Drug Interactions

Drug Interactions

- A form of adverse drug reactions.
- An interaction occur 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 poly-pharmacy (multiple drug use), non-prescription use of herbal and complementary medicines, and food- and drink – drug interactions.

Drug Interactions

- **Rational use of more than one drug at a time can greatly benefit patients, but adverse interactions are not uncommon, and may be catastrophic.**
- **These interactions are usually avoidable.**
- **The greater the number of drugs taken, the more likely there will be an interaction.**

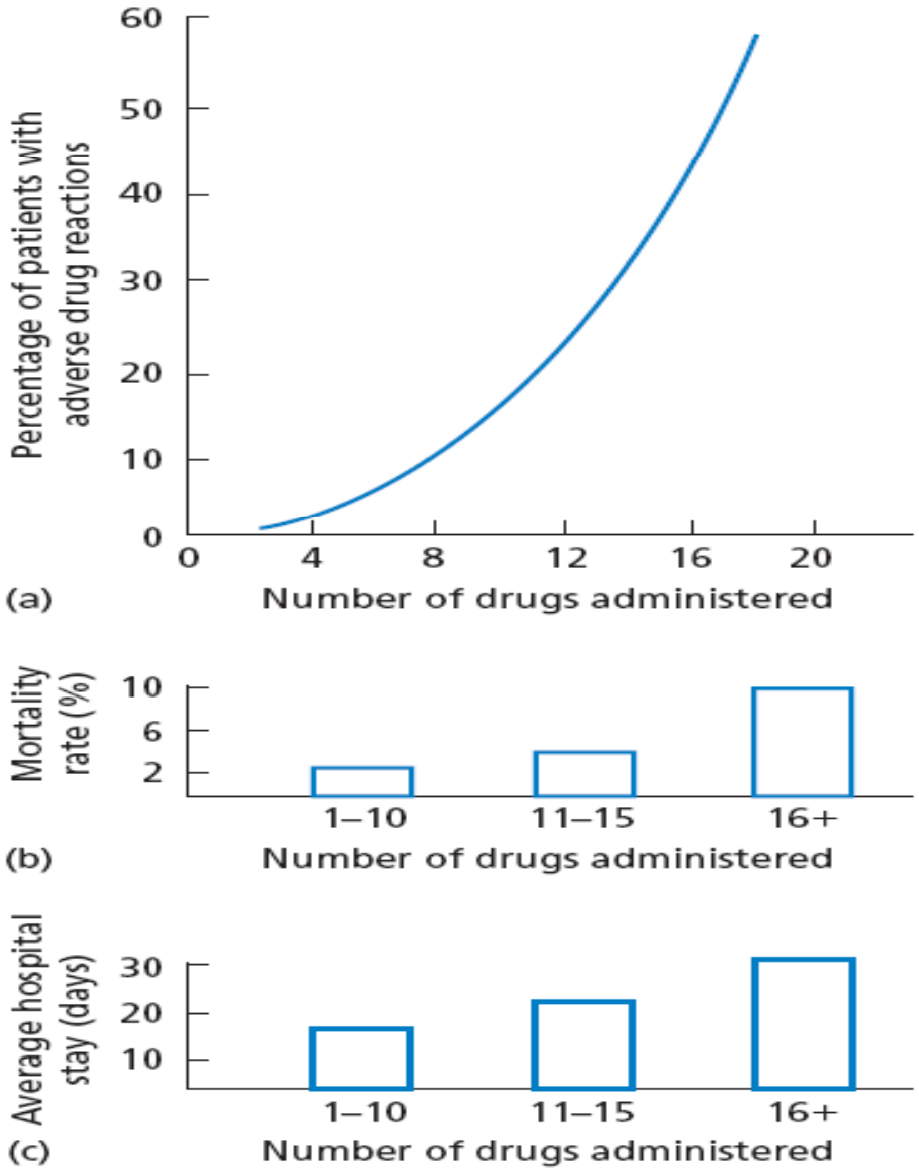

Figure 13.1: Relationship of number of drugs administered to (a) adverse drug reactions, (b) mortality rate and (c) average duration of hospital stay. (Redrawn by permission of the British Medical Journal from Smith JW et al. *Annals of Internal Medicine* 1966; 65: 631.)

Drug Interactions

Epidemiology:

- **It is difficult to obtain an accurate estimate of the incidence of drug interactions.**
- **In hospital in-patients, the incidence of drug interactions range from 1-2 %.**
- **In out-pateints, incidence of interactions ranged from 2-4 %.**
- **Other studies reported much higher incidence rates (7% and 22%, respectively).**

Drug Interactions

- **The frequency of such interactions is probably underestimated by the poor therapeutic outcome to an underlying disease.**
- **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.**

Drug Interactions

Susceptible patients:

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

Drug Interactions

There are three kinds of mechanism:

1. **Pharmaceutical interactions**
2. **Pharmacodynamic interactions**
3. **Pharmacokinetic interactions**

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

Drug Interactions

- **Many elderly individuals not uncommonly have several co-morbid conditions, needing several drugs.**
- **When a drug results in an adverse effect, it may be treated by another drug, which may add to the problem.**
- **Drug interactions can be useful, of no consequence, or harmful.**

Drug Interactions

Useful Interactions:

A. Increased 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 (examples):**

1. An antiplatelet drug with a fibrinolytic in treating myocardial infarction.

Drug Interactions

2. **The use of a β_2 agonist with a glucocorticoid in the treatment of asthma to cause bronchodilation and suppress inflammation, respectively.**
3. **Drug resistance via synthesis of a microbial enzyme that degrades antibiotic (penicillinase-producing staphylococci) can be countered by using a combination of the antibiotic (amoxicillin) with an inhibitor of the enzyme (clavulanic acid).**

Drug Interactions

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 is overcome by administering imipenem in combination with cilastin, a specific renal dipeptidase inhibitor.**

Drug Interactions

6. **The use of the combination of ritonavir and saquinavir in antiretroviral therapy.**

- **Saquinavir increases the systemic bioavailability of ritonavir by:**

a. **inhibiting its degradation by gastrointestinal CYP3A**

b. **inhibiting its fecal elimination by blocking the P-glycoprotein that pumps it back into the intestinal lumen.**

Drug Interactions

B. Minimize adverse effects:

- **Predictable adverse effects can sometimes be averted by the use of drug combinations.**

1. **Isoniazid neuropathy is caused by pyridoxine deficiency, and is prevented by the prophylactic use of this vitamin.**
2. **The combination of a peripheral dopa decarboxylase inhibitor (carbidopa) with levodopa permits reduction of dose, while reducing the dose-related peripheral side effects (nausea and vomiting).**

Drug Interactions

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.**

Drug Interactions

Harmful interactions:

- **It is impossible to memorize the many clinically important drug interactions, and prescribers should depend on suitable references to check for them.**
- **There are certain drugs with steep dose–response curves and serious dose-related toxicities for which drug interactions are especially liable to cause harm, and where special caution is required with concurrent therapy.**

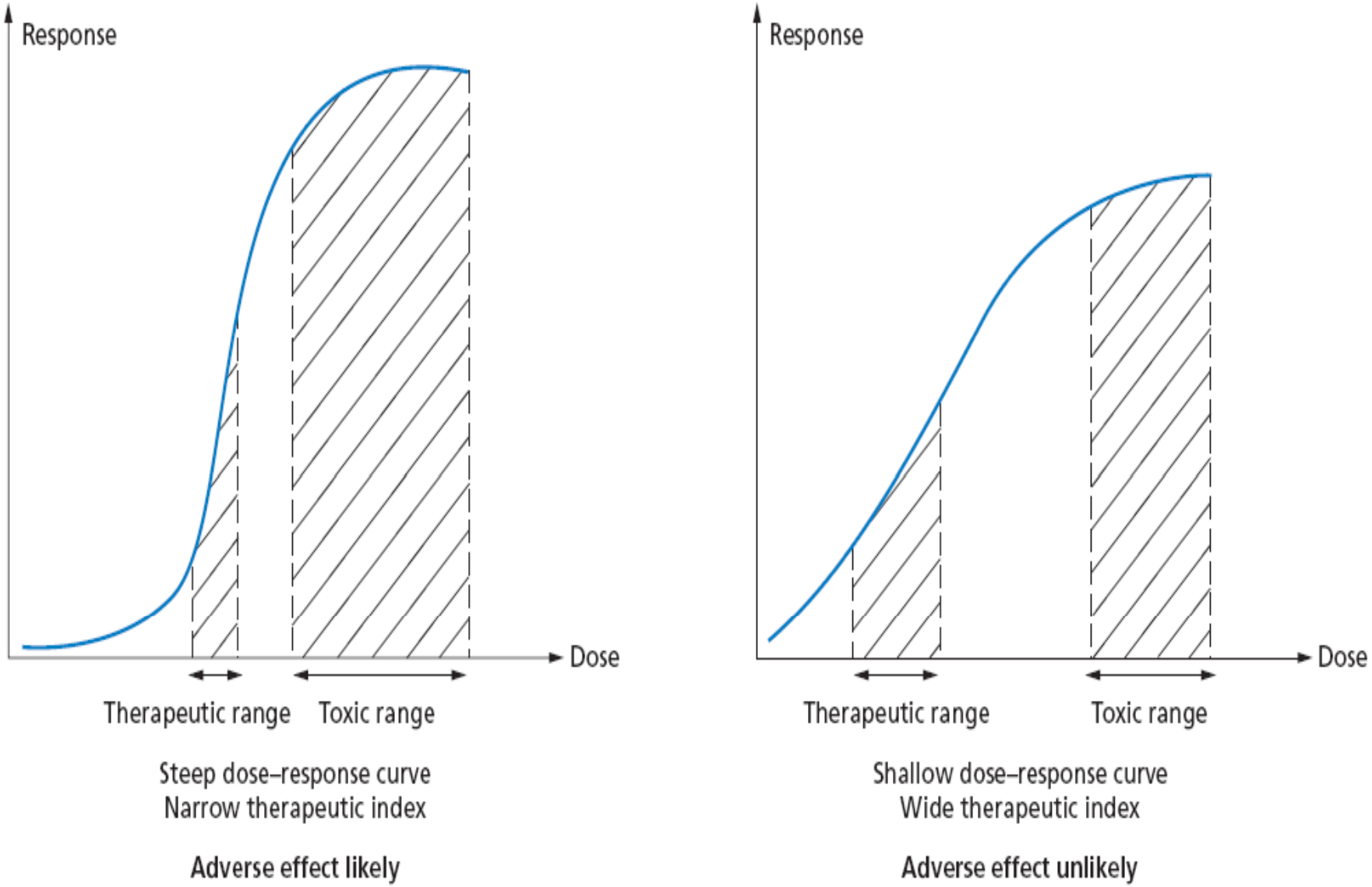

Figure 13.2: Drug dose–response curves illustrating likelihood of adverse effect if an interaction increases its blood level.

Drug Interactions

Examples of drugs with high risk of interactions:

1. **Concentration-dependent toxicity: digoxin, lithium, aminoglycosides, cytotoxic agents, warfarin.**
2. **Patient dependent on therapeutic effect: Immunosuppressants (cyclosporine, tacrolimus), glucocorticoids, oral contraceptives, antiepileptics, antiarrhythmics, antipsychotics, antiretrovirals.**

Drug Interactions

3. **Steep dose-response curves: verapamil, sulfonyureas, levodopa.**
4. **Saturable hepatic metabolism: phenytoin, (? Theophylline).**
5. **Monoamine oxidase inhibitors**

Drug Interactions

Severity of adverse drug interactions:

- **Adverse drug interactions are diverse:**
- **Unwanted pregnancy, from failure of the contraceptive pill due to concomitant medication.**
- **Hypertensive stroke, from hypertensive crisis in patients on monoamine oxidase inhibitors.**
- **Gastrointestinal or cerebral haemorrhage, in patients receiving warfarin.**

Drug Interactions

- **Cardiac arrhythmias, secondary to interactions leading to electrolyte disturbance or prolongation of the QTc interval.**
- **Blood dyscrasias, from interactions between allopurinol and azathioprine.**

Pharmaceutical Interactions

- **Inactivation of heparin with gentamicin when they are mixed.**
- **Drugs may also interact in the lumen of the gut (tetracycline with iron, and colestyramine with digoxin).**

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

Pharmacodynamic Interactions

- **They are common.**
- **Most have a simple mechanism, consisting of summation or reduction of the effects of drugs with similar or opposing actions, respectively.**

Pharmacodynamic Interactions

1. **Drowsiness caused by an H_1-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 an additive or synergistic interactions can be produced also by antidepressants, hypnotics, and some antiepileptics leading to excessive drowsiness.**

Pharmacodynamic Interactions

2. **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, and sodium and water retention.**
3. **β-blockers and verapamil may precipitate heart failure in patients with supraventricular tachycardia, because both have negative inotropic effects.**

Pharmacodynamic Interactions

4. **Warfarin inhibits the coagulation cascade, whereas aspirin influences haemostasis by inhibiting platelet function.**

- **Aspirin also predisposes to gastric bleeding by direct irritation and by inhibition of prostaglandin E_2 biosynthesis in the gastric mucosa.**
- **There the concomitant use of these drugs may cause excessive bleeding.**

Pharmacodynamic Interactions

5. **One potentially important type of pharmacodynamic drug interaction involves the interruption of physiological control loops.**

- **The use of β-blocking drugs in patients with insulin-requiring diabetes deprive them of warning about insulin-induced hypoglycaemia, which is mediated by sensations initiated by activation of β-receptors.**
- **β-blockers, therefore, will mask the signs and symptoms of hypoglycemia.**

Pharmacodynamic Interactions

6. **Alterations in fluid and electrolyte balance represent an important source of pharmacodynamic drug interactions.**

- **Combined use of diuretics with actions at different parts of the nephron (metolazone and furosemide) is valuable in the treatment of resistant edema, but such combinations readily cause excessive intravascular fluid depletion and pre-renal renal failure.**

Pharmacodynamic Interactions

- **Thiazide and loop diuretics commonly cause hypokalaemia, which increase the binding of digoxin to plasma membrane Na^+/K^+-ATPase, and hence digoxin toxicity is increased.**

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.

Pharmacodynamic Interactions

7. β_2-Agonists, salbutamol, also may reduce the plasma potassium concentration.
8. Conversely, potassium-sparing diuretics may cause hyperkalaemia if combined with potassium supplements and/or angiotensin converting enzyme inhibitors (which reduce circulating aldosterone), especially in patients with renal impairment.
9. Hyperkalaemia is one of the most common causes of fatal adverse drug reactions.

Pharmacodynamic Interactions

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 that of benzodiazepines.**
- **Vitamin K blocks the action of oral anticoagulants.**
- ***levo*-Dopa antagonizes the action of antipsychotics.**

Pharmacodynamic Interactions

10. **Neuroleptics, TCAs, and drugs producing electrolyte imbalance (diuretics) may lead to ventricular arrhythmias.**
11. **Drugs that prolong the QT interval if used concurrently can cause fatal polymorphic ventricular tachycardias (*torsade de pointes*).**
12. **Serotonin syndrome occur with combinations that affect serotonin. Selective serotonin reuptake inhibitors and MAOIs.**

- **Linezolid is an antibacterial with MAOI activity.**

Pharmacodynamic Interactions

12. **Drug or neurotransmitter uptake interactions:**

- **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 effect is prolonged for several weeks until new MAO is synthesized (for irreversible inhibitors). The same applies to amphetamines, MDMA (ecstasy), phenypropanolamine, and pseudoephedrine.**
- **Tyramine is found in cheese and red wine.**

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

Pharmacokinetic Interactions

Absorption:

1. **Changes in gastric pH due to antacids, histamine H_2-antagonists, or proton pump inhibitors may affect weak acidic drugs absorption. The change affect the rate of absorption rather than the extent. Drugs affected include aspirin, ketoconazole, itraconazole.**

Pharmacokinetic Interactions

2. **Some drugs within the GIT form chelates and complexes that are not absorbed.**

- **Tetracyclines and fluoroquinolones can complex with iron, and antacids containing calcium, magnesium, and aluminium.**
- **Bisphosphonates are often co-prescribed with calcium supplements for treatment of osteoporosis and they reduce the bioavailability of each other, leading to therapeutic failure.**

Pharmacokinetic Interactions

3. **Adsorbents such as charcoal or kaolin, or anion-exchange resins such as cholestyramine and colestipol, may reduce the absorption of many drugs (propranolol, digoxin, warfarin, TCAs, cyclosporine, *l*-thyroxine, ..).**

- **These effects can avoided or reduced if an interval of 2-3 hours is allowed between interacting drugs.**

Pharmacokinetic Interactions

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, such as TCAs, phenothiazines and antihistamines decrease gut motility and reduce gastric emptying.**
- **This can decrease or increase absorption of drugs.**

Pharmacokinetic Interactions

- **TCAs can increase dicoumarol absorption as a result of increasing the time available for its dissolution and absorption.**
- **Anticholinergics reduce the bioavailability of levodopa, as a result of increased metabolism in the intestinal mucosa.**

Pharmacokinetic Interactions

- **Opioids strongly inhibit gastric emptying and greatly reduce the absorption rate of paracetamol, without affecting the extent of absorption.**
- **Metoclopramide increases gastric emptying and increases the absorption rate of paracetamol, propranolol, mefloquine, lithium and cyclosporine.**

Pharmacokinetic Interactions

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.**
6. **Malabsorption:**

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

Pharmacokinetic Interactions

Metabolism:

- **This is the most important target of drug interactions.**

A. Enzyme inhibition:

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

Pharmacokinetic Interactions

- **Enzyme inhibition is responsible for many clinically significant interactions.**
- **Concurrent administration of an enzyme inhibitor leads to reduced metabolism of the drug and an increase in steady-state concentration.**
- **Enzyme inhibition appears to be dose-related.**

Pharmacokinetic Interactions

- **The inhibition effect will be seen faster when the inhibitor half-life is short, and will be delayed for drugs with long half-lives.**
- **Interactions of this kind are most likely to affect drugs with narrow therapeutic range such as theophylline, phenytoin, cyclosporine, and oral anticoagulants.**

Pharmacokinetic Interactions

- **Erythromycin, an inhibitor of CYP3A4, if taken by a patient on carbamazepine may lead to carbamazepine toxicity due to higher concentration.**
- **Ritonavir (as an enzyme inhibitor) in patients receiving sildenafil could increase plasma concentrations of sildenafil markedly.**
- **Grapefruit juice can markedly increase the bioavailability of nifedipine and felodipine given orally.**

Pharmacokinetic Interactions

- **A single glass of grapefruit juice can cause inhibition of CYP3A for 1-2 days, while regular consumption may continuously inhibit enzyme activity.**
- **Other drugs involved are 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.**

Pharmacokinetic Interactions

- **Clopidogrel is metabolized to active metabolite by CYP2C19 which is inhibited by proton pump inhibitors (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.**

Pharmacokinetic Interactions

- **Theophylline is not inactivated by xanthine oxidase, but rather by a form of CYP450. Theophylline has serious dose-related toxicities, which are increased by Inhibitors of the CYP450 system, including ciprofloxacin 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.**

Pharmacokinetic Interactions

- **Hepatic CYP450 inhibition also accounts for clinically important interactions with phenytoin (isoniazid) and with warfarin (sulphonamides).**
- **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, ..).**

Pharmacokinetic Interactions

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

Pharmacokinetic Interactions

- **Lidocaine is metabolized in the liver and the hepatic extraction ratio is high.**
- **Any drug that reduces hepatic blood flow (negative inotropes) will reduce hepatic clearance of lidocaine and cause it to accumulate.**
- **This accounts for the increased lidocaine concentration and toxicity that is caused by β-blocking drugs.**

Table 13.4: Interactions due to CYP450 or other enzyme inhibition

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

6-MP, 6-mercaptopurine.

Box 4.2 Examples of enzyme inhibitors frequently implicated in interactions

Antibacterials
Ciprofloxacin
Clarithromycin
Erythromycin
Isoniazid
Metronidazole

Antidepressants
Duloxetine
Fluoxetine
Fluvoxamine
Nefazodone
Paroxetine
Sertraline

Antifungals
Fluconazole
Itraconazole
Ketoconazole
Miconazole
Voriconazole

Antivirals
Amprenavir
Indinavir
Nelfinavir
Ritonavir
Saquinavir

Cardiovascular drugs
Amiodarone
Diltiazem
Quinidine
Verapamil

Gastro-intestinal drugs
Cimetidine
Esomeprazole
Omeprazole

Antirheumatic drugs
Allopurinol
Azapropazone
Phenylbutazone

Other
Aprepitant
Bupropion
Disulfiram
Grapefruit juice
Imatinib
Propoxyphene
Sodium valproate

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

Pharmacokinetic Interactions

B. Enzyme induction:

- **The most powerful enzyme inducers are the antibiotic rifampicin and the antiepileptic drugs barbiturates, phenytoin and carbamazepine.**
- **Carbamazepine (and barbiturates) can induce their own metabolism (autoinduction).**
- **Other inducers include cigarette smoking, chronic alcohol use, and the herb St John's wort.**
- **The effect develops over several days or weeks because it requires new protein synthesis.**

Pharmacokinetic Interactions

- **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.**

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

Pharmacokinetic Interactions

- **Enzyme induction appears to be dose-dependant, but can occur at any dose for some drugs.**
- **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.**
- **If the drug has active metabolites, pharmacological effect may increase.**

Pharmacokinetic Interactions

- **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, with emergence of delayed toxicity from the second drug due to what is no longer an appropriate dose.**

Pharmacokinetic Interactions

- **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 intercurrent 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.**

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 4.1 Examples of drug substrates, inducers and inhibitors of the major cytochrome P450 enzymes

P450 isoform	Substrate	Inducer	Inhibitor
CYP1A2	Caffeine Clozapine Imipramine Olanzapine Theophylline Tricyclic antide-pressants R-warfarin	Omeprazole Lansoprazole Phenytoin Tobacco smoke	Amiodarone Cimetidine Fluoroquinolones Fluvoxamine
CYP2C9	Diazepam Diclofenac Losartan Statins SSRIs S-warfarin	Barbiturates Rifampicin	Amiodarone Azole antifungals Isoniazid
CYP2C19	Cilostazol Diazepam Lansoprazole	Carbamazepine Rifampicin Omeprazole	Cimetidine Fluoxetine Tranylcypromine

CYP2D6	Amitriptyline	Dexamethasone	Amiodarone
	Codeine	Rifampicin	Bupropion
	Dihydrocodeine		Celecoxib
	Flecainide		Duloxetine
	Fluoxetine		Fluoxetine
	Haloperidol		Paroxetine
	Imipramine		Ritonavir
	Nortriptyline		Sertraline
	Olanzapine		
	Ondansetron		
	Opioids		
	Paroxetine		
	Propranolol		
	Risperidone		
	Thioridazine		
	Tramadol		
	Venlafaxine		

CYP2E1	Enflurane Halothane	Alcohol (chronic) Isoniazid	Disulfiram
CYP3A4	Amiodarone Terfenadine Ciclosporin Corticosteroids Oral contra-ceptives Tacrolimus R-warfarin Calcium channel blockers Donepezil Benzodiazepines Cilostazol	Carbamazepine Phenytoin Barbiturates Dexamethasone Primidone Rifampicin St John's wort Bosentan Efavirenz Nevirapine	Cimetidine Clarithromycin Erythromycin Itraconazole Ketoconazole Grapefruit juice Aprepitant Diltiazem Protease inhibitors Imatinib Verapamil

Pharmacokinetic Interactions

Distribution:

- **Displacement from protein-binding sites results in increased free or unbound fraction temporarily, but it falls due to enhanced elimination or distribution (clearance).**
- **Therefore, there are only few clinically important interactions due to protein binding displacement, particularly for highly protein-bound drugs and those that are not restrictively cleared especially when administered parenterally.**
- **Examples: Phenytoin, lidocaine.**

Pharmacokinetic Interactions

Elimination Interactions:

Renal Excretion: Occur 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. This can be used to enhance drug elimination in poisoning with salicylates, amphetamine, etc.**

Pharmacokinetic Interactions

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: Inhibitors of synthesis of vasodilator prostaglandins by NSAIDs increases serum lithium levels and thus toxicity.**

Table 13.5: Competitive interactions for renal tubular transport

Primary drug	Competing drug	Effect of interaction
Penicillin	Probenecid	Increased penicillin blood level
Methotrexate	Salicylates	Bone marrow suppression
	Sulphonamides	
Salicylate	Probenecid	Salicylate toxicity
Indometacin	Probenecid	Indometacin toxicity
Digoxin	Spironolactone	Increased plasma digoxin
	Amiodarone	
	Verapamil	

Pharmacokinetic Interactions

4. **Many diuretics reduce sodium absorption in the loop of Henle or the distal tubule. This leads indirectly to increased proximal tubular reabsorption of monovalent cations.**

- **Increased proximal tubular reabsorption of lithium in patients treated with lithium salts can cause lithium accumulation and toxicity.**

Pharmacokinetic Interactions

6. **Digoxin excretion is reduced by spironolactone, verapamil and amiodarone, all of which can precipitate digoxin toxicity as a consequence, although several of these interactions are complex in mechanism, involving displacement from tissue binding sites, in addition to reduced digoxin elimination.**

Pharmacokinetic Interactions

7. **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.**

Pharmacokinetic Interactions

8. **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.**
- **P-glycoproteins can be induced or inhibited by some drugs. Verapamil increases digoxin level and toxicity at this level. There is also some overlap between P-glycoproten and CYP3A4 substrates, inducers and inhibitors.**

Table 4.4 Examples of inhibitors and inducers of P-glycoprotein

Inhibitors	Atorvastatin Ciclosporin Clarithromycin Dipyridamole Erythromycin Itraconazole Ketoconazole Propafenone Quinidine Ritonavir Valspodar Verapamil
Inducers	Rifampicin St John's wort

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 *Glycyrrihizin 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.**

Drug-herb Interactions

2. **Chinese ginseng (*Panax ginseng*), Chan Su (containing bufalin) and Danshen contain digoxin-like compounds that interfere with digoxin assay leading to falsely elevated concentrations.**
3. **Alfalfa (*Medicago sativa*), Angelica (*Angelica archangelica*), Dong Quai (*Angelica polymorpha, A. dahurica, A. atropurpurea*), chamomile (بابونج), horse chestnut (كستناء), and red clover (*Trifolium pratense*) have anticoagulant properties that can increase the risk of bleeding when used with warfarin.**

Drug-herb Interactions

- **Herbal products with antiplatelet activities include Borage (*Borago officinalis*), Bromelain (أناناس) (*Ananas comosus*), capsicum (الفليفلة), feverfew, garlic, Ginkgo (*Ginkgo biloba*) and tumeric can increase the risk of bleeding when used with aspirin and other antiplatelet drugs.**
- **Enhancement of hypoglycemic effect by Asian ginseng.**
- **Enhancement of hypotensive effect by hawthorn (الزعرور).**

Drug-herb Interactions

- **Lowering of seizure threshold by evening primrose oil and *Shankapushpi*.**
- **St. John's wort (*Hypericum*) interactions – discussed.**
- **Patients usually will not volunteer that they are taking herbal products.**