Pharma-Kine-INTERA

GASTROINT. ABSORPTION

Drug AFFE. PH

↑se pH
(high pH req. by weak bases) to abs.
e.g
- INDomethacin
- Tetracyclines

Drug That ↑se pH
- Antacids
- H_2RB
- PPI

↓se pH (acidic)
(acidic pH req. by weak acid).
- Aspirin
- Azoles
- Furosemide
- Dipyridomole

Drugs ↓se pH
- Ascorbic acid
- Fruit Juices
- Aspirin

★ - Alteration of GI FLORA
- Estrogen contraceptive —Flora→ active
- Digoxin —Flora→ Inactive
- vit-K —Flora→ synthesis

ETHANOL-DOSE-DUMPING:
Affect Bioavail in Delay/Susta release
co-adm ē Alcohol. (due to dissol in ethanol)
- 40% strength → 5-Fold ↑se Cmax
- 20% strength → 2-Fold ↑se cmax
- Hydromorphone → 16-Fold ↑se

Chelation & complex

Chelates
FQ & tetracyclines
ē
- Ca^{2+}, Mg^{2+}, Al^{3+}, Bior Fe^{3+} (iron prepara)
- Antacids, milk
- charcoal doesn't bind simple comp
- g iron sulfate
- Sevelamer, bind ↓se bicarb. clear → syst. acidosis
- dietary Pou & cipro & levothyroxi

Resin/binder/Fibers
- ★ Chloestyramine
  - Digoxin
  - warfarin
  - Acetamino
  - Thiaz. diuretics
- ★ Sod. polystyrene sulfon.
  - bind ē Cation in antacids
- ★ Fiber Metamucil (For constip)
  - binds digoxin, warf. salicyl.

★ - P-GLYCOPROTEIN EFFLUX

Substrate	Inhibit	Inducers
• Digoxin	• Ritonavir	• Rifampin
• Linezolid	• Ketoconazole, Itra	• ST. John Wart
	• Cyclosporin	
	• Clari, Erythromycin	
	• Verapamil	
	• Amiodarone	

MOTILITY

↑sing
- ★ Laxatives e.g
  - Bisacodyl
  - senna
  - cascara
  - sorbitol
- ★ - psyllium & fiber ē suffi fluid.
- ★ Prokinetic AGENTS
  1. Tegaserod (5HT - Pati Anta)
  2. Methyl Nalex
  3. Metclopra
  4. Erythromycin
  5. Alvimopam
  6. Cisapride (5-HT4)

↓sing
- Anticholin e.g Alopire
- AntiHistamine (Diprenhydam)
- TCA
- opoid Narcoti

BLOOD FLOW TO GIT
- BF ↓se to GIT in case of CHD ⇒ so abs. of other drugs ↓ses
- However ē Digoxin, BF ↑s to GIT

MALABSORPTION:
- Neomycin cause malabs. = ↓abs of digoxin

DISTRIBUTION

Albumin
- quantitatively primary protein
- Itsel → basic
- BIND → Acidic / Neutral drugs

1) Salicylates
2) Warfarin
3) Ibuprofin
4) Nafacillin
5) Digoxin
6) citalopram
7) ketocona
8) phenyloid
9) prednisolone

Alpha-1-acid Glycopro (AAG)
- itsel acid
- bind basic/neutral

1) prazosin
2) Methdone
3) cocaine
4) lidocaine
5) liponavir
6) quinine
7) erythro
8) carbama. zepine

Organic Anion transporting polypep (OATP)
- Family of 11 memb influx transport. protein
- influse to hepatocytes ⇓ ↑se metabo

Location

Apple, orange & grapef juice & Rifam & resp → (inhibit) OATP1A2 ↓ BIKL

OATP 1B1 & 1B3 ↓ Liver

OATP2B1 ↓
- Heart
- SLI P1 placenta

METABOLISM

Enzyme INDUCTION
- Smoking (Polycyclic aromatic HC) → CYP1A2 ↑se metabo & ↓se level
  - clozapine
  - Haloperido
  - duloxetine
- Rifampicin, carbamazep, modafinil ⇒ Oral contraceptive [causing contra. failure]
- phenytoin ⇒ ciclosporin ⇓ Transplant rejection
- Alcohal → paracetamol ↓ Hepatotox. at lower doses
- phenytoin & Rifam → corticosteroid ↓ ↑se conic meta ↓ therap. failure

★ - ↓Hep BF = ↓extraction = ↓meta ↑level
e.g. propranolol, morphine

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

Enzym Inhibition
- Cimetidine ⊖ → MFO → ↑se level of alorvastatin
  ⇓ Also ↑se level of Anti-epileptic
- MAOI ⇒ co-adm ē Tyramine food or β-agonist/catecholamine ⇓ Hypertensive crisis
- Antibiotic → intestinal flora ⇓
  ↓vit-k
  ↑Digoxin level
  ↓ Estrogen/progestin contracep.
- Ciproflox, clarithro [CC] ⇒ Anticoagul ↑se [AC] ⇓ Bleeding
- Omeprazole → (2C19) → moclobemide ↑ (MAOI)
- Fluvoxamin → (2C19) → Diphenhydramin ↑
- Diphenhyd → (2D6)
  - Metoprolol ↑se
  - venafexaine

RENAL CLEARANCE

Urinary pH

- Reabsorp. depends upon pH

⇨ Alkaline pH = Acidic drugs → ionized & lipid insolu → ↓se reabsorp. & Vice versa for basic drugs and Acidic pH.

Antacids & $NaHCO_3$ = Alkalinization → ↑se Amphetamine Reabs; ↓se salicyl. reabs.

Active Tubular Secretion

- Probenecid ↓se ATS of penicillin
- NSAIDs & Salicylates ↓se ATS of MTX = ↑ MTX ⇩ Sometimes leads to toxicity

GFR & RBF

- Methylxanthines e.g caffeine & theobromine ⇩ ↑RBF = ↑se urinary drug excretion
- NSAIDs ↓ RBF ⇩ ↑se lithium level esp ē indomethacin

PHARMACODYNAMIC INTERACTIONS

ANTAGONISM

- Antihypertens. effect of β-blockers ē co-adm of vasopressor/vasoconstr (PE, NE, Epi)
- Naloxone — opoid
- Benzodia — flumazenil
- Vit-k — warfarin
- Levodopa — antipsychotics.
- Pentazocain + Naltrexone (opoid) (antagonis) ↳ To ↓se abusive potential ⇩ Talwin NX combo. product ⇩ To ↓se pain

Additive/Synergistic

- NSAID + Anticoag ⇩ ↑se risk of bleed
- ACEI + k+sparing diuret ⇩ Hyperkalemia
- verap + β-antag ⇨ Bradycar
- NM-block + Aminoglyco ⇨ ↑se bloc.
- primozid + Sotalol ⇨ ↑QT
- Clozapine + clo-imoxaz ⇨ ↑se bone marrow suppres.
- Alcoh + benzo ⇨ ↑se sedation.

↑se receptor Sensitivity or Toxicity

- ↓K+ due to Thiazid diure ⇩ Heart sensitiza to Digoxin Therapy
- ↓se NA↑ due to dimetic ⇩ Lithium Toxici

FOOD-DRUG INTERAC

Delayed, Extended, sustained or Enteric coated drug are most adversely affected

- Abs. of lipid soluble drug ⇩ ↑se in presc of fatty food and vice versa for H_2O-soluble
- FQ & Tetra ⇩ Milk, other diary products ⇩ Complex/chelate
- Ibandronate (For osteopor) ⇩ abs ↓se ē food.
- FQ & Phenyto in adsorb to Ca^{2+}/Fe in tube feedings

* - Grape fruit & valencia orange juice ⇩ inhibit CYP3A4 isoenzy ⇨ ↑se level of CCBs, PI, Statins, Carbamazep, midazolam
* Spanish & broccoli ⇨ Rich in vit-K ⇨ ↓ warfarin effect
* Garlic ⇨ Additive effect in comb. ē 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 hyperkalem in pre ACEIs etc

AFFECT OF FOOD ON BIOAVAIL

Reduce/Delay

- NSAIDs (Naproxen)
- Aspirin
- Acetamino
- Antibiotics (Tetra & Peneci)
- Ethanol

↑sed

- Griseofulvin
- Meloprolol
- phenytoin
- propoxyphene
- Dicumarol
- Morphine

(GMP, PDM)

NOT AFFECTED

- Theophylline
- Metronidazole

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

Metabolism Activity

Poor metabolizer (PM)	Extensive metab. (EM)	Ultra-rapid metab (UM)	Intermed metabo. (IM)	Normal meta (NM).

⇒ The effect of inhibitor/enzyinhi drug or substrate is more pronun in EM > PM OR EM > NM > PM

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

EXAMPLES:

1) OMeprazole $\xrightarrow[\text{inhibit}]{CYP2C19}$ meclobemide
2) Fluvoxamine $\xrightarrow[\text{Inhibit}]{CYP2C19}$ Diphenhydramine
3) Diphenhydra. $\xrightarrow[\text{Inhib}]{CYP2D6}$ metoprolol
   . $\xrightarrow{\quad\quad}$ venlafaxine

} More pronounced effect on EM ⇒ ↓ use AUC and Cmax lower than normal.

EFFECT ON DRUG DEVELOP.: pharmacogenomic testing

identify dosing variables in certain polymorp. population.
e.g By clinical trial in warfarin therapy we find polymor. in CYP2C19: CYP2C19 polymorp occur in 20–25% of Asian population

Some drug have been withdraw due to poly: → Troglitazone, → Mibefradil

FDA suggest test to detem polymorp.
① Invader UGT1A1 molecu. Assay = For UGT1A1 polym ⇒ ↓ level of irinotecan (Normally)
② Amplichip CYP450 genotyping = For CYP450 polymor.
③ Also recommeded test For antiepilp drugs & maraviroc usage (in HIV pt)

⇩ And For using Them

Voriconazole	Irinotecan
valproic acid	B-blocker
venlafexaine	Rifampin
Tramadol	Dapsone
Tamoxifen	celecoxib
5-FU	Omeprazole, Fluoxetine
Capacetabine	

Ethinic diff in CYP2D6 metabo. (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