



Pharmacokinetics 3

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Intended learning outcomes (ILOS):

- **Recognize** basics of Pharmacokinetics
- **Interpret** the fundamental principles of pharmacokinetics
- **Discuss** factors affecting Metabolism
- **Identify** net results of metabolism

Metabolism (Biotransformation)

*The aim of drug metabolism is to change lipid soluble drugs to water soluble metabolites to be easily excreted.

Site of Metabolism (Organs):

Liver (Hepatic) is the main site for biotransformation

Lung → Nicotine

Kidney → Vitamin D

G.I.T. & Gut flora → Histamine

Skin → Vitamin D

Plasma (Cholinesterase) → Succinylcholine

Phases of biotransformation :

I.Phase I (Non synthetic) reactions :

- **Oxidation**
- **Reduction**
- **Hydrolysis**

Results of Phase-I Metabolism:

Inactive  **Active**

prodrug

Active  **More Active**

Active

**The
commonest
fate**

Inactive

Active

Toxic

Results of Phase-I Metabolism:

1) Conversion of inactive compound to active

-Cortisone (Inactive) → Hydrocortisone = cortisol (Active)

2) Conversion of active compound to more active metabolite

- Diazepam (Active) → Nor-diazepam (Active)

3) Conversion of active compound to inactive

Adrenaline & Noradrenaline → Vanil Mandilic Acid (**inactive**)

Acetylcholine (Active) → Acetic acid + Choline (Inactive)

4) Conversion to toxic compound

Methanol -----> Formaldehyde (**blindness**)
(active) **oxidation** (toxic)

Phases of biotransformation :

II. Synthetic reaction (phase II reactions)

*Conjugation of the drug with certain acid or amino acids e.g.

Conjugation of **Paracetamol** with **glucuronic acid**.

Conjugation of **Isoniazid** (Acetylation) with **acetic acid**.

Conjugation of **salicylates** with **glycine**.

Conjugation of **Noradrenaline** with **methyl group** (→ **Active Adrenaline**).

Phase II (Synthetic) reactions:

Result
?

usually

Inactivation

with

few exceptions:

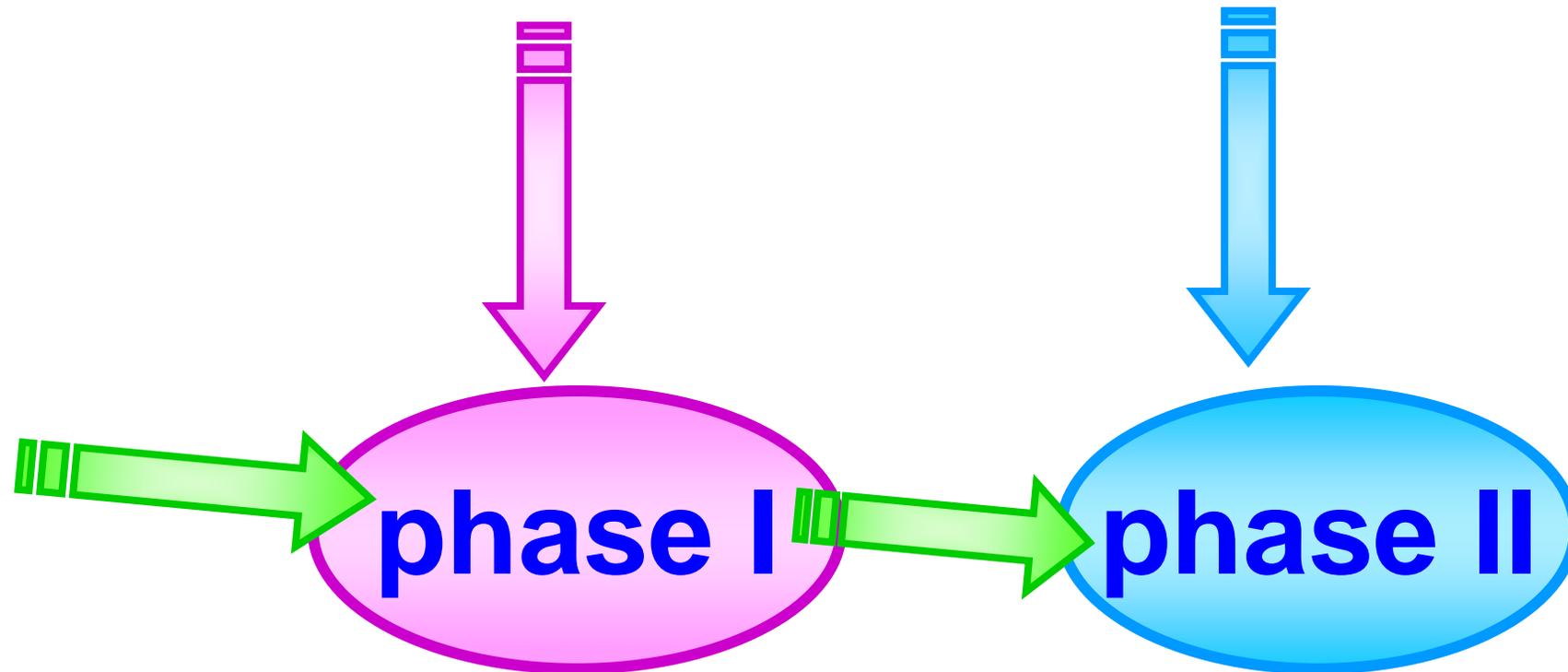
*Morphine-6- conjugate is **active**

*Noradrenaline with methyl group



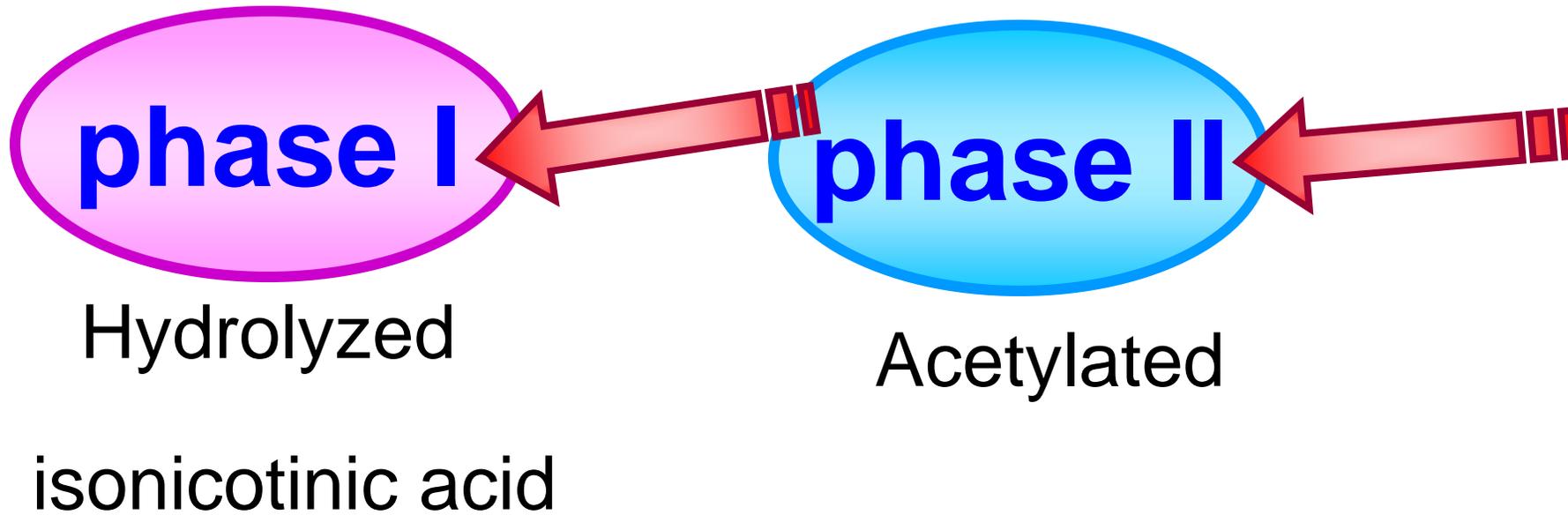
Active Adrenaline.

Most of drugs pass through:



Reverse order

Isoniazid



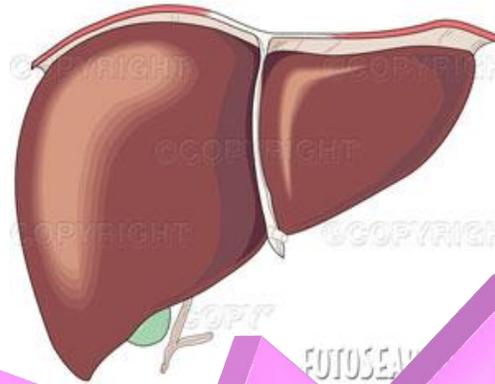
Sites of biotransformation

1- Microsomal Enzymes : Smooth Endoplasmic Reticulum

- Oxidation and reduction by **CYP450** enzymes.

- Usually act on **lipophilic** substrates

- **Inducible**



- **Glucuronide conjugation Only.**

Affected
By
Drugs
& age

2- Non Microsomal : (in all organs)

Present in liver, kidney, plasma, skin and GIT...etc
(cytoplasm and mitochondria)

- Oxidation.
- Reduction.
- Hydrolysis.



- Act on **lipophilic & hydrophilic** substrates
- **Not Inducible**

- **Conjugations**
except
~~glucuronic acid.~~

Site of Biotransformation Reactions

	Microsomal Enzymes Hepatic Microsomal Enzymes "HME"	Non -Microsomal Enzymes
1- Site	Smooth Endoplasmic Reticulum	Cytoplasm & Mitochondria
2- Organs	Mainly Hepatic	All Organs
3- Substrates	Lipophilic	Lipophilic & hydrophilic
4- Phase I Reactions:	Oxidation & Reduction	Reduction, Hydrolysis & Some Oxidative
5- Phase II Reactions	Glucuronic Acid Only	All except Glucuronic Acid
6- Induction	Inducible by drugs	Not inducible

*Factors affecting Drug Biotransformation:

1- Age: Lowering of drug metabolism occurs in **extremities** of age. **So, drug doses should be reduced.** e.g. Premature neonate can NOT conjugate **chloramphenicol** → **Fatal Grey Baby Syndrome**



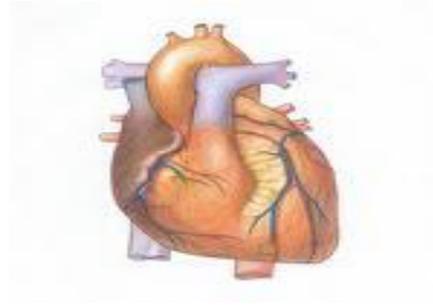
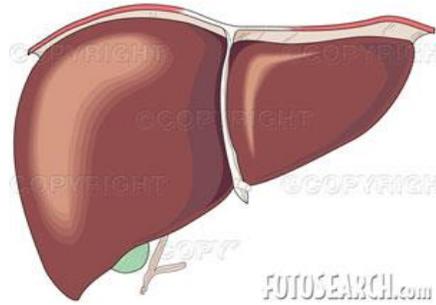
2- Sex: Estrogen in females **inhibits HME** & Androgen in males **induces HME**



3- Genetic factors: e.g. **Succinylcholine** is metabolized by pseudocholinesterase, deficiency of this enzyme → **succinylcholine apnea** (Genetic determined polymorphism).

5- Pathological factors: liver disease, heart failure.

Drug metabolism is reduced leading to increased susceptibility to drug toxicity like diazepam that may cause coma when given in therapeutic dose.



6- Starvation: Enzyme activity is decreased with inhibition of conjugation process e.g. depletion of glycine with inhibition of glycine conjugation.

7- Drugs: can stimulate (*enzyme induction*) or inhibit (*enzyme inhibition*) HME.

*Factors affecting Drug Biotransformation:

Activators (enzyme induction)

- **Increase their own rate** of degradation (Auto-induction) → Tolerance.
- **Increase degradation of other drugs.**
- **Increase the dose of concomitant drug**
- e.g. Phenytoin, phenobarbitone, Carbamazepine & Rifampicin
- **Effect:** They ↑ Metabolism of other drugs e.g. Oral anti-coagulants, ↓ Oral hypoglycemic & Oral contraceptives → their duration of action.

Inhibitors (enzyme inhibitors)

- **Inhibit their own** rate of degradation
- **Inhibit degradation of other drugs.**
- **Reduce the dose of concomitant drug**
- e.g. **A-specific:** Grapefruit juice, Sodium valproate, Erythromycin & Omeprazole.
- **Effect:** They ↓ metabolism of other drugs (e.g. Theophylline → ↑ its plasma level → Toxicity)
- **B-Non-specific (General):**
 - a- **Hepatotoxic drugs.**
 - b- **Drugs ↓ Hepatic blood flow: Propranolol**



Questions



Explain:

1. Phenytoin can reduce the effect of oral contraceptive pills.
2. Chloramphenicol is not preferred in premature infants.

Put true or false:

- 1-Conjugation is one of phase II reactions (✓)
- 2-Succinylcholine apnea is caused by prescription of HME inducers (X)





Thank You

