**Drug Metabolism**

**Drug:** Drug is a substance which may have a) medicinal b) intoxicating c) performance enhancing ord) other effects, when taken into the body and is not considered as a food.

In pharmacology, a drug is a chemical substance used in a) cure from disease/s ex- Antibiotics b) suppress the disease/s c) prevention ex- Contraceptives or d) diagnostic of disease/s ex- Barium milk. **Note:** Insulin is called a hormone when it is synthesized by the pancreaticβ(beta) cells inside thebody, but if insulin is introduced into the body from outside it is called drug.

**Medication:** A medication or medicine is a drug taken to cure and/or improve the symptoms of amedical condition or may be used as preventive medicine that has future benefit/s. Dispensing of medication is often regulated by the governments into 3 categories:

1. Over-the-counter (OTC) medication: Available in pharmacies and supermarkets without special restriction. Ex- Paracetamol, ORS (Orally rehydrating salt/solution/saline), Anti-ulcerant.
2. Behind-the-counter (BTC) medication: Dispensed by a pharmacist without needing a physician’s prescription. Ex- Multi-vitamins and Minerals.
3. Prescription-only-medicine (POM): Must be prescribed by a licensed medical professional, usually a physician. Ex- Anti-hypertensive drugs.

**Drug Used:**

1. Mediction: Taken to cure or improve of a medical condition or prevention. Ex- Antibiotics (Macrolid – Azythromycin)
2. Drug abuse: Self-administration of drug for non-therapeutic purpose. Ex- Anxiolytic.
3. Drug addiction: Periodic/ Chronic intoxication produced by repeated consumption of certain drugs. Ex- Narcotics.
4. Recreational purpose: YABA, *Cannabis Indica.*
5. Self-medication: Metronidazole.

**Drug Metabolism:** Drug (Xenobiotics) metabolism is the biochemical modification or alternation ortransformation of pharmaceutical substance/s by living organism or by the body, usually through specialized enzymatic system/s.

Transformation occurs in two major ways:

1. by reducing lipid solubility
2. by altering biological activity. Consequences of metabolism:
3. Drug metabolism equals to drug inactivation.
4. The metabolites may have-
   1. Equal activity of the drug
   2. No, or reduced activity of the drug
   3. Increased activity of the drug
   4. Toxic properties.

**Reducing lipid solubility:** Metabolic reactions tend to make a drug molecule progressively morewater soluble and so favor it’s elimination through urine.

**Altering biological activity:** The end result of metabolism usually is the elimination or abolition of the

biological activity but various steps in between may have the following consequences:-

1. Conversion of a pharmacologically active drug to an inactive substance. Ex- Most of drugs.
2. Conversion of a pharmacologically active drug to other active metabolites.

|  |  |
| --- | --- |
| **Active Drug** | **Active Metabolite** |
| Amitriptylene | Nor-triptylene |
| Codeine | Morphin |
| Diazepam | Oxazepam |
| Digitoxin | Digoxin |

1. Conversion of pharmacologically inactive substance (pro-drug) to a pharmacologically active metabolite.

|  |  |
| --- | --- |
| **Inactive Substance** | **Active metabolite** |
|  |  |
| Bacampicillin | Ampicillin |
| Benorylate | Aspirin, Paracetamol |
| Levodopa | Dopamine |
| Prednison | Prednisolone |

d) Conversion of a more toxic drug into less toxic metabolites.

|  |  |  |
| --- | --- | --- |
|  | **More Toxic** | **Less Toxic** |
|  |  |  |
|  | Phenacetine | Acetaminophen |

**Factors that modify the metabolic process:**

1. Age – Neonatal Jaundice
2. Gender
3. Race
4. Species
5. Psychological condition
6. Physiological condition
7. Diet
8. Diseased condition /Clinical condition
9. Dosage form
10. Enzyme induction
11. Enzyme inhibition
12. Genetic factor
13. Other drug administration
14. Route of administration
15. First-pass metabolism
16. Chemical properties of drug

Pregnancy category – Teratogenic effect

**In which organs metabolism take place:**

1. Liver
2. Kidney
3. Gastric mucosa
4. Lungs
5. Adrenal gland
6. Skin
7. Brain
8. Nervous system
9. Testes (Male)
10. Placenta (Female)

**Phases of Metabolic Process:**

The kidney cannot effectively eliminate lipophillic drugs that readily cross the cell membranes and are reabsorbed in the distal tubules. Therefore lipid soluble gs must be metabolized in the liver using 2 general sets of reaction.

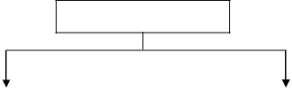
1. **Phase-I:** Convert lipophillic molecules into more hydrophilic molecules through any of thefollowings-
   1. Oxidation reaction
   2. Hydrolysis reaction
   3. Reduction reaction
2. **Phase-II:** This phase consists of conjugation reaction. Phase-II metabolism invariablyterminates biological activities.

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|  | **Absorption** |  |  |  |  | **Metabolism** |  |  |  |  |  | **Excretion** |  |
|  |  |  |  | Phase-I |  | | |  | Phase-II | |  |  |  |
|  | | |  |  |  | | |  |  |  |  |  |  |
| Drugs | | | Metabolic modified | | | | |  | Conjugate | |  | Excretion | |
|  |  |  | activity | | | | |  |  |
|  |  |  |  |  |  |  |  |  |
|  |  |  | Inactive metabolite | | | | |  | Conjugate | |  | Excretion | |
|  | Lipophillic | |  |  |  |  |  |  |  |  | Hydrophilic | | |



Phase-I & Phase-II metabolic reaction

1. **Reversal of the order of the phases:** Not all drugs undergo phase I & phase II reactions inthat order. For example, Isoniazide (anti-tubercular) is fast acetylated (it’s a phase II reaction) and then hydrolyzed to Isonicotinic acid (a phase I reaction).

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|  |  |  |  |  |  |  |  |
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|  |  |  |  |  | **DRUG** |  |  |
|  |  | **Oxidation** |  |  |  | **Conjugation** | |
|  |  |  |  |  | **Conjugation** |  |  |
|  |  | **Metabolites** |  | **Stable adducts** |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| **Polar species** | | |  |  | **Partly** | **Non-polar species** | |
|  |  |  |  |  |  |  | |
|  |  | **Kidney** |  |  |  | **Liver** |  |
|  |  |  |  |  |  |  |
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|  |  |  |  |  |  |  | |
|  |  |  |  |  |  | **Intestine** |  |
|  |  | **Renal elimination** | | |  |  |
|  |  |  |  |  |
|  |  | **(Urine)** |  |  |  |  |  |
|  |  |  |  |  |  |  | |
|  |  |  |  |  |  |  | |
|  |  |  |  |  |  | **Biliary elimination** |  |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  | |
|  |  |  |  |  |  | **Stool** |  |
|  |  |  |  | | |  |  |
|  |  |  | Flow chart of drug metabolism pathways | | | | |

**Q. Which organs eliminate or excrete drugs?**

Answer: Kidneys, Liver & Intestine, Lungs, Skin, Mouth cavity, Hair, Nail, Eye, Milk (Nursing mother) etc eliminate drugs.

A patient with renal failure may undergo extra-corporial dialysis, which removes small molecules such as drugs, electrolytes etc.

|  |  |  |
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|  | **Total body clearance (Systemic clearance) /CL Total /CLt:** This is thesum of the clearance from various drug | |
|  |
|  metabolizing and drug eliminating organs which can be calculated by – | |  |
|  | **CL Total = CL Hepatic + CL Renal + CL Pulmonary + CL others** |  |

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**Clinical conditions which may alter drug half-life:**

a. The half-life of a drug is increased by

i. Diminished renal plasma flow

ii. Diminished hepatic blood flow

iii. Decreased extraction ratio

iv. Decreased metabolism

b. The half-life of a drug decreased by

i. Increased hepatic blood flow

ii. Decreased protein binding

iii. Increased metabolism

**Foot notes:**

1. **Urine:** the fluid secreted from the blood by the kidneys, stored in the urinary bladder, dischargedthrough the urethra and usually voluntarily it is conveyed to urinary bladder by two uretor – one from each of the kidneys.
2. **pH:** In chemistry, pH is the degree of acidity or alkalinity. Natural point of pH is 7. If pH is less 7

acidity increased (maximum acidity is pH 0) and if pH is more than 7 alkalinity increased (maximum alkalinity is pH 14).

Example - Gastric juice pH = 1.0 to 5.0

* Water at 25°C pH = 7.0
* Pancreatic juice pH = 8.4 to 8.9

**Chapter 3: Infectious diseases and Management**

**Inflammation:** A reactive state ofhyperemia(increased blood flow) and exudation from blood vessels withconsequent changes in response to physical, chemical or microorganism invasion Cardinal signs are:

1. Redness
2. Swelling
3. Heat (raise of local temperature)
4. Pain
5. Loss of local function

**Hyperemia** is an excess of blood in vessels supplying an organ or other parts if the body.

**Infection:** The condition in which body or organ is invaded by a pathogenic microbial agent that under favorablecondition multiplies and produces injurious effects. Infections are usually accumulated by inflammation.



**Infectious disease:** Infectious disease is clinically evident disease from presence of pathogenic microbial agentincluding bacteria, virus, fungus, protozoa, and multicellular parasites. Infectious pathologies are usually qualified as communicable disease due to their potentiality of transmission from one to another. Transmission may occur

through physicalcontact, contaminated objects, body fluid, airborne inhalation, food, water and through vector-



borne spread.

 **Top five (05) causes of death in Bangladesh** (Ref. World Bank and Lancet-October, 2016)

i. Stroke / Cerebrovascular disease.

ii. Ischemic Heart Disease (IHD).

iii. Chronic Respiratory Disease (COPD).

iv. Diabetes.

v. Lower Respiratory Tract Infection (LRTI).

 

 CHOICE OF AN ANTIMICROBIAL DRUG DEPENDS ON THE FOLLOWING FACTORS

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1. **Patient factors**
   1. Age
   2. Renal function
   3. Hepatic function
   4. Local factor
   5. Recent antimicrobial use
   6. Timing of initiation of the therapy.
   7. Drug allergy
   8. Pregnancy and Lactation
   9. Genetic factor
2. **Drug factors**
   1. Spectrum of activity
   2. Types of activity (Bactericidal /Bacteristatic)
   3. Relative toxicity
   4. Pharmacokinetic
   5. Route of administration (Oral, IV etc)
   6. Evidence of clinical efficacy
   7. Patient benefit (Dose /Price)
3. **Microorganisms related consideration**
   1. From clinical diagnosis
   2. From clinical features

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**Failure of Chemotherapy**

1. Improper selection of drug.
2. Improper selection of dose.
3. Improper selection of route.
4. Improper selection of duration of treatment.
5. If treatment begins too late.
6. Poor host defense.
7. Trying to treat untreatable patient.
8. Prolonged antimicrobial treatment without (clinical) clear evidence of infection.
9. Failure to narrow antimicrobial therapy when causative microorganism is clearly identified.
10. Excessive use of certain antimicrobial agent.
11. Failure to take the necessary adjuvant measures.
12. Presence of dormant organisms (H. Pylori) which later give rise to a relapse.

**Chapter 4: Drug Design /Rational Drug Design**

Definition: Drug design or Rational drug design is the inventive process of finding new medications based on the knowledge of a biological target.

Types of drug design by molecular basis:

**A. Structure-based or direct drug design:** Relies on knowledge of three dimensional structure of the biologicaltarget obtained through methods such as X ray crystallography.

Pharmacophore: The particular group or arrangement of atoms in a molecule that gives the material its medicinal activity.

Pharmacophore Identification



Pharmacophore modification



Fit for the receptor

Yes

Potential drug

**B. Ligand-based or indirect drug design:** Relies on knowledge of other molecules that bind to the biological targetof interest.

Ligand: In chemistry, Ligand is an organic molecule which is attached to a central metal ion by multiple bonds.

Active site identification



Ligand fragments growing 



No

Complete growing  Fit for the receptor

Yes No



Potential drug Change fragments

