

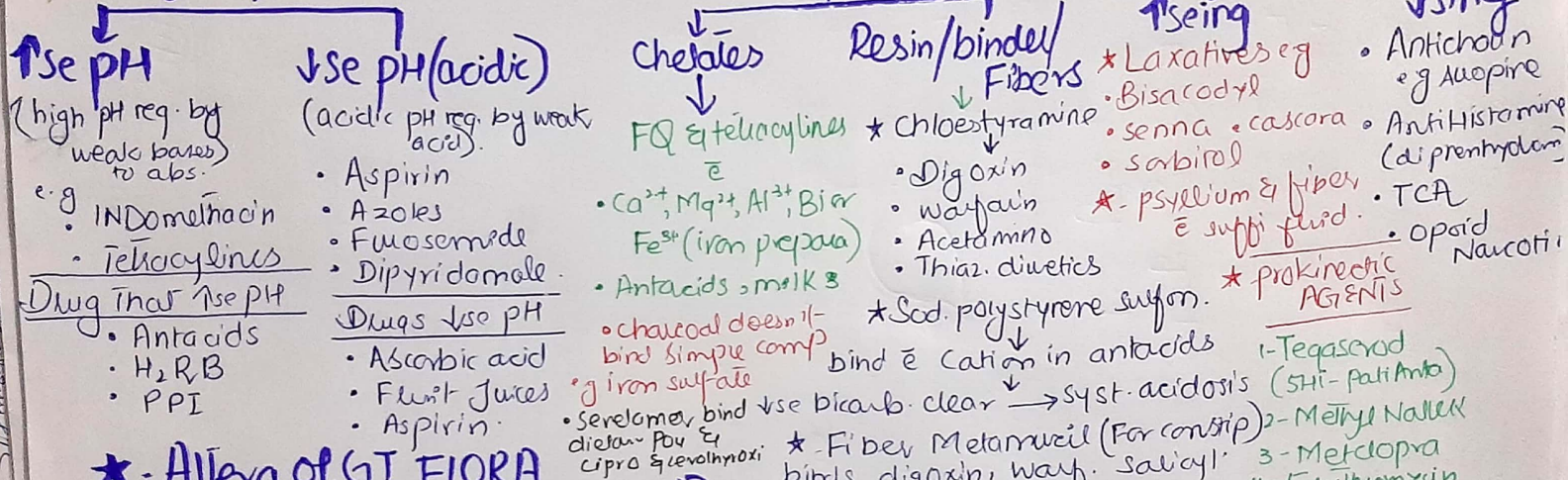
Pharma-Kine-INTERA

GASTROINT. ABSORPTION

Drug Affe. PH

Chelation & complex

MOTILITY



* Altera of GI FLORA

- Estrogen contracep **Flora** → active
- Digoxin **Flora** → Inactive
- vit-K **Flora** → synthesis

ETHANOL-DOSE-DUMPING:

Affect Bioavail in Delay/susta release
CO-aden & Alcohol (due to dissol in ethanol)
40% strength → 5-Fold ↑ use cmax
20% strength → 2-Fold ↑ use cmax
Hydromorphone → 16-Fold ↑ use

* P-Glycoprotein EFFLUX

- Substrate**
 - Digoxin
 - Linezolid
- Inhibit**
 - Ritonavir
 - Ketoconazole, itra
 - Cyclosporin
 - Clav, erythromycin
 - verapamil
 - Amiodarone
- Inducers**
 - Rifampin
 - St. John's wort

Blood Flow to GIT

- BF ↓ use to GIT in case of CHD → so abs. of other drugs ↓ use
- However ↑ Digoxin BF to GIT

MALABSORPTION: - Neomycin cause malabs. = tabs of digoxin

DISTRIBUTION

Albumin

- quantitatively primary protein
- Itself $\rightarrow$ basic
- BIND $\rightarrow$ Acidic / Neutral drugs

1) Salicylates

2) Warfarin

(7) ketoconazole

8) phenytoin

9) prednisolone

(3) Ibuprofen

(4) Nafacillin

(5) Digoxin

(6) citalopram

Alpha-1-acid
Glycoprotein
(AAG)

- iluey acid
- bind basic/neutral

1) prazosin

2) Methdone

3) cocaine

4) lidocaine

5) liponavir

6) quinine

7) erythro

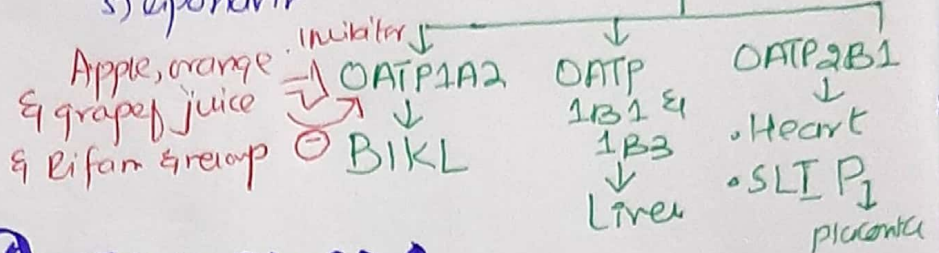
8) carbamazepine

Organic Anion
transporting polypep
(OATP)

- Family of 11 memb influx transport. protein
- Influx to hepatocytes

1st metabo

Location



METABOLISM

Enzyme INDUCTION

- Smoking (Polycyclic aromatic HC) $\Rightarrow$ CYP1A2 $\Rightarrow$ $\uparrow$ se metabo & $\downarrow$ se level

- clozapine
- Haloperidol
- duloxetine

- Rifampicin $\Rightarrow$ Oral contraceptive (causing contra. failure)
- carbamazepine
- modafinil

- Phenytoin $\Rightarrow$ ciclosporin $\downarrow$ Transplant rejection

- Alcohol $\rightarrow$ paracetamol Hepatotox. $\downarrow$ at lower doses

- Phenytoin & Rifam $\rightarrow$ corticosteroid $\uparrow$ se conic meta Therap. failure

- * $\downarrow$ Hep. BF = $\downarrow$ extraction = $\downarrow$ meta $\uparrow$ level e.g. propranolol

- * Non-hepa enzy can be invo. in metab. e.g. SSRI + Linezolid (which is MAOI)

Enzyme Inhibition

- Cimetidine $\Rightarrow$ MFO $\rightarrow$ $\uparrow$ se level of atorvastatin
- Also $\uparrow$ se level of Anti-epileptic

- MAOI $\Rightarrow$ co-admin $\bar{e}$ Tyramine food or β -agonist/catecholamine $\downarrow$ Hypertensive crisis

- Antibiotic $\rightarrow$ intestinal flora $\downarrow$ vit-K $\uparrow$ Digoxin level $\downarrow$ Estrogen/progestin (contracep.)

- Ciprofloxacin, clarithromycin $\Rightarrow$ Anticoagulant $\uparrow$ se [AC] $\downarrow$ Bleeding

- Omeprazole $\xrightarrow{2C19}$ moclobemide $\uparrow$ (MAOI)

- Fluvoxamine $\xrightarrow{2C19}$ Diphenhydramine $\uparrow$

- Diphenhydramine $\xrightarrow{2D6}$ Metoprolol $\uparrow$ se
- Venlafaxine

RENAL CLEARANCE

Urinary pH

- Reabsorp. depends upon pH

⇒ Alkaline pH = Acidic drugs
 ↓
 ionized & lipid insoluble
 ↓
 ↓ reabsorp. &
 vice versa for basic drugs
 and Acidic pH.

Antacids & NaHCO_3 = Alkalinization

↑ reabsorp. of Salicyl.
 ↓ reabsorp. of Amphetamines

Active Tubular Secretion

- Probenecid ↓ reabsorp. of penicillin
- NSAIDs & Salicylates
 ↓ reabsorp. of MTX = ↑ MTX
 Sometimes leads to toxicity

GFR & RBF

- Methylxanthines
 e.g. caffeine, theophylline
 ↓
 ↑ RBF = ↑ urinary drug excretion
- NSAIDs ↓ RBF
 ↓
 ↑ lithium level esp. in indomethacin

PHARMACODYNAMIC INTERACTIONS

ANTAGONISM

- Antihypertensive effect of β -blockers
 is co-admin of vasopressor/vasodilator
 (PE, NE, Epi).

Naloxone — opiate

Benzodiazepines — flumazenil

Vit-K — warfarin

L-Dopa — antipsychotics

Pentazocine + Naloxone
 (opiate) (antagonist)

↓
 Talwin NX comb. product
 To ↓ pain

Additive/Synergistic

- NSAID + Anticoag
 ↑ risk of bleed
- ACEI + K^+ sparing diuretic
 ↓
 Hyperkalemia
- verapamil + β -antag ⇒ Bradycardia
- NM-blocker + Aminoglycoside ⇒ ↑ block
- Primidone + Sotalolol ⇒ ↑ QT
- Clozapine + Clo-mimox ⇒ ↑ bone marrow suppress.
- Alcohol + benzo ⇒ ↑ sedation

↑ receptor sensitivity or toxicity

- ↓ K^+ due to Thiazide diuretic
 ↓
 Heart sensitized to Digoxin Therapy
- ↓ Na^+ due to diuretic
 ↓
 Lithium Toxicity

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FOOD-DRUG INTERAC

Delayed, Extended, Sustained or enteric coated drug are most adversely affected

Abs. of lipid soluble drug

↑ use in presc of fatty food
and vice versa for
H₂O-soluble

• FQ & Tetr

↓
Milk, other
dairy products
↓
Complex/chelate

Ibandronate
(For osteopor)

↓
abs ↓ use w
food.

FQ &
Phenytoin
adsorb to
Ca²⁺/Fe in
tube
feedings

* Grape fruit &
valencia orange juice

↓
Inhibit CYP3A4 isoenzyme

↑ use level of CCBs, PI, Statins
⇒ Carbamazep, midazolam

* Spinach & broccoli ⇒ Inhibit vit-K ⇒ ↓ warfarin effect

* Garlic ⇒ Additive effect in comb. w warfarin, Hepar, LMWH

* Tyramine food (aged cheese, meat, chicken liver, pickled or smoked fish, red wines) ⇒ MAOI ⇒ Hypertensive crisis

* mangoes, oranges, bananas, Dates ⇒ ↑ K⁺ ⇒ may cause hyperkalemia in pre acets etc

AFFECT OF FOOD ON BIOAVAIL

Reduce/Delay

- NSAIDs (Naproxen)
- Aspirin
- Acetaminophen
- Antibiotics (Tetr & penic)
- Ethanol

↑ used

- Griseofulvin
- Metoprolol
- Phenytoin
- Propoxyphene
- Dicumarol
- Morphine (GMP, PDM)

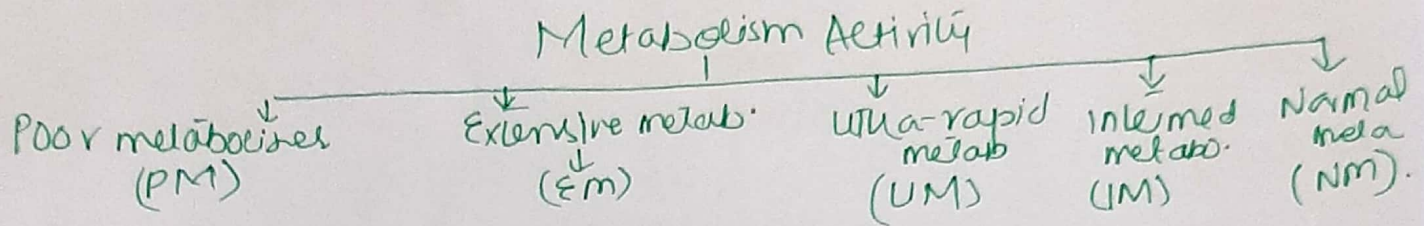
NOT AFFECTED

- Theophylline
- Metomidazole

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PHARMACOGENETICS & DRUG INTERACTION

- Polymorphism is extensively studied in CYP450, MFO, N acetyl transferase and UGT metab. enzy. sys.
- IN CYP450 = CYP2D6, 2C9, & 2C19 = extensively studied



⇒ The effect of inhibitor/enzyme in drug or substrate is more pronounced in $EM > PM$ OR $EM > NM > PM$

⇒ The effect of inducer drug: $PM > EM$ / $PM > NM > EM$ more pronounced in

EXAMPLES:

- 1) Omeprazole $\xrightarrow[\text{inhibitor}]{\text{CYP2C19}}$ metololamide
- 2) Fluvoxamine $\xrightarrow[\text{inhibitor}]{\text{CYP2C19}}$ Diphenhydramine
- 3) Diphenhydramine $\xrightarrow[\text{inhibitor}]{\text{CYP2D6}}$ metoprolol
- $\xrightarrow{"/"} \text{venlafaxine}$

} More pronounced effect on $EM \rightarrow$ ↓ use AUC and C_{max} lower than normal.

EFFECT ON DRUG DEVELOP.: pharmacogenetic testing

identify dosing variables in certain polymorphic population.

e.g By clinical trial in warfarin therapy we find polymorphism in CYP2C19: CYP2C19 polymorphism occurs in 20-25% of Asian population

Some drug have been withdrawn due to poly: $\rightarrow$ Troglitazone
 $\rightarrow$ mifepristide

FDA suggest test to determine polymorphism.

① Invader UGT1A1 molec. Assay = For UGT1A1 polymorphism $\Rightarrow$ ↓ level of irinotecan (normally)

② Amplichip CYP450 genotyping = For CYP450 polymorphism.

③ Also recommended test for antiplatelet drugs & malaviroc usage $\rightarrow$ (in HIV pt)

⇒ And for using them

Voriconazole
 valproic acid
 venlafaxine
 Tramadol
 Tamoxifen
 5-FU
 capacetabine

Irinotecan
 B-blocker
 Rifampin
 Dapsone
 Celecoxib
 Omeprazole, Fluoxetine

Ethnic diff in CYP2D6

variation in 2D6 = 10-30 fold diff in metabo.

- 1) Caucasians 7-10% PM / 1% UM
- 2) African American 8% PM
- 3) Asians > 50% PM / 1% UM