

CHAPTER 69

Drug Interactions

Drug interaction refers to modification of response to one drug by another when they are administered simultaneously or in quick succession. The modification is mostly quantitative, i.e. the response is either increased or decreased in intensity, but sometimes it is qualitative, i.e. an abnormal or a different type of response is produced. The possibility of drug interaction arises whenever a patient concurrently receives more than one drug, and the chances increase with the number of drugs taken.

Many medical conditions are treated with a combination of drugs. The components of the combination are so selected that they complement each other's action, e.g. an antibiotic is used along with an analgesic to treat a painful infective condition; adrenaline is combined with lidocaine for local anaesthesia; antitubercular drugs are combined to prevent drug resistance; mixed aerobic-anaerobic bacterial infections, are treated with a combination of antimicrobials. More commonly, multiple drugs are used to treat a patient who is suffering from two or more diseases at the same time. The chances of unintended/adverse drug interactions are greater in this later situation, because an assortment of different drugs may be administered to a patient depending on his/her diseases/symptoms.

Several drug interactions are desirable and deliberately employed in therapeutics, e.g. the

synergistic action of ACE inhibitors + diuretics to treat hypertension or sulfamethoxazole + trimethoprim to treat bacterial infection or furosemide + amiloride to prevent hypokalaemia. These are well-recognized interactions and do not pose any undue risk to the patient. The focus of attention in this chapter are drug interactions which may interfere with the therapeutic outcome or be responsible for adverse effects, or may even be fatal (bleeding due to excessive anticoagulant action).

The severity of drug interactions in most cases is highly unpredictable. However the doctor must

Regular medication drugs

(Likely to be involved in drug interactions)

1. Antidiabetics
2. Antihypertensives
3. Antianginal drugs
4. Antiarthritic drugs
5. Antiepileptic drugs
6. Antiparkinsonian drugs
7. Oral contraceptives
8. Anticoagulants
9. Antiasthmatic drugs
10. Psychopharmacological agents
11. Antipeptic ulcer drugs
12. Corticosteroids
13. Antitubercular drugs
14. Anti-HIV drugs

know which drugs are not to be prescribed concurrently. More importantly, a large section of patients may be receiving one or several drugs for their chronic medical conditions like hypertension, diabetes, arthritis, etc. (*see box* for regular medication drug classes employed commonly). The physician may prescribe certain drugs which may interact with those already being taken by the patient and result in adverse consequences. It is, therefore, imperative for the doctor to elicit a detailed drug history of the patient and record all the medication that he/she is currently on. The list of potential adverse drug interactions is already quite long and constantly growing. It is practically impossible for anyone to know/remember all possible drug interactions. Fortunately, the clinically important and common drug interactions that may be encountered in routine practice are relatively few. Some of these are listed in Table 69.1. More exhaustive compilations and documentation are available in specialized books, monographs, review articles and computer database on the subject, but these also need constant updating.

Certain types of drugs (*see box*) can be identified that are most likely to be involved in clinically important drug interactions. The physician may take special care and pay attention to the possibility of drug interactions when the patient is receiving one or more of such medications, or when the doctor intends to prescribe any of such drugs.

Types of drugs most likely to be involved in clinically important drug interactions

- Drugs with narrow safety margin, e.g. aminoglycoside antibiotics, digoxin, lithium.
- Drugs affecting closely regulated body functions, e.g. antihypertensives, antidiabetics, anticoagulants.
- Highly plasma protein bound drugs like NSAIDs, oral anticoagulants, sulfonyleureas.
- Drugs metabolized by saturation kinetics, e.g. phenytoin, theophylline.

MECHANISM OF DRUG INTERACTIONS

Drug interactions can be broadly divided into *pharmacokinetic* and *pharmacodynamic* interactions. In certain cases, however, the mechanisms are complex and may not be well understood. Few interactions take place even outside the body when drug solutions are mixed before administration.

Pharmacokinetic interactions

These interactions alter the concentration of the object drug at its site of action (and consequently the intensity of response) by affecting its absorption, distribution, metabolism or excretion.

Pharmacokinetic interactions

- Alteration of absorption or first-pass metabolism
- Displacement of plasma protein bound drug
- Alteration of drug binding to tissues affecting volume of distribution and clearance
- Inhibition/induction of metabolism
- Alteration of excretion

Absorption Absorption of an orally administered drug can be affected by other concurrently ingested drugs. This is mostly due to formation of insoluble and poorly absorbed complexes in the gut lumen, as occurs between tetracyclines and calcium/iron salts, antacids or sucralfate. Phenytoin absorption is decreased by sucralfate due to binding in the g.i. lumen. Such interactions can be minimized by administering the two drugs with a gap of 2–3 hours so that they do not come in contact with each other in the g.i.t. Ketoconazole absorption is reduced by H₂ blockers and proton pump inhibitors because they reduce gastric acidity which promotes dissolution and absorption of ketoconazole. Antibiotics like ampicillin, tetracyclines, cotrimoxazole markedly reduce gut flora that normally deconjugates oral contraceptive steroids secreted in the bile as glucuronides and permits their enterohepatic circulation. Several instances of contraceptive failure have been reported with concurrent use of these

antibiotics due to lowering of the contraceptive blood levels. Alteration of gut motility by atropinic drugs, tricyclic antidepressants, opioids and prokinetic drugs like metoclopramide or cisapride can also affect drug absorption.

Distribution Interactions involving drug distribution are 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, sulfonylureas, certain NSAIDs and antiepileptics are particularly liable to displacement interactions. Another requirement is that the displacing drug should bind to the same sites on the plasma proteins with higher affinity. Displacement of bound drug will initially raise the concentration of the free and active form of the drug in plasma that may result in toxicity. However, such effects are usually brief, because the free form rapidly gets distributed, metabolized and excreted, so that steady-state levels are only marginally elevated. The clinical outcome of displacement interactions is generally significant only when displacement extends to tissue binding sites as well, or is accompanied by inhibition of metabolism and/or excretion. Quinidine has been shown to reduce the binding of digoxin to tissue proteins as well as its renal and biliary clearance by inhibiting the efflux transporter P-glycoprotein, resulting in nearly doubling of digoxin blood levels and toxicity.

Metabolism Certain drugs reduce or enhance the rate of metabolism of other drugs. They may thus affect the bioavailability (if the drug undergoes extensive first pass metabolism in liver) and the plasma half-life of the drug (if the drug is primarily eliminated by metabolism). Inhibition of drug metabolism may be due to competition for the same CYP450 isoenzyme or cofactor, and attains clinical significance mostly for drugs that are metabolized by saturation kinetics. Macrolide antibiotics, azole antifungals, chloramphenicol, omeprazole, SSRIs, HIV-protease inhibitors,

cimetidine, ciprofloxacin and metronidazole are some important inhibitors of metabolism of multiple drugs. Risk of statin induced myopathy is increased by fibrates, niacin, erythromycin, azole antifungals and HIV-protease inhibitors, probably due to inhibition of statin metabolism. Because lidocaine metabolism is dependent on hepatic blood flow, propranolol has been found to prolong its $t_{1/2}$ by reducing blood flow to the liver.

A number of drugs induce microsomal drug metabolizing enzymes and enhance biotransformation of several drugs (including their own in many cases). Induction involves gene mediated increased synthesis of certain CYP450 isoenzymes; takes 1–2 weeks of medication with the inducer to produce maximal effect (contrast inhibition of metabolism which develops quickly) and regresses gradually over 1–3 weeks after discontinuation of the inducer. Barbiturates, phenytoin, carbamazepine, rifampin, cigarette smoking, chronic alcoholism and certain pollutants are important microsomal enzyme inducers. Instances of failure of antimicrobial therapy with metronidazole, doxycycline or chloramphenicol have occurred in patients who are on long-term medication with an inducing drug. Contraceptive failure and loss of therapeutic effect of many other drugs have occurred due to enzyme induction. On the other hand, the 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.

Excretion Interaction involving excretion are important mostly in case of drugs actively secreted by tubular transport mechanisms, e.g. probenecid inhibits tubular secretion of penicillins and cephalosporins and prolongs their plasma $t_{1/2}$. This is particularly utilized in the single dose treatment of gonorrhoea. Aspirin blocks the uricosuric action of probenecid and decreases tubular secretion of methotrexate. Change in the pH of urine can also affect excretion of weakly acidic or weakly basic drugs. This has been

Table 69.1: Selected clinically important drug interactions

<i>Precipitant drug*</i>	<i>Object drug[‡]</i>	<i>Likely interaction and comments</i>
1. Ampicillin Amoxicillin	Oral contraceptives Oral anticoagulants	Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception. Inhibition of gut flora → decreased vit K production in gut → risk of bleeding; Monitor INR and reduce anticoagulant dose if needed.
2. Probenecid	Penicillin Ampicillin Cephalosporins	Inhibition of tubular secretion → prolongation of antibiotic action; Desirable interaction utilized for single dose therapy.
3. Allopurinol	Ampicillin 6-Mercaptopurine Azathioprine Warfarin Theophylline	Increased incidence of rashes; Avoid concurrent use. Inhibition of metabolism; Reduce dose of 6-MP/azathioprine to 1/3. Inhibition of metabolism; Monitor and reduce dose of object drug.
4. Carbenicillin Ticarcillin	Aspirin and other antiplatelet drugs	Perturbation of surface receptors on platelets → additive platelet inhibition → risk of bleeding; Avoid concurrent use.
5. Ceftriaxone Cefoperazone	Oral anticoagulants	Additive hypoprothrombinaemia → bleeding; Monitor INR and reduce dose of anticoagulant.
6. Sulfonamides Cotrimoxazole	Phenytoin Warfarin Sulfonylureas Thiazide diuretics Oral contraceptives	Displacement [§] + inhibition of metabolism → phenytoin toxicity; Avoid concurrent use. Displacement + inhibition of metabolism + decreased production of vit K in gut → risk of bleeding; Monitor INR and reduce dose of warfarin. Displacement + inhibition of metabolism → hypoglycaemia; Avoid concurrent use. Increased incidence of thrombocytopenia; Avoid concurrent use. Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception.
7. Metronidazole Tinidazole Cefoperazone	Alcohol	Accumulation of acetaldehyde → disulfiram-like or bizarre reactions; Warn the patient not to drink alcohol.
8. Metronidazole Tinidazole	Lithium salts Warfarin	Decreased excretion → Li ⁺ toxicity; Monitor Li ⁺ level and reduce lithium dose. Inhibition of metabolism → risk of bleeding; Avoid concurrent use.
9. Ciprofloxacin Norfloxacin Pefloxacin	Theophylline Warfarin	Inhibition of metabolism → toxicity of object drug; Monitor and reduce dose of object drug.
10. Erythromycin Clarithromycin Ketoconazole Itraconazole Fluconazole Protease inhibitors	Terfenadine Astemizole Cisapride Phenytoin Carbamazepine Warfarin Sulfonylureas Diazepam Theophylline Cyclosporine HIV protease inhibitors Statins	Inhibition of metabolism by CYP3A4 → rise in blood level of object drug → dangerous ventricular arrhythmia; Concurrent use contraindicated. Inhibition of metabolism by CYP3A4 → toxicity of object drug; Avoid concurrent use or readjust dose of object drug. Inhibition of metabolism, higher risk of myopathy; Avoid concurrent use.

* Precipitant drug is the drug, which alters the action/pharmacokinetics of the other drug.

‡ Object drug is the drug whose action/pharmacokinetics is altered.

§ Displacement of plasma protein bound drug.

Contd...

Contd...

Precipitant drug	Object drug	Likely interaction and comments
11. Gemfibrozil Nicotinic acid	Statins	Increased risk of myopathy; Caution in concurrent use.
12. Tetracyclines	Oral contraceptives	Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception.
	Lithium salts	Rise in plasma Li ⁺ level due to decreased excretion; Avoid use of tetracycline or monitor and reduce dose of lithium.
13. Iron salts Calcium salts Antacids Sucralfate	Tetracyclines Fluoroquinolones	Decreased absorption due to formation of complexes in g.i.t. → failure of antibiotic therapy; Stagger drug administration by 2–3 hours.
14. Furosemide	Minocycline	Enhanced vestibular toxicity; Avoid concurrent use.
	Aminoglycoside antibiotics	Additive ototoxicity and nephrotoxicity; Avoid concurrent use.
15. Diuretics	Tetracycline	Antianabolic effect of tetracycline increases urea production which is retained by the diuretic; Avoid concurrent use.
	Lithium	Decreased excretion—rise in Li ⁺ level—toxicity; Reduce dose of lithium and monitor level.
	Digoxin	Hypokalaemia caused by diuretic increases digoxin toxicity; Give K ⁺ sparing diuretic/K ⁺ supplements.
16. Tetracyclines Chloramphenicol Macrolide antibiotics Clindamycin	Penicillins Cephalosporins	Bactericidal action of penicillins and cephalosporins may be antagonized by the bacteriostatic antibiotics; Avoid concurrent use.
17. Clindamycin	Erythromycin Clarithromycin Azithromycin Chloramphenicol	Mutual antagonism of antibacterial action due to proximal binding sites on bacterial ribosomes; Avoid concurrent use.
18. Phenobarbitone Phenytoin Carbamazepine Rifampin	Metronidazole Doxycycline Chloramphenicol Protease inhibitors Warfarin Corticosteroids Oral contraceptives Sulfonyl ureas Antidepressants	Induction of metabolism → loss of efficacy of object drug; Avoid concurrent use or increase dose of object drug with monitoring.
19. Chloramphenicol	Warfarin Phenytoin Sulfonylureas	Inhibition of metabolism → toxicity of the object drug. Avoid concurrent use or monitor and reduce dose of object drug.
20. NSAIDs	Ciprofloxacin and other fluoroquinolones	Enhanced CNS toxicity, seizures; Avoid concurrent use.
21. Aspirin and other NSAIDs	Sulfonylureas Phenytoin Valproate Methotrexate	Displacement and/or reduced elimination → toxicity of object drug; Avoid concurrent use/substitute NSAID with paracetamol.
	Warfarin	Enhanced risk of bleeding due to antiplatelet action and gastric mucosal damage; Avoid concurrent use.
	Heparin	Reduced antihypertensive effect due to inhibition of renal PG synthesis; Avoid concurrent use.
	ACE inhibitors	
	β blockers	
	Thiazide diuretics	
	Furosemide	Reduced diuretic action due to PG synthesis inhibition in kidney; Avoid concurrent use.

Contd...

Contd...

<i>Precipitant drug</i>	<i>Object drug</i>	<i>Likely interaction and comments</i>	
Aspirin and other NSAIDs	Alcohol	Increased risk of gastric mucosal damage and gastric bleeding; Concurrent use contraindicated.	
22. Aspirin	Corticosteroids		
	Spironolactone		Reduced K ⁺ conserving action due to decreased tubular secretion of canrenone (active metabolite of spironolactone); Avoid concurrent use.
23. Chronic alcoholism	Paracetamol	Hepatotoxic dose of paracetamol is reduced; doses ≤ 3 g/day are safe.	
24. Chlorpromazine	Morphine	Enhanced CNS and respiratory depression; Avoid concurrent use.	
Imipramine and other TCAs			Pethidine
25. Chlorpromazine			Codeine
	Haloperidol	Levodopa-carbidopa	Antagonism of antiparkinsonian effect; Concurrent use contraindicated.
Metoclopramide			
26. Levodopa-carbidopa	ACE inhibitors	Excessive postural hypotension; Reduce dose of antihypertensives.	
27. TCAs	Vasodilators		
	Prazosin		
28. Promethazine	Adrenaline (added to local anaesthetic)	Potentiation due to neuronal uptake inhibition → rise in BP; Use plain local anaesthetic solution.	
			Alcohol
Opioids	Diazepam and other benzodiazepines	Additive CNS and respiratory depression, motor impairment; Avoid concurrent use.	
Antipsychotics			
29. Cimetidine	Diazepam and other benzodiazepines	Inhibition of metabolism → exaggerated CNS depression; Avoid concurrent use or reduce benzodiazepine dose.	
Isoniazid			
30. Sildenafil	Nitrates	Marked potentiation → precipitous fall in BP; Concurrent use contraindicated.	
Tadalafil			
31. Propranolol	Adrenaline (injected with local anaesthetic)	Rise in BP due to blockade of vasodilator action of adrenaline that enters systemic circulation; Avoid adrenaline containing local anaesthetic.	
32. Lidocaine	Lidocaine	Reduced hepatic clearance of lidocaine; Ceiling amount used in local anaesthesia is reduced.	
	β-blockers	Enhanced bradycardia and hypotension; Avoid concurrent use.	
	Quinidine and other antiarrhythmic drugs	Exaggerated cardiac depression, precipitation of arrhythmias; Avoid concurrent use.	

NSAIDs: Nonsteroidal antiinflammatory drugs

TCAs: Tricyclic antidepressants

utilized in the treatment of poisonings. Diuretics and to some extent tetracyclines, ACE inhibitors and certain NSAIDs have been found to raise steady-state blood levels of lithium by promoting its tubular reabsorption.

Pharmacodynamic interactions

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. The phenomena of synergism and antagonism are described in Chapter 4, and are deliberately utilized in therapeutics for various purposes. Of clinical significance are the in-advertent concurrent administration of synergistic or antagonistic pair of drugs with adverse consequences. Some examples are:

1. Excessive sedation, respiratory depression, motor incoordination due to concurrent administration of a benzodiazepine

- (diazepam), a sedating antihistaminic (promethazine), a neuroleptic (chlorpromazine), an opioid (morphine) or drinking alcoholic beverage while taking any of the above drugs.
2. Excessive fall in BP and fainting due to concurrent administration of α_1 adrenergic blockers, vasodilators, ACE inhibitors, high ceiling diuretics and cardiac depressants.
 3. Pronounced and asymptomatic hypoglycaemia can occur when propranolol is administered to diabetics receiving insulin/sulfonylureas, due to blockade of β adrenoceptors which contribute to recovery from hypoglycaemia as well as some hypoglycaemic symptoms.
 4. Additive prolongation of prothrombin time and bleeding by administration of ceftriaxone or cefoperazone to a patient on oral anticoagulants.
 5. Excessive platelet inhibition resulting in bleeding due to simultaneous use of aspirin/ticlopidine/clopidogrel and carbenicillin.
 6. Increased risk of bleeding due to concurrent use of antiplatelet drugs (aspirin, clopidogrel) with anticoagulants (warfarin).
 7. Marked bradycardia due to administration of propranolol in digitalized patients.
 8. Precipitous fall in BP and myocardial ischaemia due to use of sildenafil by patients receiving organic nitrates, because nitrates increase generation of cGMP, while sildenafil prevents its degradation by inhibiting PDE 5.
 9. Severe hyperkalaemia by concurrent use of ACE inhibitors and K^+ sparing diuretics.
 10. Additive ototoxicity due to use of an aminoglycoside antibiotic in a patient receiving furosemide.
 11. Antagonism of bactericidal action of β -lactam antibiotic by combining it with a bacteriostatic drug like tetracycline, erythromycin or clindamycin.
 12. Mutual antagonism of antibacterial action of macrolides, clindamycin and chloramphenicol due to interference with each other's binding to the bacterial 50S ribosome.
 13. Reduction in antihypertensive action of clonidine by chlorpromazine and imipramine, possibly due to blockade of central action of clonidine.
 14. Attenuation of antihypertensive effect of ACE inhibitors/ β blockers/diuretics by NSAIDs due to inhibition of renal PG synthesis.
 15. Blunting of K^+ conserving action of spironolactone by aspirin, because it inhibits the tubular secretion of canrenone (an active metabolite of spironolactone).
 16. Blockade of antiparkinsonian action of levodopa by neuroleptics and metoclopramide having antidopaminergic action.
- Abnormal responses sometimes result from pharmacodynamic interaction between certain drugs, e.g. metronidazole and cefoperazone inhibit the enzyme aldehyde dehydrogenase resulting in bizarre distressing symptoms if the patient drinks alcohol. The basis of certain interactions is not explained, e.g. ampicillin has produced high incidence of skin rashes in patients treated with allopurinol.

Drug interactions before administration

Certain drugs react with each other and get inactivated if their solutions are mixed before administration. In combined oral or parenteral formulations, the manufacturers take care that such incompatibilities do not take place. 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.
- Thiopentone sodium when mixed with succinylcholine or morphine.
- Heparin when mixed with penicillin/gentamicin/hydrocortisone.
- Noradrenaline when added to sodium bicarbonate solution.

In general, it is advisable to avoid mixing of any two or more parenteral drugs before injecting.

Comment Not all patients taking interacting drugs experience adverse consequences, but it is advisable to take due precautions to avoid mishaps in all cases where interactions are possible. That two drugs have the potential to interact does not necessarily contraindicate their concurrent use. In many cases, knowledge of the nature and mechanism of the possible interaction

may permit their concurrent use provided appropriate dose adjustments are made or other corrective measures are taken. A list of significant and common drug interactions that may be encountered in clinical practice is given in Table 69.1, along with the suggested corrective measure. However, 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.