Pharmacokinetic and pharmacodynamic drug interactions

Drug interactions
Lecture 1

- Introduction
- Absorption based interactions

Drug interaction

When 1 drug alters the effects of another drug

e.g. Drug A causes Drug B to have ...

- Increased or reduced effect
- Slower or more rapid effect
- New or increased side effects

TYPE OF INTERACTION

Unidirectional

Bidirectional

Pharmacokinetic & Pharmacodynamic interactions

Me

Pharmacokinetic: **Amount of drug in blood is altered**

Pharmacodynamic: **Amount of drug in blood remains the same, but its effect is altered**

ADME

Absorption

Distribution

Metabolism

Excretion

Absorption based interactions

One drug make the absorption of another drug …

- Faster or slower
- Less or more complete

Mechanisms

- pH
- Gastric emptying and intestinal motility
- Physico-chemical interaction

Changes in pH of G.I.T. contents

Stomach pH is variable.

Antacids pH ↑

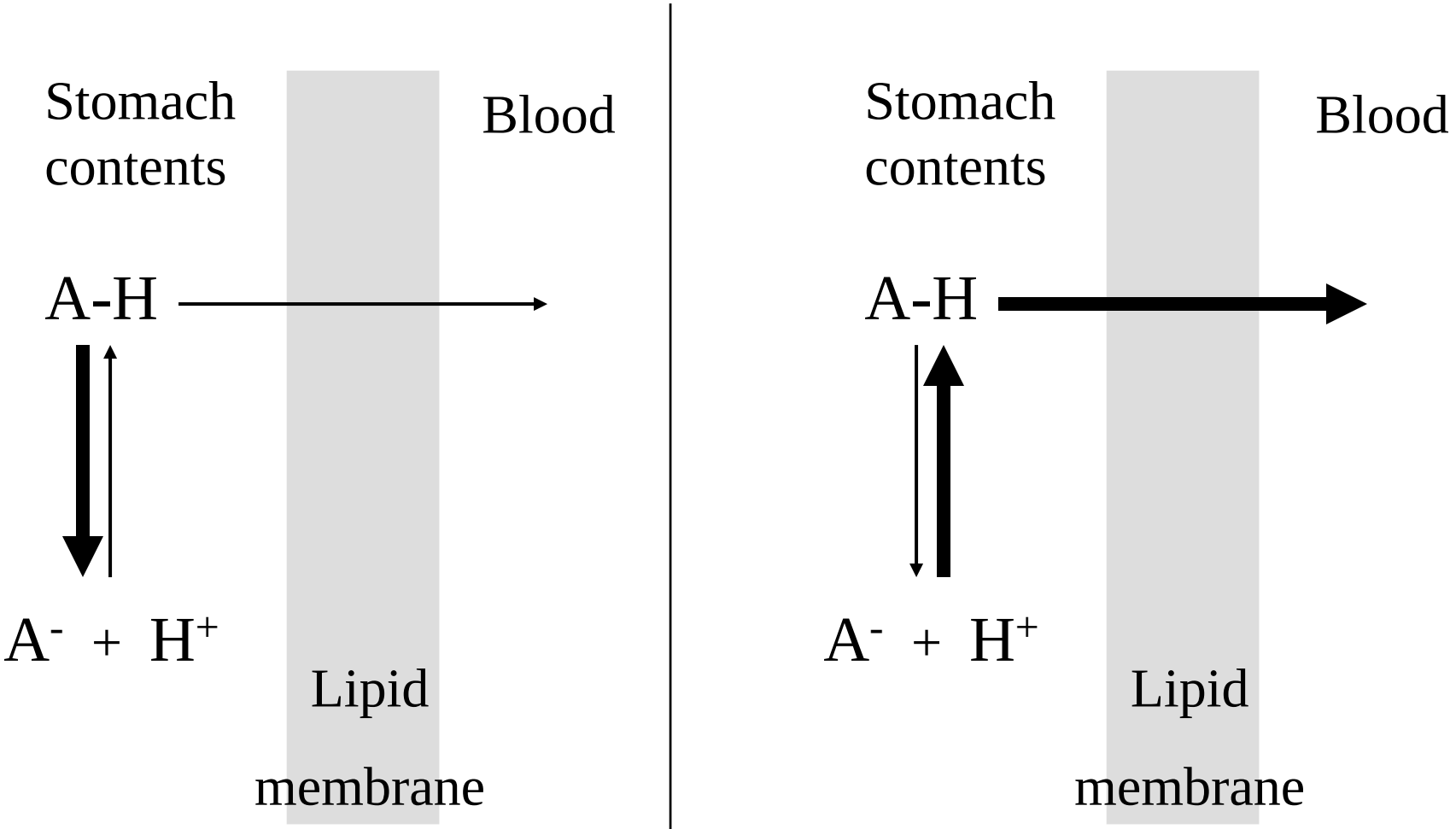
Alcohol and some foods cause acid secretion. pH ↓

Small and large intestine.

pH always near neutral.

No significant changes seen.

Alleged mechanism



Theory

Antacids

↓

Less acidic stomach contents

↓

More ionisation

↓

Slower absorption

Alcohol

↓

More acidic stomach contents

↓

Less ionisation

↓

Faster absorption

Above is for acid drug. ***Opposite pattern for a basic drug.***

Practice

- Most drug absorption occurs from the ***intestine***, not the stomach (Surface area + Blood flow).

- ***Changes in rate of absorption from the stomach are of little consequence.***

- Acidity also changes the rate of dissolution of acid drugs. Antacids make them **dissolve quicker** which cancels out (or even) exceeds the effect of **ionisation changes.**

Clinical significance

Changes in pH of G.I.T. contents

Very little (if any).

Gastric emptying and intestinal motility

Drug absorption from small intestine is much more efficient than from the stomach.

Drug A alters rate of gastric emptying.

Rate of absorption of **drug B** is also altered.

Drugs altering rate of gastric emptying

- *Opiate analgesics* (e.g. Morphine, pethidine) ***Much slower***
- *Antimuscarinic drugs* (e.g. Atropine, propantheline) ***Slower***
- *Tri-cyclic anti-depressants* - **antimuscarinic** side-effects (e.g. Imipramine) ***Slower***
- ***Muscarinic agents*** ***(e.g.*** **Bethanechol)** ***Faster***

Clinical significance
Multiple dosing

With multiple dosing:

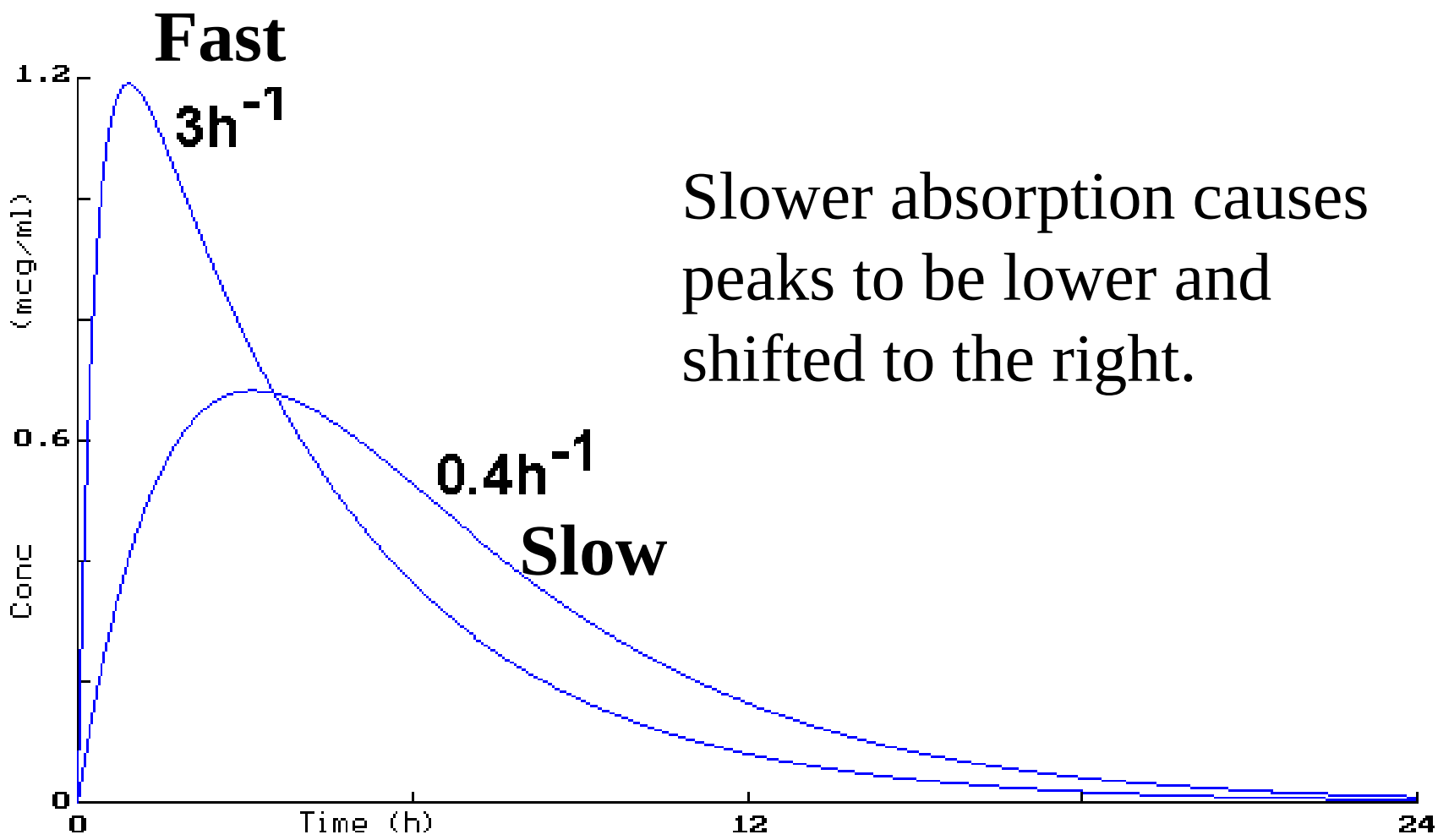
$$Css = \frac{F.Dose}{Cl.\tau}$$

Css depends upon **extent** of absorption (**F**), **not rate** (**Ka**).

Changes in gastric emptying generally affect the rate rather than the extent of drug absorption.

Not of great clinical significance.

Clinical significance, Single dose



Slower absorption causes peaks to be lower and shifted to the right.

Clinical significance

Single dose

If blood levels of the affected drug need to arise above a certain level to be effective (e.g. pain killer), a reduced rate of absorption could theoretically be significant.

Examples that would cause real clinical concern are hard to find.

Physico-chemical interactions

Two drugs bind together within the G.I.T. contents and then neither is absorbed.

Examples:

- **Tetracycline**
- **Colestyramine**
- **Charcoal**

Tetracyclines and polyvalent cations

e.g. Ca^{2+}, Al^{3+}, Mg^{2+} or Fe^{2+}
Form non-absorbable chelates with tetracyclines.

Iron tablets - Fe^{2+}
Antacids - Al^{3+}, Mg^{2+} etc
Dairy products (Milk, cheese) - Ca^{2+}

Effect is considerable. Antacids can reduce absorption of tetracyclines by 80%.

Solution: Leave a 2 hour gap between the two drugs.

Colestyramine and acidic drugs

Colestyramine: Basic anion exchange resin.

Purpose: Bind to bile acids, prevent their re-absorption, force body to synthesis new bile acids from cholesterol, reduce cholesterol load in body.

Problem: Non-selective. Binds any acidic molecule, inc. acidic drugs.

Examples: Thyroxine, valproate, thyroxine may show reduced absorption..

Charcoal

Therapeutic use rather than interaction.

Charcoal absorbs most drugs.

Used in over-doses.

Given within 1 hour of : digoxin, phenytoin, aspirin (etc) overdose, reduces absorption by up to 95%

Terms with which you should be familiar

- **Pharmacokinetic interaction**
- **Pharmacodynamic interaction**

CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION

Complexation/Chelation

Altered GI Transit

Altered Gastric pH

Example: H-2 blockers + ketoconazole

Impact: dissolution of ketoconazole is decreased, resulting in reduced absorption

CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM

Induction of Metabolism

rifampin **+ theophylline**

Inhibition of Metabolism

Example: *cimetidine* + theophylline

Impact: cimetidine reduces the clearance of theophylline causing an increase in adverse effects

CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM
ALTERATIONS IN RENAL CLEARANCE

Increase in Renal Blood Flow

Example: hydralazine + digoxin

Impact: hydralazine *increases* the renal clearance of digoxin

CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM
ALTERATIONS IN RENAL CLEARANCE

Increase in Renal Blood Flow
Inhibition of Active Tubular Secretion

Example: probenecid + penicillin

Impact: probenecid <u>prolongs</u> the half-life of penicillin, allowing single dose therapy

CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM
ALTERATIONS IN RENAL CLEARANCE

Increase in Renal Blood Flow
Inhibition of Active Tubular Secretion
Alterations in Tubular Reabsorption

Example: antacids + aspirin

Impact: antacids reduce the tubular reabsorption of salicylate via an increase in urine pH

FACTORS WHICH ALTER HEPATIC BLOOD FLOW

Increased Flow

- Glucagon
- Isoproterenol
- Phentolamine
- Phenobarbital
- High-protein meal
- Viral hepatitis

Decreased Flow

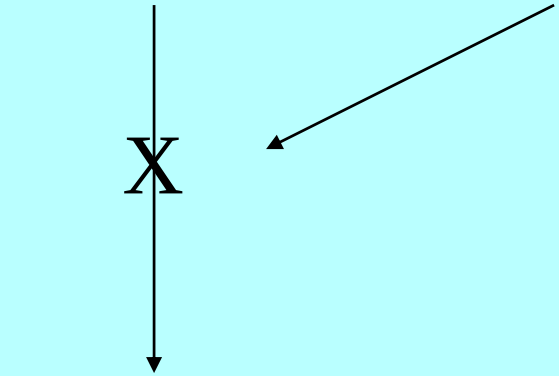
- Propranolol
- Norepinephrine
- Anesthetics
- Labetalol
- Upright posture
- Hypovolemia
- CHF
- cirrhosis

What you should be able to do

- Distinguish pharmacokinetic from pharmacodynamic interactions.
- Cite examples of drugs etc that might alter gastro-intestinal pH or motility and explain how such changes might lead to altered drug absorption
- Identify cases where one drug might bind to and prevent the absorption of another drug.
- Assess the practical clinical significance of the above theoretical interaction mechanisms.

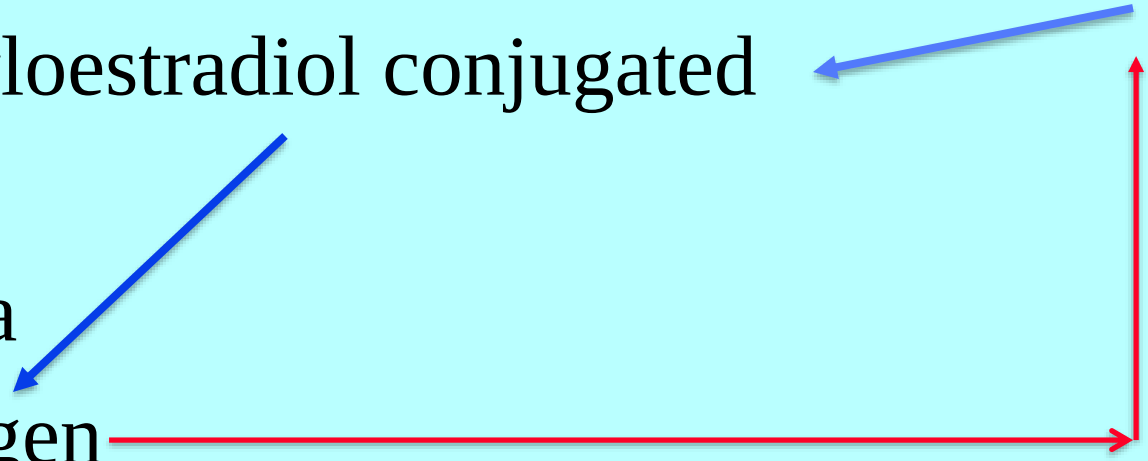
Drug interaction

- **Parkinson** :
- L.Dopa + Carbidopa (extracerebral dopa carboxylas inhi



Drug interaction

- Antibiotics + Ethinyloestardiol ⟶ Liver
- Ethinyloestradiol conjugated
- Flora
- Oestrogen



Pharmacodynamic interactions;

It means alteration of the dug action without change in its serum concentration by pharmacokinetic factors.

EX., Propranolol + verapamil → **Synergistic or additive effect**

Synergism means =1+1=3

Additive means= 1+1=2

Potentiation means= 1+ 0=2

Antagonism means 1+1=0 or 0.5

On the other hand

Effect at the receptor site
- **Antiadrenegic**
- **anticholinergic**