# Drug Interactions

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# 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 poly-pharmacy (multiple drug use ), non-prescription use of herbal and complementary medicines, and food- and drink – drug interactions.

# Drug Interactions

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

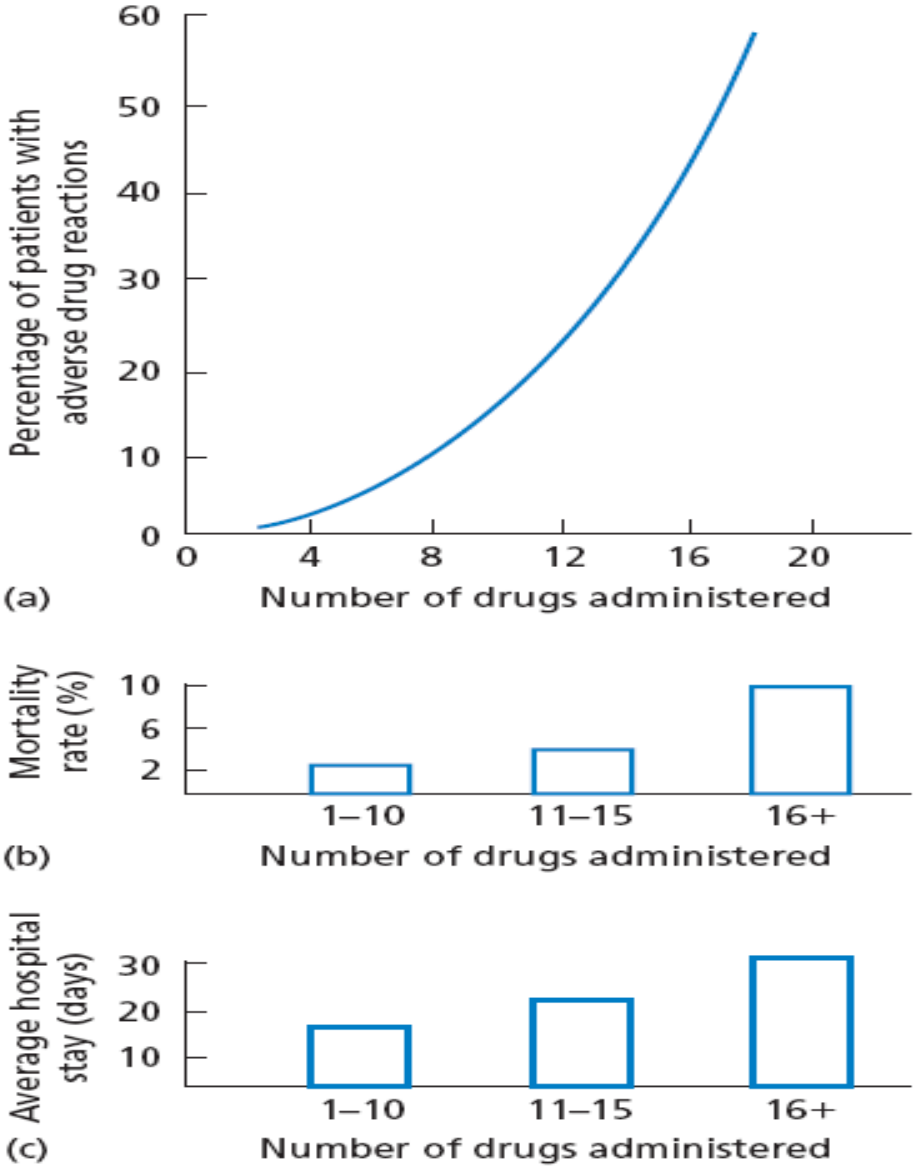


**Figure 13.1:** Relationship of number of drugs administered to (a) adverse drug reactions, (b) mortality rate and (c) average duration of hospital stay. (Redrawn by permission of the British Medical Journal from Smith JW et al. *Annals of Internal Medicine* 1966; 65: 631.)

# 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.**
- **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 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

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

# Drug Interactions

**Useful Interactions (examples):**

**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.**

# Drug Interactions

2. **The use of a $\beta_2$ 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).**

# 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 inactivation can be overcome by administering imipenem in combination with cilastatin, a specific renal dipeptidase inhibitor.**

# Drug Interactions

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.**

# 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 of levodopa, while reducing the dose-related peripheral adverse 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.**

# Drug Interactions

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

# Drug Interactions

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.**

# Drug Interactions

**Mechanisms of drug interactions:**

1. **Chemical (Pharmaceutical) interactions**
2. **Pharmacodynamic interactions**
3. **Pharmacokinetic interactions**

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

# Chemical 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.**

# Chemical Interactions

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 $H_1$-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.**

# Pharmacodynamic Interactions

- **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.**

# Pharmacodynamic Interactions

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, and because of sodium and water retention.**

# Pharmacodynamic Interactions

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 $E_2$ biosynthesis in the gastric mucosa.**

# Pharmacodynamic Interactions

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.**

# Pharmacodynamic Interactions

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 cause excessive intravascular fluid depletion, electrolyte loss, 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.**

7. **$\beta_2$-Agonists (salbutamol) also may reduce the plasma potassium concentration.**

# Pharmacodynamic Interactions

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.**

- **Hyperkalaemia is one of the most common causes of fatal adverse drug reactions.**

# Pharmacodynamic Interactions

9. **Antagonistic interactions:**

- **The bronchodilator action of selective $\beta_2$-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.**

# Pharmacodynamic Interactions

10. Neuroleptics and tricyclic antidepressants (TCAs) given with drugs producing electrolyte imbalance (diuretics) may cause ventricular arrhythmias.
11. Drugs that prolong the QTc interval if used concurrently can cause fatal polymorphic ventricular tachycardia (*torsade de pointes*).
12. Serotonin syndrome occurs with combinations that increase serotonin. (Selective serotonin reuptake inhibitors and MAOIs).

- Linezolid is an antibacterial with MAOI activity.

# Pharmacodynamic Interactions

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 $H_2$-antagonists, or proton pump inhibitors may affect weak acidic drugs absorption.**

- **Drugs affected include aspirin, itraconazole...**

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

# Pharmacokinetic Interactions

- **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 (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).**

# 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 (TCAs, phenothiazines and antihistamines) decrease gut motility and reduce gastric emptying.**
- **This can decrease or increase absorption of drugs. (How?)**

# Pharmacokinetic Interactions

- ✓ **Anticholinergics reduce the bioavailability of levodopa, as a result of increased metabolism in the intestinal mucosa.**
- ✓ **Opioids inhibit gastric emptying and 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:

- **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.**

# Pharmacokinetic 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?)**

# Pharmacokinetic Interactions

- ✓ **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.**

# Pharmacokinetic Interactions

- ✓ **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).**

# Pharmacokinetic Interactions

- ✓ **Enzyme inhibition usually results in increased pharmacological effect, but when the affected drug is a pro-drug, a reduced pharmacological effect may result.**
- **Clopidogrel is metabolized to an active metabolite by CYP2C19 which is inhibited by a proton pump inhibitor (lansoprazole) leading to reduced effectiveness of clopidogrel.**

# Pharmacokinetic Interactions

- ✓ **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).**

# Pharmacokinetic Interactions

- **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.**

# Pharmacokinetic Interactions

- ✓ **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, ..).**

# Pharmacokinetic Interactions

- **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 reduces hepatic blood flow (negative inotropes, β-blockers, $H_2$-blockers) reduce hepatic clearance of lidocaine leading to its accumulation and toxicity.**

# Pharmacokinetic Interactions

## 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.

# Pharmacokinetic Interactions

- **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.**

# Pharmacokinetic Interactions

- **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.**

# 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, leading to an increase in drug concentration and emergence of delayed toxicity. (The dose is NO longer appropriate).**

# 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 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.**

# 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).**
- **It is clinically important for highly protein-bound drugs.**
- **Examples: phenytoin, lidocaine, warfarin…**

# Pharmacokinetic Interactions

**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).**

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

# Pharmacokinetic Interactions

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.**

# Pharmacokinetic Interactions

5. **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!!**

# Pharmacokinetic Interactions

6. **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.**

# Pharmacokinetic Interactions

- **P-glycoproteins can be induced or inhibited by some drugs.**
- **There is also some overlap between P-glycoproten and CYP3A4 substrates, inducers and inhibitors.**

# 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

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

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