Pharmacology

Subject : Drug interaction

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Every Drug Interaction is Harmful ????

NO

- Several drug interactions are deliberately employed in therapeutics, e.g.
  - **ACE inhibitors + diuretics** to treat hypertension or
  - **Sulfamethoxazole + Trimethoprim** to treat bacterial infection or
  - **Furosemide + amiloride** to prevent hypokalaemia.

Drug interactions

يصير تأثير لدواء على دواء آخر (يعني بأثروا ع بعض او بيتداخل ال interaction الهم)

- It is the modification of the effect of one drug (the object drug) by the prior or concomitant administration of another.

بصير تغيير على ال action تبع الدواء الي اخدته هلا فبصير التأثير by prior (اما دواء انا باخده من قبل، أو اخدت معه دواء بنفس الوقت

Doctor should elicit a **detailed drug history** of the patient and record all the medication that he/ she is currently on.

Consequences of drug interactions

1) **Loss of therapeutic effect** بكون ما حكالك انه بياخد دواء.. فبيرجعلك بعد فترة وبقلك ما استفدت
2) **Toxicity** بكون السبب اما خربطة منك او المريض بياخد ادوية ما حكالك عنها
3) **Unexpected increase in pharmacological activity**
4) **Beneficial effects e.g additive & potentiation (intended) or antagonism (unintended).**
5) **Chemical or physical interaction**

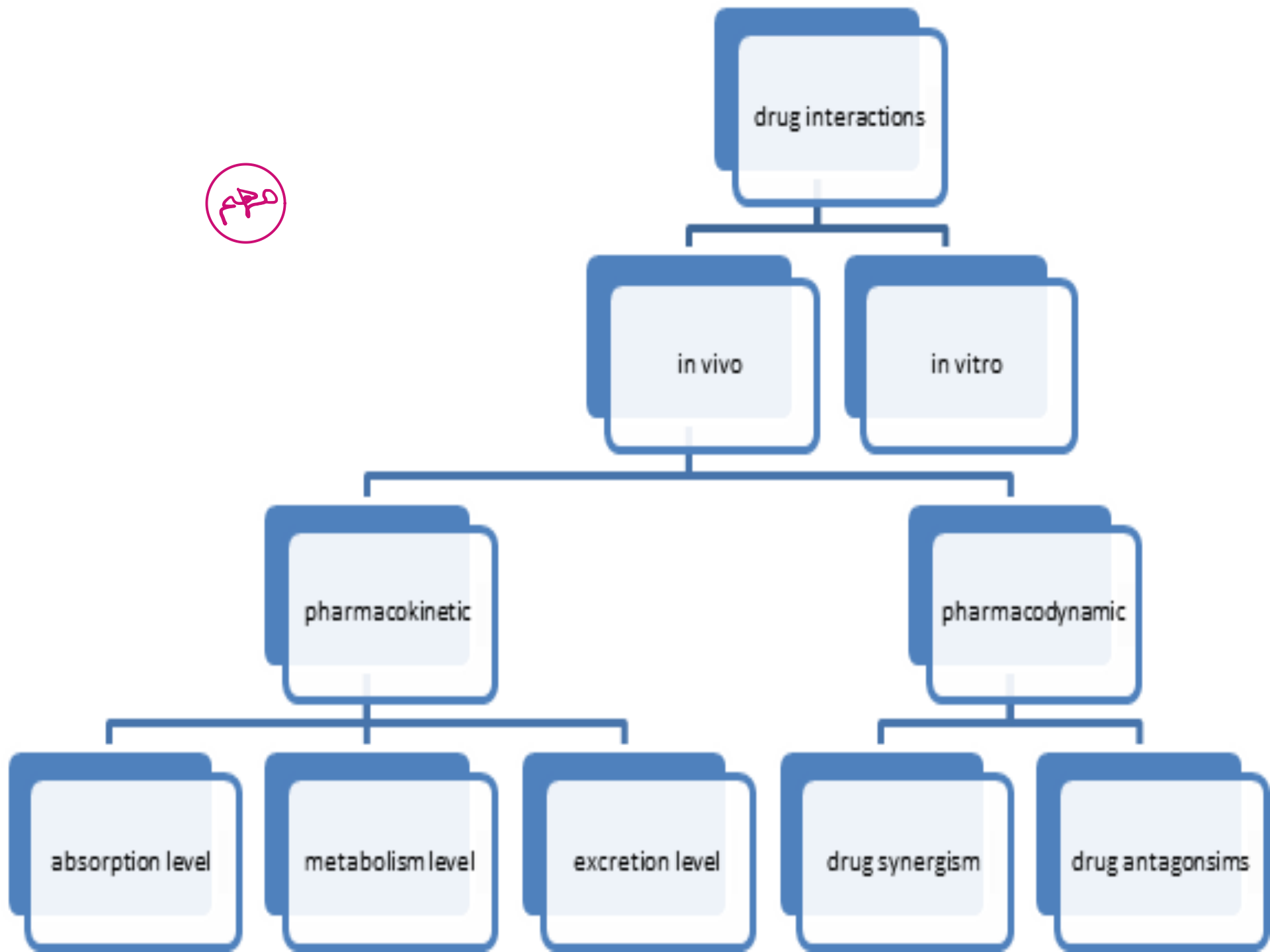
e.g I.V incompatibility in fluid or syringes mixture. لما يصير interaction بين دوائين اثناء التحضير أو انت خلطت اكتر من دواء بنفس الإبرة... فاتغيرت خصائص الدوا بشكل كبير وصار loss effect

ممكن يصير عند أي خطوة من خطوات الدواء (من أول ما دخل الجسم لحد ما يخرج منه).

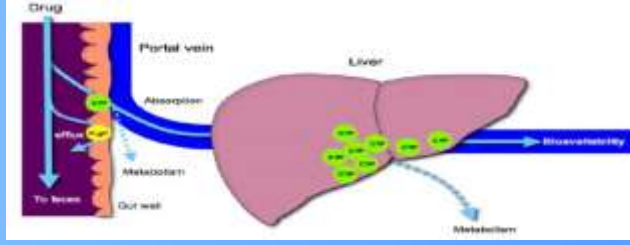
MECHANISM OF DRUG INTERACTIONS

- Drug interactions can be broadly divided into
  - **Pharmaceutical Interaction**
    - During dosage form preparation or at time of administrations.
    - Dissolving the drug in solvent,
    - Mixing drugs in powder, solution or injection forms.
  - **Pharmacokinetic (ADME)**
    - Absorption (Complex or Chelate formation, Altered stomach pH, Ionization, GIT motility, First Pass Metabolism)
    - Distribution (Protein binding)
    - Metabolism (Enzyme induction/inhibition)
    - Excretion (Altered pH, Ionization, Entero-hepatic recirculation)
  - **Pharmacodynamic (At receptor or tissue level)**

هون ممكن يوصل الدواء لل receptor level ف يلاقي دواء بعاكسه بال action


مهم
drug interactions
in vivo
in vitro
pharmacokinetic
pharmacodynamic
absorption level
metabolism level
excretion level
drug synergism
drug antagonsims

ABSORPTION



- **Insoluble and poorly absorbed complexes** in the gut
  - Example:-
    - Tetracyclines and calcium/iron salts.
  - Minimized by administering the two drugs with a **gap of 2-3 hours.** لازم نفصل بين اخد الدواء والأكل حوالي ساعتين ل 3 ساعات
- **Alteration in Entero-hepatic recirculation** أخدناعنه سابقًا
  - Antibiotics like Tetracyclines (Broad Spectrum) markedly **reduce gut flora** that normally deconjugates oral contraceptive steroids secreted in the bile as glucuronides and permits their **Entero-hepatic recirculation**. **Contraceptive failure** when concurrent use of antibiotics due to lowering of the contraceptive blood levels.

الاشياء الي ممكن تأثر على absorption:

1) انه المريض ياخد دواء وياكل معه شي فممكن تعمل drug interaction (drug food interactions) ال tetracyclines هو عبارة عن antibiotic هلأ لو المريض اخده وشرب معه لبن... الكالسيوم مع tetracycline رح يعملو insoluble complex فالمريض رح يرجعلك ويقلك انه ما استفاد وحرارته لسا عالية يعني زي كانه ما اخد دواء

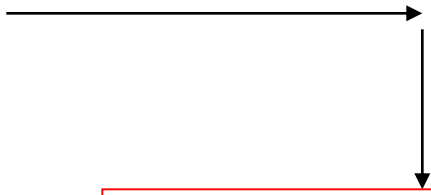
2) ال gut flora هي عبارة عن بكتيريا صديقة النا وموجودة بال intestine هي ال gut flora بتعمل لبعض الأدوية متل ادوية منع الحمل deconjugation عشان تحميها من entro hepatic recirculation ف ما بصرلها تكسر بال liver
هلا ال tetracycline بس تاخدو المراة مع ادوية منع الحمل رح يقلل ال gut flora فادوية منع الحمل مارح تلاقي شي يحميها فبتتكسر بال liver (هون ال tetracycline عمل interaction مع contraceptive فالنتيجة انه المريضة بتجي عندك بعد فترة وبتطلع pregnant

a) *Altered intestinal bacterial flora ;*

EX., **40% or more of the administered digoxin dose is metabolised by the intestinal flora.**

في بعض ال antibiotic بكون عندها large number of flora

Antibiotics kill a large number of the normal flora of the intestine



Increase digoxin conc. and increase its toxicity

حكينا عنه بالمحاضرة ٩

b) Complexation or chelation;

EX1., Tetracycline interacts with iron preparations

or

Milk (Ca^{2+}) ⟶ **Unabsorpable complex**

بصير عندي combination بين دوائين ف بتعملي insoluble complex (unabsorption complex)
ما الها فايدة وبتطلع خارج الجسم

ما حكت عنه "خلينا بالمثال الأول"

Ex2., Antacid (aluminum or magnesium) hydroxide

Decrease absorption of ciprofloxacin by 85% due to chelation

c) Drug-induced mucosal damage.

مريض اخد دواء يستخدم في chemotherapy (cancer treatment) هاد الدواء عمل mucosal لل damage (المكان الي بصير فيه ال absorption) ف صار مو نافع يعني صار not absorped

Antineoplastic agents

e.g., **cyclophosphamide**
vincristine
procarbazine

بيجي مريض وهو بيتعالج باستخدام ال cyclophosphamide ف الي بصير انه عمل mucosal لل damage وهو بياخد ال digoxin فبيجيك ويقلك ما نفع معي الدواء

Inhibit absorption of several drugs eg., digoxin

d) Altered motility

common

Metoclopramide (antiemitic)

بقلل ال gastric empting بخلي المعدة تفضى ببطء يعني ال absorption رح يصير بفترة أطول فبصير toxicity

Increase absorption of cyclosporine due to the increase of stomach empting time

Increase the toxicity of cyclosporine

أول ما نحكي distribution لازم نحط بالبال "plasma protein"

DISTRIBUTION

- **Primarily due to displacement** of one drug from its binding sites on plasma proteins by another drug.
- Drugs highly bound to plasma proteins that have a relatively small volume of distribution like oral anticoagulants, are particularly liable to displacement interactions.
- The drug which is in unbound form is active while portion which is in bound form woks as temporary storage.
- When the drug is displaced by the other drug or chemical the unbound form of the active drug becomes more leading to toxic level in the blood and **presenting as toxicity.**

بكون في دواء مرتبط بال p.p. بس بيجي دواء تاني اله higher affinity فبشيل الدواء الأول وهو بيرتبط بداله... الدواء الي انفك رح يزيد ال free تبعه بال circulation فبصير عندي toxicity.

e) Displaced protein binding

It depends on the affinity of the drug to plasma protein.
The most likely bound drugs is capable to displace others.
The free drug is increased by displacement by another drug with higher affinity.

مرضى ال chronic لازم نكون حذرين وواعين بالأدوية الي بنعطيهم اياها لانه في كتير ادوية منهم بتعمل interaction مع دواء تاني فبروح المفعول تبعه

أول ما نحكي metabolism لازم نحكي بالنا "cp450"

Phenytoin is a highly bound to plasma protein (90%), and warfarin (99%)

بس 1% منه الي بيعطيني effect فلو زادت ال free عن 1% بتعمل bleeding

Drugs that displace these agents are **Aspirin** **Sulfonamides**

warfarin من أعلى affinity هيم

مريض بياخد warfarin ممكن يصير معه صداع وياخد aspirin بال aspirin رح يفك ارتباط ال warfarin بال p.p. فبتزيد نسبة ال free تبعته ورح يسببلي bleeding

Metabolism

SOME IMPORTANT INHIBITORS OF METABOLISM OF MULTIPLE DRUGS:

اول ما نحكي metabolism لازم يخطر ببالنا ال Cp450 "هو انزيم بس في ادوية بتحفزه كتير وبتخليه يكسرها بزيادة وفي ادوية بتثبطه وما بتخليه يكسرها بالشكل المطلوب"

- Macrolide antibiotics,
- Azole antifungals,
- Chloramphenicol,
- Omeprazole, SSRIs,
- HIV -protease inhibitors,
- Cimetidine,
- Quinolones (Ciprofloxacin)
- Metronidazole.

} antibiotic

f) Altered metabolism

The effect of one drug on the metabolism of the other is well documented. The liver is the major site of drug metabolism but other organs can also do e.g., WBC,skin,lung, and GIT.

CYP450 family is the major metabolizing enzyme in phase I (oxidation process).

Therefore, the effect of drugs on the rate of metabolism of others can involve the following examples.

Eg., Enzyme inhibition;

- It is the decrease of the rate of metabolism of a drug by another one .
- This will lead to the increase of the concentration of the target drug and leading to the increase of its toxicity .

- Inhibition of the enzyme may be due to the competition on its binding sites.

When an enzyme inducer (e.g. carbamazepine) is administered with an inhibitor (verapamil)

في ناس بياخدوا inhibitor+inducer بنفس الوقت ← النتيجة no effect

The effect of the inhibitor will be predominant

Ex.,Erythromycin inhibit metabolism of ***astemazole and terfenadine***

Increase the serum conc.
of the antihistaminic leading to
increasing the life threatening
cardiotoxicity

IMPORTANT MICROSOMAL ENZYME INDUCERS (RBC)

مجموعة من الأدوية بتزود ال activity لل metabolism enzyme وبصير أعلى من الطبيعي فبتضل نسبة قليلة للعلاج بصير عندي loss of effect

- Barbiturates,
- Phenytoin
- Carbamazepine
- Rifampin
- Cigarette smoking
- Chronic alcoholism

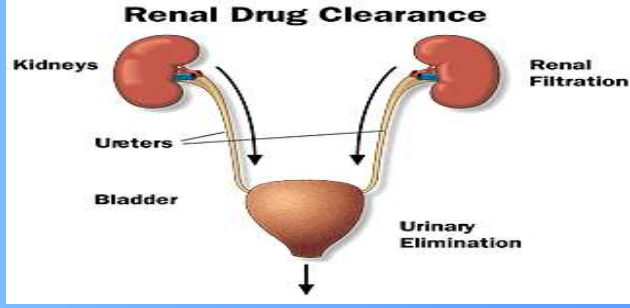
لما يكون المريض مدخن أو بيشرب كحول وما قلك ويصير عنده صداع وياخد دواء وما يجيب مفعول ويصير يحكي الدواء مو نافع بس ما بيعرف انه المشكلة جسمه بكسر بالدواء بسرعة فما بيستفيد منه

مريضة TP وبتاخد دواء rifampicin وبرضو بتاخد أدوية منع حمل.ءء فجأة بتلاقي حالها حامل
(لأنه ال rifampicin بيزيد metabolism تبع ادوية منع الحمل فبقل مفعولهم

- Contraceptive failure and loss of therapeutic effect of many other drugs have occurred due to enzyme induction (Patient taking Rifampicin)
- Toxic dose of paracetamol is lower in chronic alcoholics and in those on enzyme inducing medication, because one of the metabolites of paracetamol is responsible for its overdose hepatotoxicity

سيبكم منه

EXCRETION



- Interaction involving excretion are important mostly in case of **drugs actively secreted by tubular transport** mechanisms. Chemical interaction The alteration of urinary pH alters the process of reabsorption of the drug leading to increase or decrease excretion.
- Probenecid inhibits tubular secretion of penicillins and cephalosporins .

- Alkalization of urine increases the excretion of barbiturates

Renal excretion:

- Active tubular secretion

It occurs in the proximal tubules.
The drug combines with a specific protein to pass through the proximal tubules.

When a drug has a competitive reactivity to the protein that is responsible for active transport of another drug .This will reduce such a drug excretion increasing its con. and hence its toxicity.

EX., Probenecid ..... → Decreases tubular secretion of methotrexate.

PHARMACODYNAMIC INTERACTIONS

على مستوى ال receptor ما اله علاقة بال dose

- These interactions derive from modification of the action of one drug at the target site by another drug, **independent of a change in its concentration**.

- This may result in an **enhanced response (synergism)**, an **attenuated response (antagonism)** or an abnormal response.

حكينا عنهم في محاضرة ١١

PHARMACODYNAMIC INTERACTIONS

- **1-Addition or summation** : the resultant action is the algebric sum of the individual actions of the two drugs combined. In such case only half the normal dose of each drug is required to produce the desired effect. e.g. histamine and ACH on B.P. 1+1=2 لو اخد نص جرعة الأول ونص جرعة التاني بتعطيني ال effect المطلوب
- **2-Synergism:** both drugs are biologically active, but when combined, the net effect is more than the sum of their individual effects e.g. sulphonamide and trimethoprim. 1+1=3
- **3-Potentiation:** this occurs when one drug has no apparent action on one system but increase the effect of another drug on that system. e.g. barbiturates potentiate the analgesic effect of salicylates. 1+0=2

PHARMACODYNAMIC INTERACTIONS

- **4-Antagonism:** this occurs when drugs with opposing actions are given simultaneously it may be:
- Physiological antagonism: drugs with opposing actions on the same physiological system e.g. histamine and adrenaline.
- Chemical antagonism : one drug reacts chemically with an active drug to form an inactive compound e.g. heparin and protamine sulphate.
- Pharmacological antagonism:
- Competitive antagonism:

بينفصل مباشرة

- Reversible e.g. atropine and Ach.

بضل شويتين قبل ما ينفصل

- Irreversible e.g. noradrenaline and phenoxybenzamine .
- Non competitive antagonism e.g. acetyl choline and hexamethonium or D-tubocurarine on autonomic ganglia.

- Excessive fall in BP and fainting due to concurrent administration of α1 adrenergic blockers, vasodilators, ACE inhibitors.

- Increased risk of bleeding due to concurrent use of antiplatelet drugs (aspirin, clopidogrel) with anticoagulants (warfarin).

DRUG INTERACTIONS BEFORE ADMINISTRATION

- Certain drugs react with each other and get inactivated **if their solutions are mixed before administration.**

لو خلطت اكتر من دواء مع بعض بصير عندي interaction

- In practice situations, these in vitro interactions occur when injectable drugs are mixed in the same syringe or infusion bottle.

Some examples are:

- Penicillin G or ampicillin mixed with gentamicin or another aminoglycoside antibiotic.

مثال على خلط أدوية

- Heparin when mixed with penicillin gentamicin/hydrocortisone.

“ It is prudent to consider the possibility of drug interaction whenever two or more drugs are prescribed to a patient, or any drug is added to what the patient is already taking”

DRUG INTERACTIONS MAY BE ANTAGONISTIC

مطلوب حفظ اول مثال واخر مثال

PRIMARY DRUG	INTERACTS WITH	RESULTING IN
SALBUTAMOL	-PROPRANOLOL	ANTIAGONISM OF BRONCHODILATION
ANTIHYPER-TENSIVES	-NSAIDS	ANTAGONISM OF HYPOTENSIVE EFFECT (Na^+ - RETENTION)
	- SELECTIVE COX 2 INHIBITORS	NO SIGNIFICANT EFFECTS ON Na
SULPHONAMIDES	-L. ANAETHETICS -(PABA)	ANTAGONISM OF ANTIMICROBIAL EFFECTS
WARFARIN	OESTROGENS	WARFARIN EFFECT ANTAGONIZED BY INCREASED CLOTTING FACTOR SYNTHESIS
OPIOIDS	NALOXONE	ANTAGONISM

Thanks