DRUG INTERACTIONS

One of the factors modifying drug action

Objectives

By the end of this session, you should:

- **Understand the main mechanisms of drug interactions**
- **Know the major groups of drugs involved in drug interactions**
- **Understand how to take steps to avoid or minimise the effects of drug interactions on the patient**

DEFINITION

Measurable modification (in magnitude or duration) of the action of one drug by prior or concomitant administration of another substance (including prescription and nonprescription drugs, food or alcohol).

mechanism

Pharmacokinetic/ pharmacodynamic

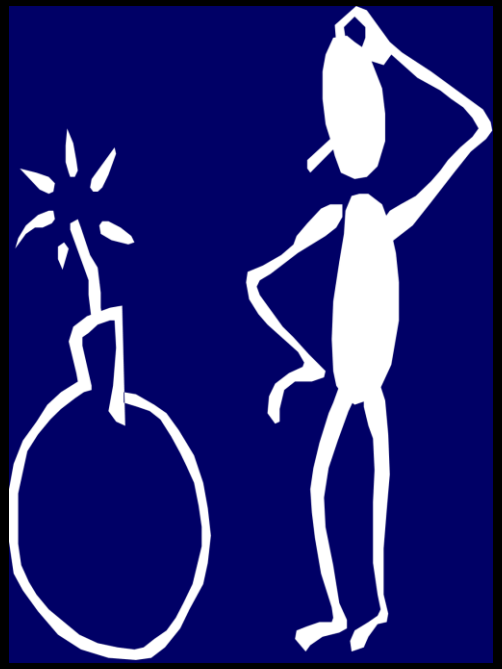
Effect

- ✓ Desirable
- ✓ adverse

Interpretation

Harmful Effects

Unknown Effects



Synergistic/ Beneficial Effects

Classification of Drug Interactions

Pharmacokinetic

Δ in drug absorption, distribution, metabolism or excretion

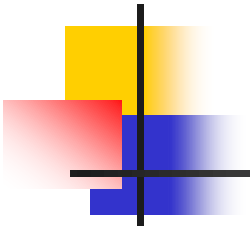
Pharmacodynamic

Alteration of pharmacological effect at *standard* drug concentrations

"All drugs known to humans are poisons, only the amount or dose determine the effects."

Paracelsus, 1490 - 1541

It is when the interaction leads to adverse consequences that it comes to the attention of the patient and physician.



Clinically desirable drug interactions

PRINCIPLES

drug interactions

Index drug: drug which has its effect **enhanced** or *cancelled* by the interacting drug

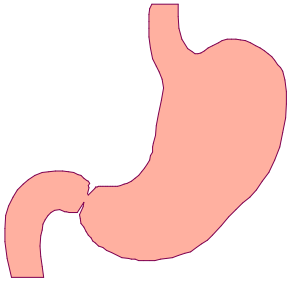
Interactions outside the body
chemical interactions

- React physically or chemically with each other before administration to the patient
- Drugs mixed before parenteral administration, may interact and decrease the activity of one or both components.
- Drugs never mixed before parenteral administration unless they have been proved by rigorous testing to be chemically compatible.

Examples

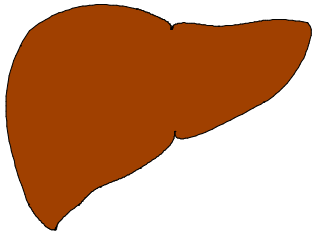
- Thiopentone and succinylcholine should never be mixed in the same syringe
- Antipseudomonal penicillins inactivate the aminoglycosides
- Phenytoin never to be given in 5% Dextrose drip.
- Insulin glargine should not be mixed with any other insulin

Pharmacokinetic Interactions



Decreased absorption from GI tract

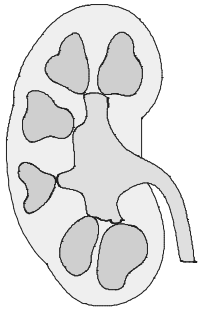
- Alterations in pH
- **Complex formation with ions**
- **Interference w/transport protein (i.e. P-gp)**
- **Pre-systemic enteric metabolism**



Changes in hepatic metabolism

Interference with transport proteins

- Interference with phase I or II drug metabolism



Decreased renal excretion

Interference with glomerular filtration, tubular secretion or other mechanisms

A 4 year old child prescribed iron syrup for anemia(Hb: 9.5 gm).His mother used to give milk with syrup to avoid bad taste. After 4 months of therapy Hb was still 9.5 gm.

- ✓ Why there is no increase in Hb?
- ✓ How can this be prevented

Interactions at the level ofAbsorption

best known example

- oral tetracyclines and metal cations; a cation–tetracycline complex that cannot be absorbed.
- Cholestyramine & colestipol bind a number of anionic drugs and ↓absorption of levothyroxine &warfarin.
- Sucralfate interferes with absorption of phenytoin
- Proton pump inhibitors and H2 blockers impair dissolution and absorption of ketoconazole by raising the pH

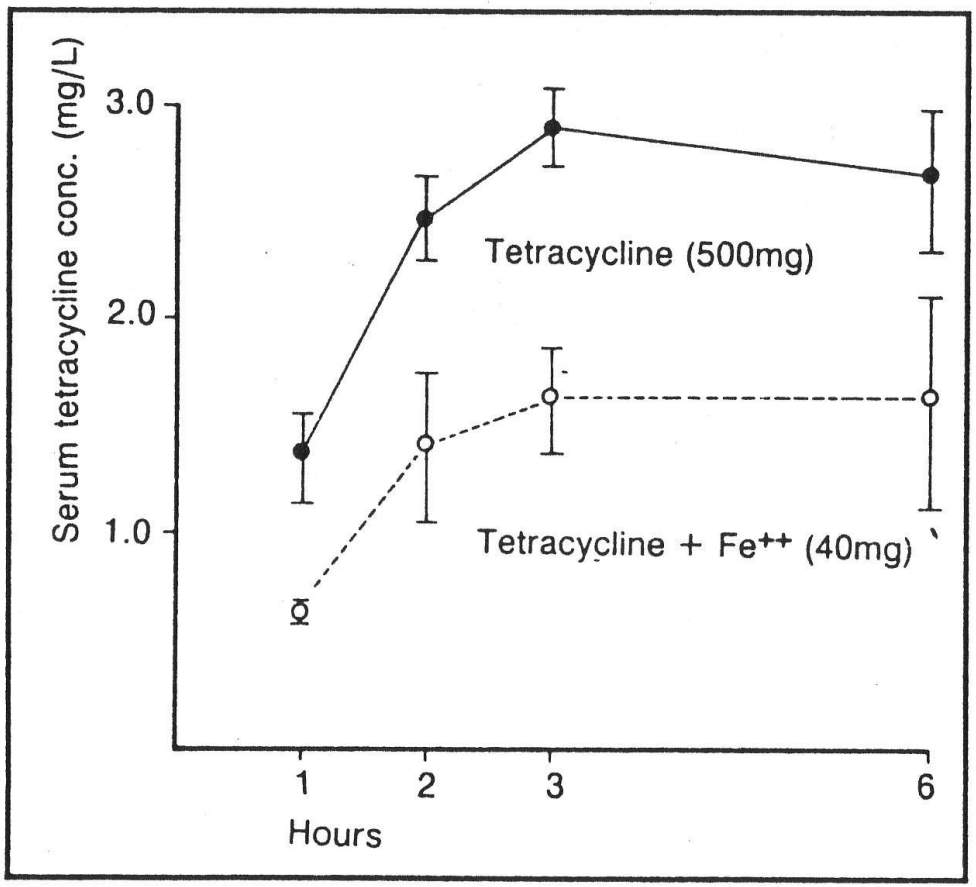


Fig. 6. *Interference with drug absorption:* Reduced absorption of tetracycline caused by simultaneous ingestion of ferrous sulphate. Serum concentrations of tetracyclines (mg/L) are given on the y axis (●—● = tetracycline alone; ○---○ = tetracycline with ferrous sulphate) [after Neuvonen et al. British Medical Journal 4: 532, 1970; by permission of author and editor].

Interactions :Oral Bioavailability

affecting gastric emptying:

- rate of gastric emptying alters rate of drug absorption, but not the extent of drug bioavailability.
- rate of gastric emptying important when a rapid onset of effect of the drug is desired.

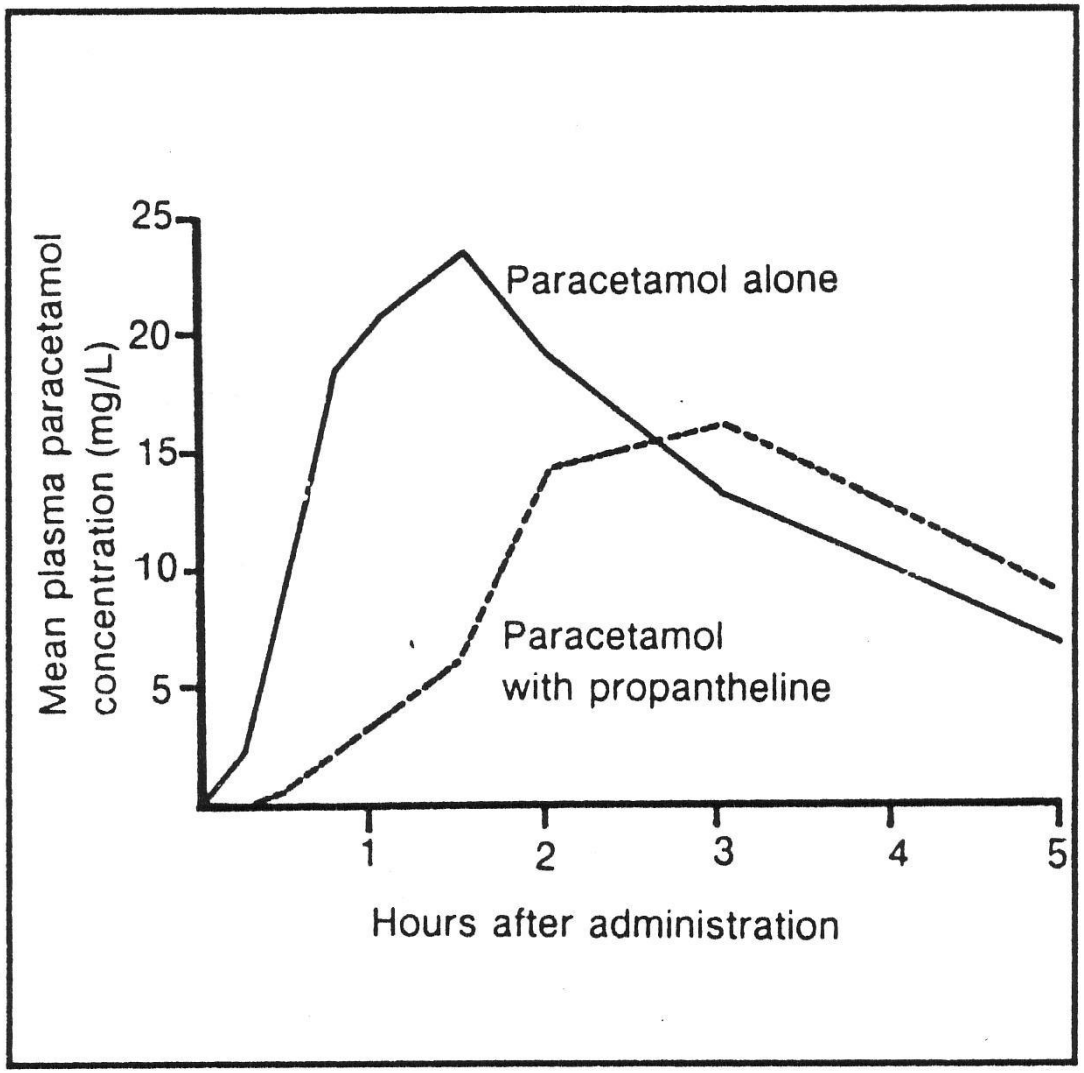


Fig. 3. *Change in the rate of drug absorption:* Reduced rate of absorption of oral paracetamol (1.5g) by propantheline (30mg intravenously) [after Nimmo et al. British Medical Journal 1: 587, 1973; by permission of author and editor].

Distribution Interactions

Displacement from plasma protein binding sites

Displacement from tissue protein binding sites

Distribution interactions

- **Displacement of one drug by another**
- **Very high binding & narrow margins of safety**

to be clinically important

aspirin + Warfarin

Valproate + phenytoin

kernicterus – displacement of bilirubin by NSAID'S drugs, Sulphonamides

- **Displacement from tissue proteins**

quinidine displaces digoxin – digoxin intoxication

Protein-Binding Interactions

Phenylbutazone ,oxyphenbutazone, indomethacin

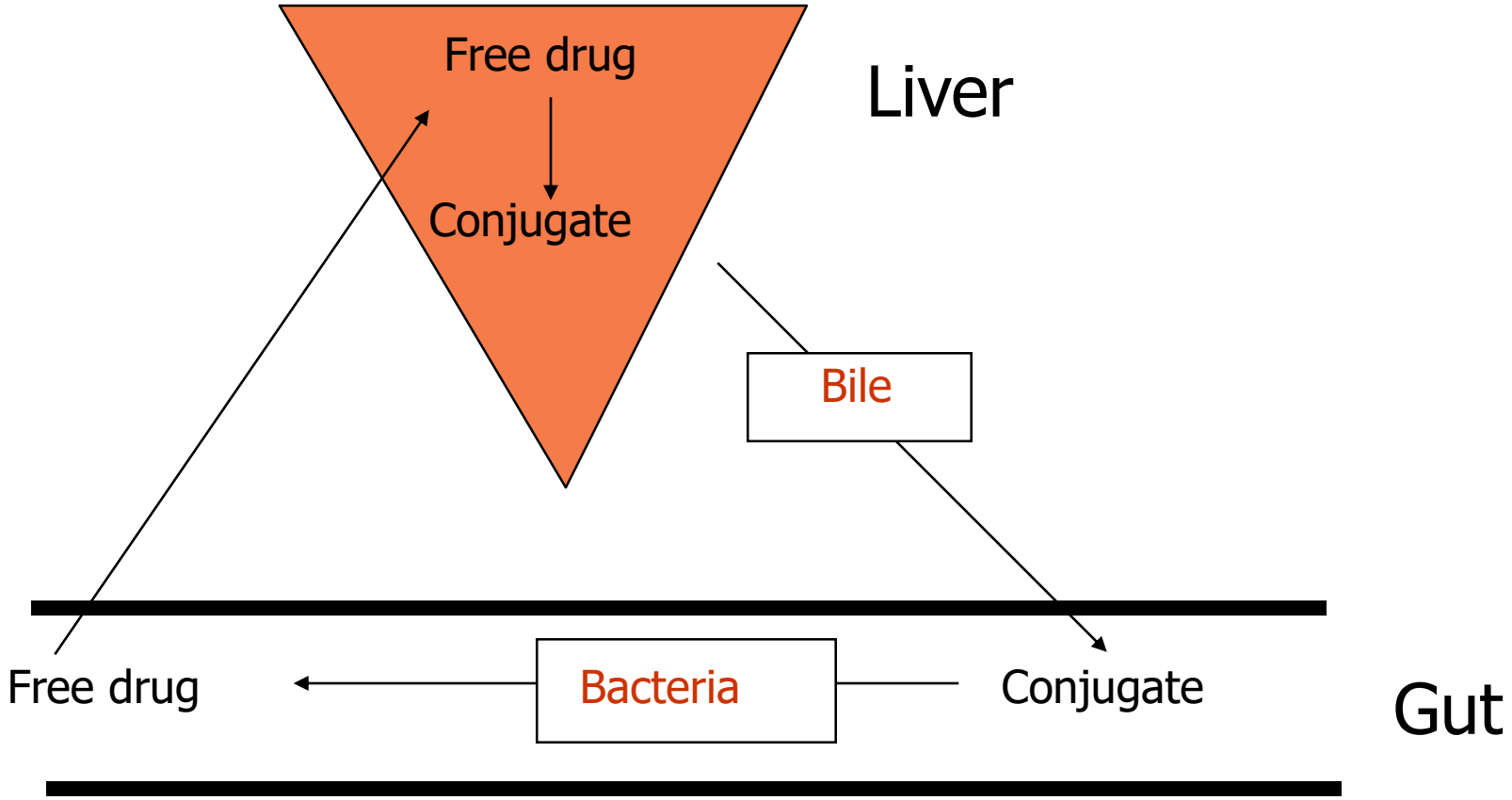
↓

Displace warfarin sodium from its PP binding sites

↓

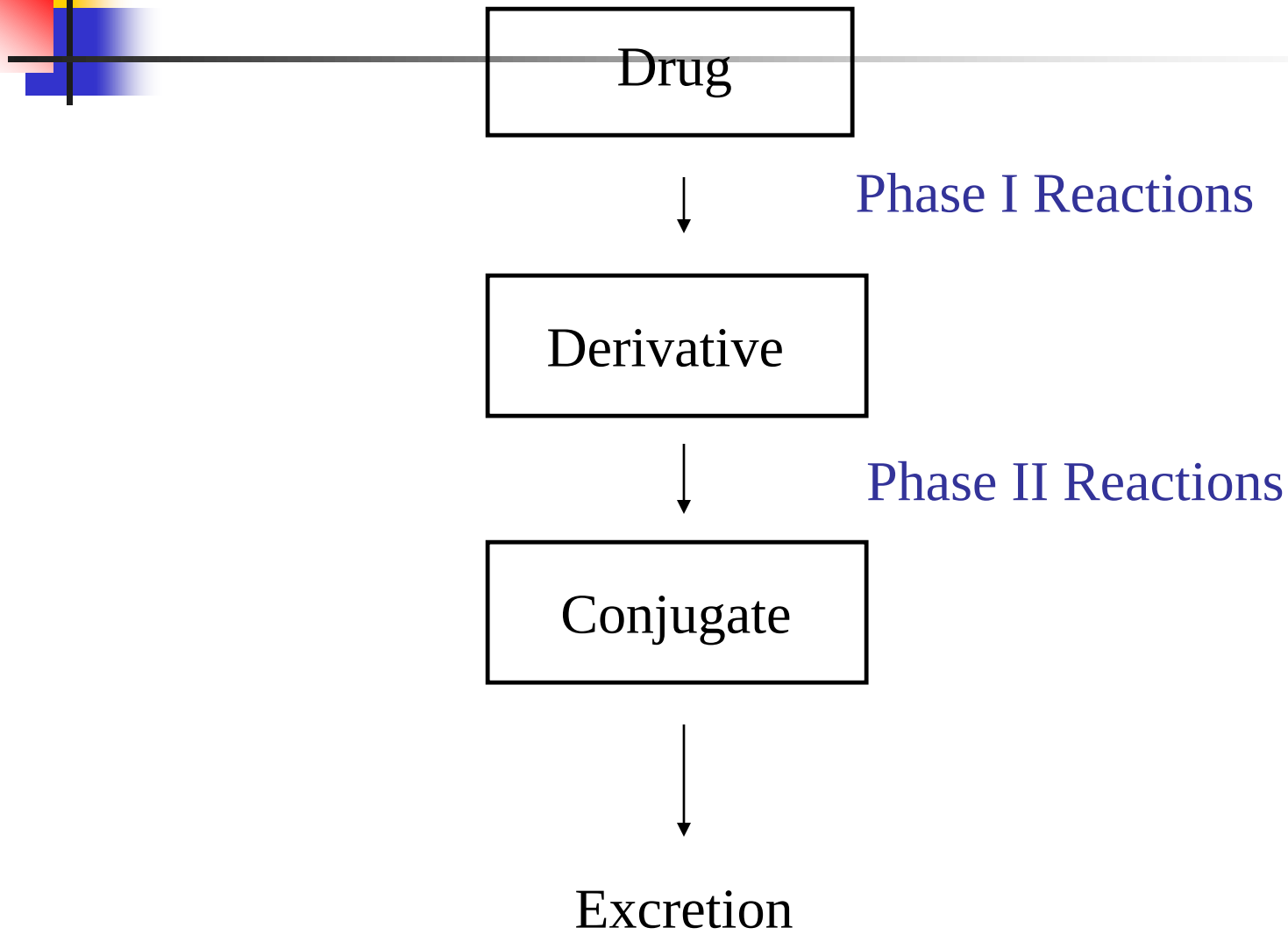
Severe bleeding episode

Interactions via Enterohepatic Circulation

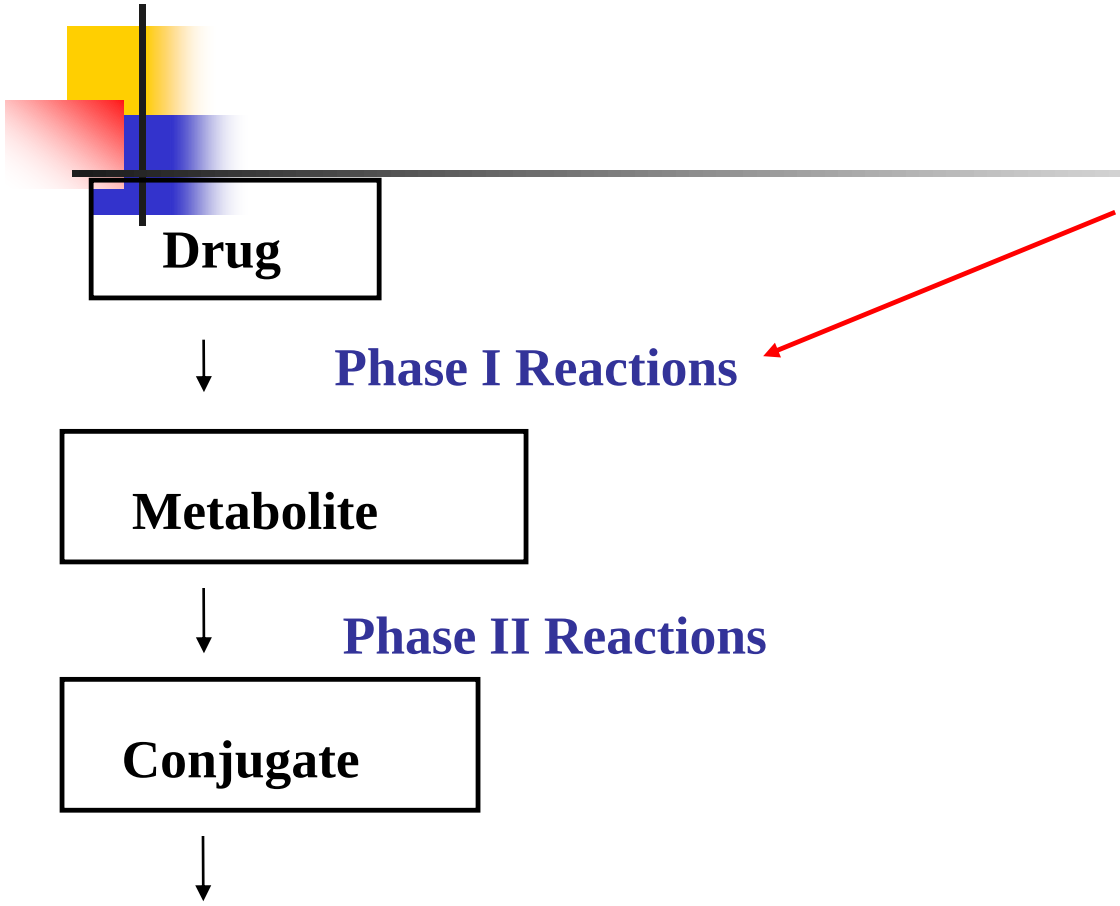


Pharmacokinetic Interactions: Drug Metabolism

Liver Metabolism: Phase I & Phase II reactions



Pharmacokinetic Interactions: Drug Metabolism

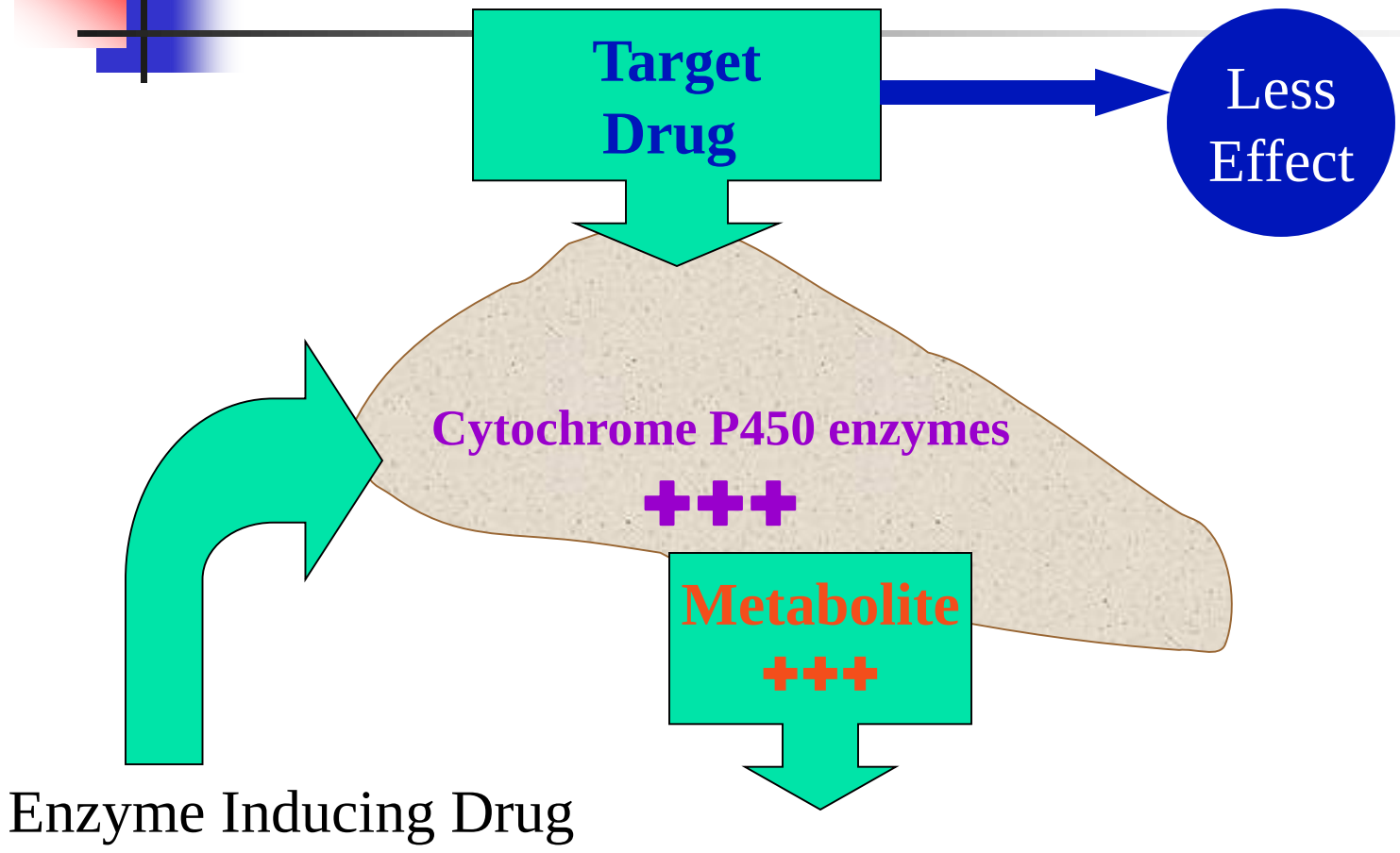


Property of enzymes in Phase I reactions is INDUCTION

Particular Drug Groups are known to cause Induction / Inhibition of Phase I enzymes

This will effect the metabolism of other drugs

Enzyme inducers reduce the effect of the target drug



Examples of enzyme inducers

- Phenytoin
- Phenobarbitone
- Carbamazepine
- Nevirapine
- Rifampicin
- Chronic alcohol intake
- Smoking

CASE

A 30 yr old female patient was prescribed ciprofloxacin 500 mg twice daily for UTI

She is a known case of bronchial asthma on theophylline 300 mg twice daily

After 4 days ,she presented with restlessness ,irritability ,insomnia ,palpitation and tremor

How would you explain these signs and symptoms

Metabolism (biotransformation)

- **Impact on cytochrome P450**
  - There are different **isoforms of CYP450**
  - The most important are CYP450 **3A4, 2D6**
  - **Inducers:** phenytoin, carbamazepine, barbiturates, rifampicin, griseofulvin, extract from St. Johns Worth (Hypericum perforatum)

Enzyme Inhibitors

- Erythromycin
- Ciprofloxacin
- Metronidazole
- Chloramphenicol
- Sulphonamides
- Acute alcohol
- Allopurinol
- Isoniazid
- Sodium valproate
- Cimetidine
- Amiodarone
- Fluconazole

Examples

- ✓ HMG-CoA reductase inhibitors metabolized by CYP3A4

Given along with erthromycin , diltiazem or Azole antifungals -↑ risk of myopathy

- ✓ Antihistaminics resulting in QTc interval prolongation if combined with CYP3A4 inhibitors
- ✓ Sodium valproate inhibits metabolism of phenytoin

- Mrs Mehta,45 year old ,has been on lithium carbonate 300 mg daily ,since 5 yrs for Maniac depressive illness. Recently she was diagnosed to have stage 1 HT for which she was prescribed hydrochlorthiazide 25 mg daily.After 2 wks she came to the EMD with severe tremor,ataxia ,nystagmus

Explain the reason ?

Excretion Interaction
Lithium + Thiazides

Probable mechanism:

- Thiazides cause diuresis and initial sodium loss.
- Compensatory sodium retention in proximal tubules.
- Proximal tubules do not distinguish sodium from lithium.
- Lithium also retained and accumulates.

Pharmacokinetic interactions

- **Excretion – mainly renal**
- **Inhibition of tubular secretion**
  Uricosuric drug probenecid decrease tubular secretion of some drugs, e.g. Penicilins,
- **Thiazide diuretics** cause relative Na^+ depletion and thereby they indirectly increase **Li^+** reabsorbtion
- Decreased renal clearence of Li^+ = CNS toxicity

Mechanisms of drug interactions

II. Pharmacokinetic interactions

- Excretion – inhibition of tubular secretion examples

Primary drug	Competing drug	Effect of interaction
Methotrexate	Salicylates Sulfonamides	Bone-marrow suppression
Digoxin	Amiodarone Verapamil	Increased plasma digoxin

Pharmacodynamic interactions

- ↑or ↓ pharmacological effects through effect on same receptor or same or different physiological or biochemical pathway:
- Clinicallly important examples:

1. warfarin + aspirin

increased risk of bleeding (both PK and PD interaction, aspirin is OTC drug!)

2. Diuretics (eg. furosemide) + digoxin

Hypokalemia during diuretic therapy increase toxicity of digoxin (competition for Na^+K^+-ATPase)

Pharmacodynamic interactions

3.ACE-inhibitors + potassium sparing diuretics

ACE-I increase pottasium levels already increased by potassium sparing diuretics (e.g. spironolactone) – risk of hyperkalemia and arrythmias

4. β- blockers + verapamil (Ca $^{2+}$ channel blocker):

potentiation of negative chronotropic & inotropic effects: serious bradycardia and cardiac arrest

5. β-blockers and insulin

sudden hypoglyceamia without any warning!

Mr Gautam,62 year old ,was complaining of pain in both knee joints for which diclofenac 50 mg twice daily was prescribed by his physician.He is a known hypertensive well controlled with Enalapril 10 mg daily. When he came for review after 2 months ,his B.P was 160/100 mm of Hg .What could be the cause of his elevated B.P

DRUG INTERACTIONS

Risk situations

Low therapeutic ratio

Steep dose-response curve

Complicated patient

Elderly / organ failure

Complex pharmacokinetics of drug
- presystemic metabolism
- saturation kinetics

Disastrous effect of therapeutic failure

More than one prescriber

Food drug Interaction

- Cytochrome P-450 in GI and liver
- Grapefruit juice concentrate will inhibit this enzyme
- Many drugs for AIDS, HTN
- Effects occur 24 hours after ingestion

Drugs known to interact with grapefruit juice

- Anti-hypertensives (filodipine, nifedipine, nimodipine, nicardipine, isradipine)
- Immunosuppressants (cyclosporine, tacrolimus)
- Antihistamines (astemizole)
- Protease inhibitors (saquinavir)
- Lipid-Lowering Drugs (atorvastatin, lovastatin, simvastatin)
- Anti-anxiety, anti-depressants (buspirone,diazepam, midazolam, triazolam, zaleplon,

Food -Effects on Drugs

—Patients on low sodium diets will reabsorb more lithium along with sodium; patients on high sodium diets will excrete more lithium and need higher doses

Food Effects on Drug Action: MAOIs

- Monoamine oxidase inhibitors (MAOI) interact with pressor agents in foods (tyramine,)
- Pressors are generally deaminated rapidly by MAO; MAOIs prevent the breakdown of tyramine and other pressors
- Significant intake of high-tyramine foods (aged cheeses, cured meats) by pts on MAOIs can precipitate hypertensive crisis

Food- Effects on Drug Action: Caffeine

- Increases adverse effects of stimulants such as amphetamines, methylphenidate, theophylline, causing nervousness, tremor, insomnia
- Counters the antianxiety effect of tranquilizers

Warfarin, Vitamin K

Vitamin K important in coagulation (blood clotting)

Warfarin (an anticoagulant) → **inhibits coagulation**

Too much Vitamin K
(Vitamin supplements, leafy greens)

Reduced effectiveness of warfarin

Food Effects on Drug Action: Warfarin

- Other foods with anticlotting qualities may also have an effect (garlic, onions)

Food drug Interaction

- High fiber diet may decrease the absorption of tricyclic antidepressants such as amitriptyline.
- Digoxin should not be taken with high phytate foods such as wheat bran or oatmeal.
- Levodopa not with HPD

Things to Remember

- Interactions are easily forgotten when prescribing
- Interactions are difficult to remember
- Many interactions probably remain undescribed – so look out for them
- The chances of interaction are 60 times higher in a patient taking 5 drugs than in one taking 2.

A drug M is injected IV into a laboratory subject. It is noted to have high serum protein binding. Which of the following is most likely to be increased as a result?

A. Drug interaction
B. Distribution of the drug to tissue sites
C. Renal excretion
D. Liver metabolism