Drug interactions

• Are considered adverse drug reactions.

• An interaction occurs when the effects of one drug are altered by the co-administration of another drug, herbal medicine, food, drink or other environmental agents.

• Increased in importance because of the widespread use of **polypharmacy** (multiple drug use), non-prescription use of herbal and complementary medicines, and food- and drink – drug interactions.

• The greater the number of drugs taken, the more likely there will be an interaction.

• Although rational use of more than one drug at a time can greatly benefit patients, adverse interactions are not uncommon, and may be catastrophic.

• **Drug interactions are usually avoidable.**

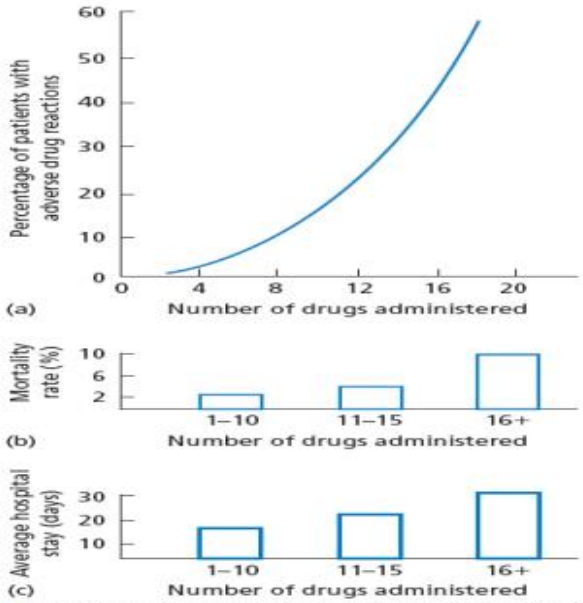

Figure 13.1: Relationship of number of drugs administered to (a) adverse drug reactions, (b) mortality rate and (c) average duration of hospital stay. (Redrawn by permission of the British Medical Journal from Smith JW et al. *Annals of Internal Medicine* 1966; 65: 631.)

(Notice that the curve is not linear = the adverse drug reactions (drug interactions) increase out of proportion of the increase in the number of drugs used)

Epidemiology:

• **It is difficult to obtain an accurate estimate of the incidence of drug interactions.** (because of lack of reporting)

• In hospital in-patients, the incidence of drug interactions ranges from 1-2 %.

• In out-patients, incidence of interactions ranged from 2-4 %. (Higher because in-patients are under observation)

• Other studies reported much higher incidence rates (7% and 22%, respectively).

• The frequency of such interactions is probably underestimated.

- Epileptic patients suffer from much greater rejection rates of transplants than non-epileptics, due to **induction of the metabolism of** immunosuppressant corticosteroids by antiepileptic drugs.
  (When the metabolism is induced, the elimination is accelerated, and the concentration is reduced at the site of action => rejection)

Susceptible patients:

1. Those with polypharmacy.
2. Those with hepatic or renal disease.
3. Those with long-term therapy for chronic diseases (HIV infection, epilepsy, diabetes, patients in intensive care, transplant patients, patients undergoing complicated surgical procedures ..).
4. **Those with more than one prescriber.**
5. Critically ill and elderly patients (altered homeostatic mechanisms).
6. Elderly patients.

• **Drug interactions can be: useful, of no consequence, or harmful.**

Useful interactions	
A. Increased therapeutic effect Drugs can be used in combination *to enhance their effectiveness.* Disease is often caused by complex processes, and drugs that influence different components of the disease mechanism may have additive effects:	1. An antiplatelet drug with a fibrinolytic in treating myocardial infarction. 2. The use of **a β2 agonist** with **a glucocorticoid** in the treatment of bronchial asthma to cause **bronchodilation** and **suppress inflammation**, respectively. 3. Drug resistance via synthesis of a microbial enzyme that degrades an antibiotic (*penicillinase-producing staphylococci*) can be countered by using a combination of the antibiotic (amoxicillin) with an inhibitor of the enzyme (clavulanic acid) 4. Combinations of antimicrobial drugs are used *to prevent the selection of drug-resistant organisms in tuberculosis.* 5. Imipenem is partly inactivated by a dipeptidase in the kidney. This inactivation can be overcome by administering imipenem in combination with cilastatin, a specific renal dipeptidase inhibitor. 6. The use of the combination of ritonavir and saquinavir in antiretroviral therapy. Ritonavir increases the systemic bioavailability of saquinavir by: a. inhibiting its first-pass gastrointestinal effect (**CYP3A**). b. inhibiting its fecal elimination by blocking the **P-glycoprotein** that pumps it back into the intestinal lumen.
B. Minimize adverse effects: Predictable adverse effects can sometimes be averted by the use of drug combinations.	1. Isoniazid neuropathy is caused by pyridoxine (vitamin B6) deficiency and is prevented by the prophylactic use of this vitamin. Isoniazid inhibits the activation of vitamin B6. This inhibition is competitive, so increasing the concentration of vitamin B6 will overcome the inhibition. 2. The combination of a peripheral dopa decarboxylase inhibitor (carbidopa) with levodopa *permits reduction of dose of levodopa*, while reducing the dose-related peripheral adverse effects (nausea and vomiting ...).
C. Block acutely an adverse effect: Drugs can be used to block an undesired or toxic effect:	1. A cholinesterase inhibitor to reverse neuromuscular blockade. 2. Naloxone to treat opioid overdose. 3. Vitamin K or fresh plasma to reverse the effect of warfarin.

Harmful interactions:

• It is impossible to memorize the many clinically important drug interactions, and prescribers should depend on suitable references to check for them.

Some Severe adverse drug interactions:

1. Unwanted pregnancy, from failure of the contraceptive pill due to concomitant medication, usually enzyme inducers.

2. Stroke, from hypertensive crisis in patients on monoamine oxidase inhibitors.

Foods rich in tyramine (cheese, wine, etc.) are metabolized by monoamine oxidase. Inhibiting this enzyme will cause accumulation of tyramine which is taken up by sympathetic nerve terminals and displaces catecholamines. Catecholamines go out of the nerve terminals => hypertensive crisis, stroke, MI, damage of different organs.

3. Gastrointestinal or cerebral hemorrhage, in patients receiving anticoagulants (warfarin).

4. Cardiac arrhythmias, **secondary to interactions leading to** electrolyte disturbances or prolongation of the QTc interval.

5. Blood dyscrasias, from interactions between allopurinol and azathioprine.

The dose of azathioprine should be decreased لاقل من الربع because allopurinol inhibits the metabolism of azathioprine.

Chemical (Pharmaceutical) Interactions: Mainly these interactions occur *outside* the body if the drugs are mixed together before injection:	1. Inactivation of heparin with gentamicin. 2. Inactivation of heparin with hydrocortisone. 3. Inactivation of gentamicin with hydrocortisone. 4. Inactivation of penicillin with hydrocortisone. 5. Aminoglycosides and penicillins inactivate each other. 6. Diazepam can be precipitated by infusion fluids. 7. Phenytoin can be precipitated by infusion fluids.
Pharmacodynamic Interactions: Common.	1. *Drowsiness* caused by an **H1 -blocking antihistamine** and **alcohol**. Patients must be warned of the dangers of consuming alcohol concurrently when antihistamines are prescribed, especially if they drive or operate machinery. Such interactions can be produced also by **antidepressants, hypnotics, and some anti-epileptics** leading to excessive drowsiness. 2. **β-blockers** and **verapamil** may precipitate *heart failure in patients with supra-ventricular tachycardia*, because both have negative inotropic effects. The combination may also cause *heart block and asystole.* 3. **Antihypertensive drugs** may be *less effective* by concurrent use of **non-steroidal anti-inflammatory drugs**, because of inhibition of biosynthesis of vasodilator prostaglandins in the kidney (leading to renal damage), and because of sodium and water retention. 4. **Warfarin** inhibits the coagulation cascade, whereas **aspirin** influences hemostasis by inhibiting platelet function. Therefore, the concomitant use of these drugs may cause **excessive bleeding**. Aspirin also predisposes to *gastric bleeding* by direct irritation and by inhibition of prostaglandin E2 biosynthesis in the gastric mucosa. 5. One potentially important type of pharmacodynamic drug interactions involves **the interruption of physiological control loops.** The use of **β-blocking drugs** in patients with **insulin**-dependent diabetics *deprive them of insulin-induced hypoglycemia warning signs*, which are mediated by sensations initiated by activation of β-receptors. They mask the signs and symptoms of hypoglycemia.

	6. Combined use of diuretics with actions at different parts of the nephron (indapamide or metolazone with furosemide) is valuable in the treatment of resistant edema, but such combination readily *causes excessive intravascular fluid depletion, electrolyte loss, and "pre-renal" renal failure.* **Thiazide** and **loop diuretics** commonly cause **hypokalemia**, which increase the binding of digoxin to plasma membrane Na+/K+ -ATPase, and hence digoxin toxicity is increased. (Please refer to 018 videos from 45:00 to 47:00) 7. **β2 -Agonists (salbutamol)** also may *reduce the plasma potassium concentration.* (Shifts potassium from extracellular to intracellular - total potassium is not affected) 8. Conversely, **potassium-sparing diuretics** may cause **hyperkalemia** if combined with **potassium supplements and/or angiotensin converting enzyme inhibitors** (which reduce circulating aldosterone), especially in patients with renal impairment. **Hyperkalemia is one of the most common causes of fatal adverse drug reactions.** 9. **Antagonistic interactions:** - The bronchodilator action of selective β2 -agonists will be antagonized by β-blockers. - The opioid antagonist naloxone blocks actions of opioids. - Flumazenil blocks the action of benzodiazepines. - Vitamin K blocks the action of oral anticoagulants (warfarin). - levo-Dopa antagonizes the action of antipsychotics. 10. **Neuroleptics** and **tricyclic antidepressants (TCAs)** given with **drugs producing electrolyte imbalance (diuretics)** may cause *ventricular arrhythmias.* Drugs that prolong the QTc interval if used concurrently can cause fatal polymorphic ventricular tachycardia (**torsade de pointes**). 11. *Serotonin syndrome* occurs with combinations that increase serotonin. (**Selective serotonin reuptake inhibitors** and **MAOIs**). **Linezolid** is an antibacterial with MAOI activity. 12. **MAOIs** can prevent metabolism of **tyramine** in the gut which is taken up by adrenergic nerve terminals, releasing catecholamine and causing *hypertensive crisis, fatal intracranial hemorrhage and cardiac arrest.* The same applies to **amphetamines, phenylpropanolamine, and pseudoephedrine.** **Tyramine** is found in cheese and red wine…
Pharmacokinetic interactions	**Absorption:** 1. Changes in gastric pH due to antacids, histamine H2 -antagonists, or proton pump inhibitors may affect weak acidic drugs absorption. (Increasing the pH will cause less absorption of acidic drugs and more absorption of alkaline drugs) Drugs affected include aspirin, itraconazole...

2. Some drugs within the GIT form chelates that are not absorbed:
- **Tetracyclines and fluoroquinolones** can complex with **iron**, and **antacids containing calcium, magnesium, and aluminum**.
- **Bisphosphonates** are often co-prescribed with **calcium supplements** for treatment of osteoporosis, and they reduce the bioavailability of each other, leading to therapeutic failure.

3. Adsorbents such as **charcoal** or **kaolin**, or anion-exchange resins (**cholestyramine** and **colestipol**) may reduce the absorption of many drugs (**propranolol, digoxin, warfarin, TCAs, cyclosporine, l-thyroxine**, ..).
These effects can be avoided or reduced if an interval of 2-3 hours is allowed between administration of interacting drugs (**spacing of drug administration**).

4. Drugs that affect the rate of gastric emptying can affect absorption of other drugs absorbed in the upper part of the small intestine. **Drugs with anticholinergic effects** (**TCAs, phenothiazines and antihistamines**) decrease gut motility and reduce gastric emptying.
This can decrease or increase absorption of drugs. (**How?**)
(It depends on the normal site of absorption of the drug. If gastric emptying is reduced, then absorption of drugs absorbed in the stomach increases while absorption of drugs absorbed in the intestine is delayed)
- Anticholinergics reduce the bioavailability of levodopa, as a result of (Reduced motility of GIT =>) increased metabolism in the intestinal mucosa.
- Opioids inhibit gastric emptying and reduce the absorption rate of paracetamol, without affecting the extent of absorption.
- Metoclopramide (prokinetic) increases gastric emptying and increases the absorption rate of paracetamol, propranolol, mefloquine, lithium and cyclosporine.

5. Induction or inhibition of drug transport proteins: Drugs that **inhibit P-glycoprotein** such as **verapamil** may *increase bioavailability of digoxin, and thus its toxicity.*
P-glycoprotein is an efflux protein that prevent entry of some drugs into intestinal cells => prevents their absorption.
Inhibition of P-glycoprotein increases drugs absorption.

6. Malabsorption:
- **Neomycin** may cause a malabsorption syndrome causing reduced absorption of drugs.
- **Orlistat**, an inhibitor of pancreatic lipases, reduces absorption of co-administered fat-soluble drugs and vitamins

Metabolism:

Is the most important target of drug interactions.

A. Enzyme inhibition:

- The time-course is often *more rapid* than that for enzyme induction, since it depends on *the presence of high-enough concentration of the inhibiting drug at the metabolic site.*

- Enzyme inhibition is responsible for many clinically significant drug interactions.
- Concurrent administration of an enzyme inhibitor leads to reduced metabolism of the drug and an increase in its steady-state concentration.
- **Enzyme inhibition is dose related**.
- The inhibition effect will be seen faster when the inhibitor half-life is short, and will be delayed for drugs with long half-lives. (**Why?**)
  (Steady-state (therapeutic) concentration needs at least 4 half-life to be achieved after repeated administration. A drug with half-life of 2 hours will reach steady-state in 8 hours, while a drug with half life of 1 day will reach steady state in 4 days)
- **Such interactions are most likely to affect drugs with narrow therapeutic** range such as: **theophylline, phenytoin, cyclosporine, and oral anticoagulants**
  - Erythromycin, *an inhibitor of CYP3A4*, may lead to carbamazepine toxicity *due to inhibition of its metabolism leading to higher concentration.*
  - Ritonavir (*an enzyme inhibitor*) in patients receiving sildenafil could increase plasma concentrations of sildenafil markedly.
  - Grapefruit juice, *an inhibitor of CYP3A4*, can markedly increase the bioavailability of nifedipine and felodipine given orally.
    A single glass of grapefruit juice can cause inhibition of CYP3A for 1-2 days, while regular consumption may continuously inhibit enzyme activity. (simvastatin, tacrolimus, and cyclosporine).
- **Enzyme inhibition usually results in increased pharmacological effect, but when the affected drug is a pro-drug, a reduced pharmacological effect may result.**
  A pro-drug is an inactive drug that need to be metabolized to be active
  - Clopidogrel *is metabolized to an active metabolite by CYP2C19* which is *inhibited by a proton pump inhibitor* (**lansoprazole**) leading to reduced effectiveness of clopidogrel.
  - Xanthine oxidase is responsible for inactivation of 6-mercaptopurine, a metabolite of azathioprine. Allopurinol *markedly potentiates these drugs by inhibiting xanthine oxidase*.
  - Theophylline is not inactivated by xanthine oxidase, but rather by several CYPs (CYP1A2).
    Theophylline has serious dose-related toxicities, which are *increased by Inhibitors of the CYP450 system*, such as cimetidine, ciprofloxacin, erythromycin and clarithromycin.
    Severe exacerbations in asthmatic patients are often precipitated by chest infections, so an awareness of these interactions before commencing antibiotic treatment is essential.
  - Hepatic CYP450 inhibition also accounts for clinically important interactions with **phenytoin** (**isoniazid**) and with **warfarin** (**sulfonamides**).
  - Non-selective monoamine oxidase inhibitors (phenelzine) *potentiate the action of indirectly acting amines* such as tyramine,

which is present in a wide variety of fermented products (cheese, wine, ..).

- **Clinically important impairment of drug metabolism may also result indirectly from hemodynamic effects rather than enzyme inhibition**.

- Lidocaine is metabolized in the liver and the hepatic extraction ratio is high.
  Drugs that reduce hepatic blood flow (**negative inotropes, β-blockers, H2 -blockers**) reduce hepatic clearance of lidocaine leading to its accumulation and toxicity.

B. Enzyme induction:

• **The most powerful enzyme inducers are** the antibiotic **rifampicin** and the **antiepileptic drugs** barbiturates, phenytoin and carbamazepine.

• **Carbamazepine** can induce its own metabolism (**autoinduction**).

• Other inducers include cigarette smoking, chronic alcohol use, and the herb **St John's wort**.

• **The induction effect develops over several days or weeks because it requires new protein synthesis.**

• Similarly, **the effect generally persists for the same time period after withdrawal of the inducing agent.**

• Inducers with short half-life (rifampicin) will induce metabolism more rapidly than those with long half-life (phenytoin) because they reach steady-state concentrations more rapidly.

• **Enzyme induction is dose-dependent**.

• Enzyme induction usually results in reduced pharmacological effect of the affected drug.

- There is a risk of therapeutic failure in patients taking cyclosporine, tacrolimus, HIV-protease inhibitors, irinotecan, and imatinib when patients take St John's wort (for depression).

• **If the drug has active metabolites, induction increases its pharmacological effect.** (pro-drug)

• The dose of the drug may need to be increased in the presence of the inducer to attain the therapeutic effect.

• **Withdrawal of an inducing agent** during continued administration of a second drug can **result in a slow decline in enzyme activity**, leading to an increase in drug concentration and emergence of delayed toxicity. (**The dose is NO longer appropriate**).

- When a patient receiving warfarin receives treatment with an enzyme inducer for a new medical event, the dose of warfarin may need to be increased.
- When the inter-current problem is resolved and the inducing drug is discontinued and the patient is left with the larger dose of warfarin, **bleeding** may result from an excessive effect of warfarin days or weeks later, as the effect of the enzyme inducer gradually wears off.

Distribution:

• Displacement from protein-binding sites **results in increased free or unbound fraction temporarily**, but it falls due to enhanced elimination or distribution (clearance).

• It is clinically important for **highly protein-bound drugs**.

• Examples: phenytoin, lidocaine, warfarin…

Elimination Interactions:

Renal Excretion: at the following levels:

1. Changes in urinary pH: Weakly acidic drugs are ionized at alkaline pH, and thus, are unable to be reabsorbed. Therefore, making urine more alkaline enhances the excretion of acidic drugs. Conversely, the elimination of weak bases is enhanced in acidic urine.
   • Change of urine pH can be used to enhance drug elimination in cases of poisoning (salicylates, amphetamine, etc.).
2. Changes in active renal tubule excretion: Probenecid increases plasma concentrations of penicillins by delaying their renal excretion.
   • Salicylates and other NSAIDs can cause life-threatening methotrexate toxicity by inhibiting this process.
3. Changes in renal blood flow: Inhibition of synthesis of vasodilator prostaglandins by NSAIDs increases serum lithium levels and thus toxicity.
4. Many diuretics reduce sodium reabsorption in the loop of Henle or the distal tubule. **This leads indirectly to increased proximal tubular reabsorption of monovalent cations.**
   • In patients treated with lithium salts, increased proximal tubular reabsorption of lithium can lead to lithium accumulation and toxicity.

Biliary excretion and the entero-hepatic circulation:

• Antibiotics which eliminate gut flora reduce the metabolism of drug conjugates back into the parent drug and thus it is quickly lost from the body reducing its plasma concentration and its pharmacological effect.

• This results in therapeutic failure as occurs in patients taking oral contraceptive concomitantly with broad-spectrum antibiotics.

• **Be careful, this interaction is NOT well recognized!!**

Drug transporter proteins:

• P-glycoprotein acts as efflux pump in renal proximal tubules, hepatocytes, intestinal mucosa, pancreas and blood-brain-barrier.

• It exports drugs into urine, bile and intestinal lumen; and reduces drug accumulation in CNS, respectively.

• P-glycoproteins can be induced or inhibited by some drugs.

• There is also some overlap between P-glycoprotein and CYP3A4 substrates, inducers and inhibitors.

A drug interaction can result from one or a combination of these mechanisms.

Drug-food Interactions

• Food can cause clinically important interactions via an effect on drug absorption and gastrointestinal motility:

a) Iron & antibiotics should NOT ideally be taken with food.

b) Tyramine and MAOIs.

c) Grapefruit juice and calcium-channel blockers (inhibit CYP3A4 and P-glycoprotein).

d) Cruciferous vegetables (Brussel sprouts, cabbage, broccoli) are inducers of CYP1A2.

Drug-herb Interactions

• Up to 24% of hospital patients report use of herbal remedies.

1. Extracts of Glycyrrhizin glabra (liquorice عرق السوس) used for peptic ulcers can cause interactions in patients taking diuretics and digoxin.

• It may exacerbate hypokalemia induced by diuretics and cause digoxin toxicity.

• It also causes sodium and water retention like aldosterone and exacerbate heart failure and edema, and antagonize antihypertensive drugs action.

2. **Chamomile (بابونج),** and **horse chestnut (كستناء) have anticoagulant properties that can increase the risk of bleeding when used with warfarin.**

3. Herbal products with **antiplatelet activity** include **Bromelain (أناناس), capsicum (الفليفلة)**, **garlic (الثوم),** and **turmeric (الكركم),** can increase the risk of bleeding **when used with aspirin and other antiplatelet drugs**.

4. **Enhancement of hypotensive** effect by **hawthorn (الزعرور)**

• Take history of herbal product intake because patients usually will NOT volunteer this information.

Extra tables help in memorization:

Table 4.2 Examples of interactions due to enzyme induction

Drug affected	Inducing agent	Clinical outcome
Oral contraceptives	Rifampicin	Therapeutic failure of contraceptives
	Rifabutin	Additional contraceptive precautions required
	Modafinil	Increased oestrogen dose required
Ciclosporin	Phenytoin Carbamazepine St John's wort	Decreased ciclosporin levels with possibility of transplant rejection
Paracetamol	Alcohol (chronic)	In overdose, hepatotoxicity may occur at lower doses
Corticosteroids	Phenytoin Rifampicin	Increased metabolism with possibility of therapeutic failure

Table 13.1: Interactions outside the body

Mixture	Result
Thiopentone and suxamethonium	Precipitation
Diazepam and infusion fluids	Precipitation
Phenytoin and infusion fluids	Precipitation
Heparin and hydrocortisone	Inactivation of heparin
Gentamicin and hydrocortisone	Inactivation of gentamicin
Penicillin and hydrocortisone	Inactivation of penicillin

Table 13.2: Interactions secondary to drug-induced alterations of fluid and electrolyte balance

Primary drug	Interacting drug effect	Result of interaction
Digoxin	Diuretic-induced hypokalaemia	Digoxin toxicity
Lidocaine	Diuretic-induced hypokalaemia	Antagonism of anti-dysrhythmic effects
Diuretics	NSAID-induced salt and water retention	Antagonism of diuretic effects
Lithium	Diuretic-induced reduction in lithium clearance	Raised plasma lithium
Angiotensin converting enzyme inhibitor	Potassium chloride and/or potassium-retaining diuretic-induced hyperkalaemia	Hyperkalaemia

NSAID, non-steroidal anti-inflammatory drug.

Table 4.5 Examples of additive or synergistic interactions

Interacting drugs	Pharmacological effect
NSAID, warfarin, clopidogrel	Increased risk of bleeding
ACE inhibitors and K-sparing diuretic	Increased risk of hyperkalaemia
Verapamil and β-adrenergic antagonists	Bradycardia and asystole
Neuromuscular blockers and aminoglycosides	Increased neuromuscular blockade
Alcohol and benzodiazepines	Increased sedation
Pimozide and sotalol	Increased risk of QT interval prolongation
Clozapine and co-trimoxazole	Increased risk of bone marrow suppression

Table 13.4: Interactions due to CYP450 or other enzyme inhibition

Primary drug	Inhibiting drug	Effect of interaction
Phenytoin	Isoniazid Cimetidine Chloramphenicol	Phenytoin intoxication
Warfarin	Allopurinol Metronidazole Phenylbutazone Co-trimoxazole	Haemorrhage
Azathioprine, 6-MP	Allopurinol	Bone-marrow suppression
Theophylline	Cimetidine Erythromycin	Theophylline toxicity
Cisapride	Erythromycin Ketoconazole	Ventricular tachycardia

6-MP, 6-mercaptopurine.

Table 4.3 Examples of interactions due to enzyme inhibition

Drug affected	Inhibiting agent	Clinical outcome
Anticoagulants (oral)	Ciprofloxacin Clarithromycin	Anticoagulant effect increased and risk of bleeding
Azathioprine	Allopurinol	Enhancement of effect with increased toxicity
Clopidogrel	Lansoprazole	Reduced anti-platelet effect
Carbamazepine Phenytoin Sodium valproate	Cimetidine	Antiepileptic levels increased with risk of toxicity
Sildenafil	Ritonavir	Enhancement of sildenafil effect with risk of hypotension

Table 13.3: Interactions due to enzyme induction

Primary drug	Inducing agent	Effect of interaction
Warfarin	Barbiturates Ethanol Rifampicin	Decreased anticoagulation
Oral contraceptives	Rifampicin	Pregnancy
Prednisolone/ ciclosporin	Anticonvulsants	Reduced immunosuppression (graft rejection)
Theophylline	Smoking	Decreased plasma theophylline

Drug interactions – past papers

* = repeated question :)

- A kidney transplant patient receiving ciclosporin and steroids developed rejection. Which drug may have caused this?

Phenytoin

- Example of useful drug interaction? ***

Use of vitamin B6 in patients taking isoniazid for tuberculosis

- What drug interaction is useful?

Beta 2 agonist and inhaled steroids for treatment of asthma

- Patient with drug use history of metoprolol (along with many other drugs) took bupropion and developed bradycardia. What interaction occurred? * [same idea different answers / see next question]

Bupropion inhibited the metabolism of metoprolol

- A 61-year-old male had a 40-year history of smoking a pack of cigarettes per day. He was in fair health and used to swim 60 minutes per week. He was under treatment for hypertension with metoprolol and amlodipine for three years. He was advised to take 150 mg bupropion daily for one week then twice daily. After starting the medication, he went to swim and found himself gasping for breath about 40 meters. The patient visited a clinic and found to have dyspnea and a pulse of 40/min which was regular. He was given an advice after which he had no further episodes of dyspnea with exertion. Which of the following is the most reasonable advice?

a. reduce amlodipine dose to one half

b. replace amlodipine with nifedipine

c. reduce metoprolol dose to one half

d. stop metoprolol altogether immediately

e. stop amlodipine

- A patient on monoamine oxidase inhibitor for depression and eat cheese. Developed severe occipital headache and blood pressure of 200/130 resistant to nitroprusside infusion. This interaction is cause by?

Inhibition of tyramine metabolism in the GI tract by MOAI

- A patient with depression who takes monoamine oxidase inhibitor. Which food he should not take? **

Fermented cheese

- Drug that causes lithium toxicity by inhibiting its elimination from the body? **

Thiazide diuretics

- A patient developed lithium toxicity, mostly due to? **

Hydrochlorothiazide

- NSAID enhance lithium toxicity by?

Decreased blood flow

- NSAID *increase methotrexate toxicity by?*

By competing on its active excretion in proximal tubules

- *Which doesn't affect the absorption of other drugs?*

Xanthine oxidase inhibitors

- *Woman taking a lot of drugs was given a drug with a weird name that's known to prolong QT interval and then she developed torsade de point. After discontinuing her medications, the arrhythmia subsided. What drug is responsible for this interaction? * [same idea different answers / see next question]*

Can't remember but it's one of the CYP450 inhibitors :(

- *Long QT interval is caused by?*

Macrolides

- *Rifampicin and warfarin interaction, wrong about it?*

A pharmacodynamic interaction

- *Patient with hypertension managed with lisinopril, atenolol and nifedipine. Developed tuberculosis and was managed with antituberculosis medications. Several weeks later the patient developed high blood pressure readings. The most likely drug causing this? ***

Rifampin

- *Liquorice induces digoxin toxicity with diuretics mostly through?*

Exacerbation of hypokalemia

- *Interaction between digoxin and thiazide diuretics?*

Thiazide induced hypokalemia increase digoxin toxicity

- *Interaction caused by the use of* ACEI *and spironolactone?*

Hyperkalemia

- *The drug that increases gut motility?*

Metoclopramide

- *Patient with hypothyroidism treated with levothyroxine and recently he has dyslipidemia treated with cholestyramine, the expected outcome is?*

Return of hypothyroidism symptoms

- *The drug which decreases the effectiveness of clopidogrel?*

Lansoprazole

- *Mismatch?*

Sildenafil and ritonavir >>> hypertension

- *The drug which antagonizes the action of antihypertensive drug?*

Naproxen

❖ The consumption of regular grapefruit will increase the bioavailability of? **

Cyclosporine + Nifedipine

❖ Interact with dairy products?

Ciprofloxacin

❖ Serotonin syndrome is caused by?

Linezolid

❖ Which of the following drugs may reduce clearance of other drugs by reducing hepatic blood flow? **

a. propranolol b. hydralazine c. digoxin d. nifedipine e. lidocaine

❖ Which of the following drugs may reduce the INR when co-administered with warfarin?

a. isoniazid b. garlic c. macrolide antibiotics d. metronidazole e. St John' wort

❖ Which of the following is the most dangerous adverse effect of both loop and thiazide diuretics?

a. hyperglycemia b. hypokalemia c. hypocalcemia d. dyslipidemia e. hyperuricemia

❖ A 52-year-old woman was treated with warfarin for atrial fibrillation (therapeutic INR range: 2-3). She was started on rifampicin therapy as part of treatment for tuberculosis before few days. After that she had a transient ischemic attack and demonstrated subtherapeutic INR values (1-1.5). Three months of sequential increases in the warfarin dosage were necessary to reach a therapeutic INR. However, four weeks after rifampicin discontinuation she had hematuria, and an excessively high INR was observed (7.2). which of the following is the most appropriate action?

a. replace rifampin with isoniazid

b. replace warfarin with heparin

c. reduction of warfarin dose

d. replace warfarin with enoxaparin

e. discontinue warfarin

❖ 58 years, female, 15 years with controlled DM. Was diagnosed with NTN and SND and started on thiazide, enalapril, simvastatin and aspirin. 1 month later her glycemic control was disrupted. Most likely cause is?

hydrochlorothiazide

❖ Patient on carbamazepine for tonic clonic seizure but he still had frequent attacks of seizures so valproic acid was added. Several weeks later the patient developed neurological symptoms of diplopia and ataxia. What is the most likely explanation?

Valproic acid decreased the metabolism of carbamazepine