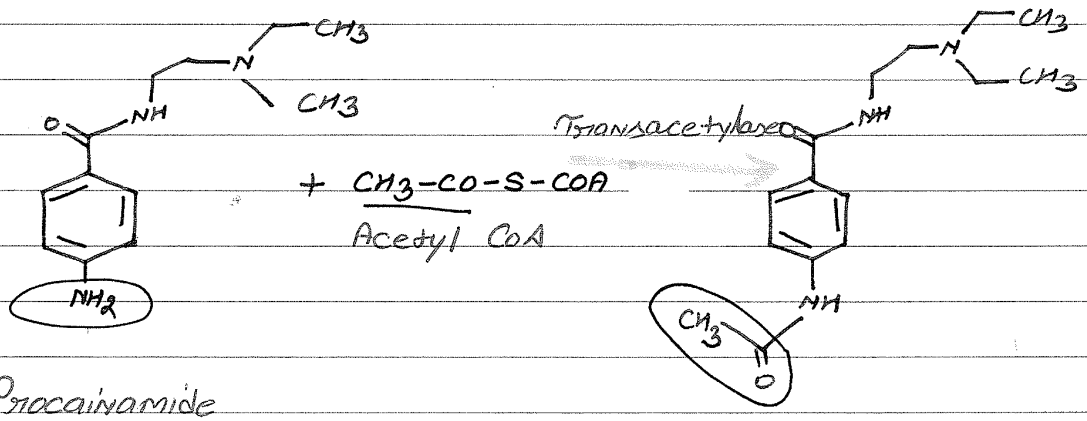
Acetylation is reaction of amino group involving transfer of Acetyl CoA to primary aliphatic and aromatic Amines, amino acid, Sulfonamide gp.

Drug like p-amino benzoic Acid, Dapsone, procainamide and a number of Sulfonamides are undergo acetylation.

N-acetyltransferase enzyme primary present in liver catalyzes the reaction & transfer acetyl gp from Acetyl CoA to the xenobiotic or its phase I Metabolite.

Ex- <u>Procainamide</u> undergoes N-acetylation



Procainamide

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5. Methylation

It is mainly for the metabolism of endogenous compounds (more active) rather than drugs.

Methylation results in O-Methyl Metabolites that may have great or greater pharmacological Activity & lipophilicity then the parent molecule.

Methionine transfers Methyl gp to the substrate via Activated intermediate S-adenosylmethionine in the presence of Methyltransferase.

Methylation involves O-Methylated, N-Methylated or S-Methylated Metabolites.

ATP + Methionine —(Methionine Adenosine Transferase)→ S-Adenosylmethionine + PPi Phosphate

S-Adenosylmethionine + RZH —(Methyl transferase)→ RZCH$_3$ + S-Adenosyl homocysteine

Z = O, NH, S

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Factors Affecting Drug Metabolism

Physiological factors
Chemical factors
Genetic factors
Altered physiological factors
Stereochemical factors

1. Physiological factors

Age The drug metabolic rate varies b/w Age groups mostly owing to differences in enzyme content, enzyme activity.

The microsomal enzyme system is not fully formed in neonates (up to 12 months) and new-borns (2 months to 1 yr) as a result, many medications are digested slowly. Caffeine, for example, has a half-life of [four days in neonates] vs [four hours in adults]

Gender There are differences in metabolism b/w man & women may be due to presence of sex hormones

- N-demethylation of erythromycin was higher in females than in males.

Diet Lower protein diet decreases, whereas higher protein diet increases Drug Metabolism Capacity.

- Grape fruit juice inhibit metabolism of many Drugs
- Deficiency of Vit A, B_2, B_3, E and minerals leads to

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2. Genetic Factors

Genetic factor influences rate of Oxidation of some drugs like phenytoin, phenylbutazone etc.

3. Altered physiological factors.

Pregnancy On pregnancy metabolism of some drugs Decreases while others increases.

e.g. metabolism of phenytoin increases, whereas phenobarbitone and pethidine metabolism Decreases

Hormonal Imbalance

Hypothyroidism increases the Drug Metabolism.

Hyperthyroidism Decreases drug metabolism

4. Stereoselectivity

Reduction of ketone to stereoisomeric Alcohols and Hydroxylation of Enantiotropic protons on phenyl rings by MOA are Example of product stereoselectivity

5. Environmental Factors

Cigarette smokers act as enzyme inducers.

Chronic alcoholism lead to Enzyme induction

Pesticides may act as Enzyme inducers

At higher Altitudes rate of Biotransformation Decreases