Drug-Drug Interactions

The pharmacokinetics as well as the pharmacodynamic effects of drug can be altered by the previous or concurrent administration of another drug. While such an interaction may be therapeutically beneficial occasionally, in many instances it may result in adverse effects. The long term use of potent drugs and self-medication has resulted in an increase in the incidence of adverse drug interactions. Every time a physician prescribes an additional drug, he or she is adding to the risk of these interactions. It has been estimated that patients in hospital, who are receiving more than six drugs at a time, have a 6 to 7 times greater incidence of adverse effects (including those due to drug interactions) than those who are receiving less than six drugs. Also, about *7% of all adverse drug reactions are estimated to be due to drug interactions*, and account for approximately one-third of the mortality of such patients. *The elderly are more prone to drug interactions*, not only because they receive more drugs than younger patients, but because in them the pharmacokinetics of drugs are d fferent.

The adverse drug interactions of clinical importance are relatively few and many of these can be predicted if their pharmacodynamic effects, salient pharmacokinetic properties and mechanisms of action are known and logically applied in the clinical setting.

Mechanisms of drug interactions

The important mechanisms responsible for drug interactions can be classified as follows:

(a) **Pharmaceutical interactions** or interactions occurring outside the body.

(b) **Pharmacokinetic interactions** or interactions due to alterations in the absorption, distribution, metabolism or excretion of one drug by another.

(c) **Pharmacodynamic interactions** or interactions due to alterations in the pharmacological action of one drug by another, at or near the target site of action, and may involve the basic mechanism by which these drugs act.

I. PHARMACEUTICAL INTERACTIONS

Drugs may be *inactivated* or *precipitated* from solution if mixed in syringes or added to blood or infusion fluids prior to administration. Generally the manufacturer's literature provides specific warnings and guidelines which should be checked. It is advisable *to avoid mixing drugs in infusion solutions* unless it is known that the mixture is safe (e.g. potassium chloride and insulin).

Avoid using the following drug combinations for intravenous therapy.

(a) Antibiotics and large volumes of transfusion fluids.

(b) Blood, plasma, sodium bicarbonate, lactate or mannitol with any drug.

(c) Highly acidic solutions (e.g. dextrose and laevulose) with sodium or potassium salts of sulphonamides, barbiturates, methicillin, penicillin, ampicillin, heparin and aminophylline

(d) Heparin and tetracyclines, gentamicin, noradrenaline and hydrocortisone

(e) Hydrocortisone hemisuccinate with ampicillin, methicillin, carbenicillin and the tetracyclines

(f) Succinylcholine with thiopentone sodium

(g) Short and long-acting insulins (s.c.)

II. PHARMACOKINETIC INTERACTIONS

These interactions may take place during absorption, metabolism, distribution and excretion of drugs, factors which are important for the biavailability of a drug at its target site of action. The interactions can be anticipated but their extent cannot be predicted because there are marked individual variations in their pharmacokinetic properties. The clinically important interactions are the following:

1. Drug absorption interactions

One drug **may retard the rate or extent of absorption** of another drug in a variety of ways. For instance, an alteration in the rate of absorption of a drug with a long plasma half-life (warfarin) will have little effect since the drug will eventually be absorbed. However, when the drug has a short plasma half-life (procainamide), reduction in the rate of absorption means that an effective therapeutic concentration in the plasma may never be achieved. A delay in the rate of absorption is also important with drugs such as analgesics and hypnotics, where a rapid effect is required. Some important causes of absorption interactions are as follows:

(a) **Intraluminal binding or chelation of drugs.** Drugs may react chemically to form **unabsorbable chelates,** viz. iron and tetracycline, aluminium, magnesium or calcium containing antacids with tetracycline. Drug absorption may be reduced by **adsorbents**, such as kaolin or charcoal and by anion exchange resins such as cholestyramine and colestipol, e.g. inhibition of digoxin absorption by anion exchange resins. Sucralfate reduces absorption of phenytion, and liquid paraffin reduces absorption of fat-soluble vitamins.

(b) **Gastrointestinal motility and transit time.** Most drugs are absorbed from the first part of the small intestine and *the rate of gastric emptying* will influence their rate of absorption. Drugs such as opiates, anticholinergics, tricyclic antidepressants, antihistaminics and phenothiazines slow gastric emptying time, whereas metoclopramide and domperidone increase it. This type of interaction is **important with drugs** such as antibiotics or analgesics **when rapid peak plasma concentrations are desirable.** Thus, a combination of metoclopramide with analgesics has been used in the treatment of an acute attack of migraine.

(c) **Alterations in the pH of gastrointestinal fluids.** Basic drugs are ionized, become less lipid soluble and are poorly absorbed in an acidic medium whereas the reverse is true for acidic drugs in an alkaline medium. The unsupervised intake of **antacids** may thus interfere with the absorption of many acidic drugs (aspirin, barbiturates and warfarin). A marked reduction in gastric acidity by **H_2-blockers** and **omeprazole** decrease the absorption of ketoconazole.

(d) **Alterations in gut bacterial flora. Broad spectrum antibiotics** (cephalosporins and erythromycin) adversely affect the gut bacterial flora and may affect the action of a number of drugs. **Sulphasalazine** is biotransformed into an active metabolite by gut flora, **l-dopa** is converted into dopamine, and **digoxin** is partly metabolized by them. Thus, the effect of sulphasalazine will be reduced while the effect of the other drugs will be augmented if the gut flora are reduced, and may lead to toxicity. The toxicity of **oral anticoagulants** can be increased following a decrease in the vitamin K availability from these bacteria. It has been reported recently that in some women broad spectrum antibiotics interfere with the antifertility action of **oral contraceptive pills**. The mechanism involved is disruption of the enterohepatic cycling of the

hormones by a reduction of the gut bacteria responsible for the deconjugation and reabsorption of the active parent drug.

(e) **Mucosal damage.** The long term use of drugs likely to induce gut mucosal damage such as neomycin, phenformin, mefenamic acid and cytotoxic agents, can **impair** the **absorption** of other drugs, particularly those which are normally poorly absorbed (digoxin or phenytoin). Colchicine can induce pernicious anaemia by interfering with vitamin B_{12} absorption.

(f) **Other mechanisms.** Corticosteroids inhibit calcium absorption, while phenobarbitone reduces griseofulvin absorption, and folic acid absorption is reduced by drugs like phenytoin and nitrofurantoin leading to folic acid deficiency and megaloblastic anaemia.

2. Drug distribution interactions

One drug may alter the distribution of another and thereby affect the concentration of the unbound active drug at the site of action. The majority of acidic drugs are transported partially bound to plasma proteins. The free drug exists in equilibrium with the bound drug and only the former is available for pharmacological activity. Displacement (**displacement interaction**) of the bound drug by another drug, with greater affinity for *plasma protein binding* (*see* Chapter 2), will lead to release of relatively large amounts of the free drug with an augmented action and likely toxicity. Similarly, drugs may be displaced from *tissue binding sites*, viz. quinidine displaces digoxin from its skeletal muscle binding sites, and mepacrine can displace primaquine. Some examples of displace-ment interactions are given in Table 18.1.

3. Drug metabolism interactions

Among the major sites for drug interactions are **the hepatic drug-metabolizing microsomal enzymes.** One drug may interfere with the metabolism of another drug by either inducing or inhibiting these enzymes. In addition, extrahepatic enzyme inhibition may also be the cause of drug interactions.

(a) **Enzyme induction.** Some drugs and environmental chemicals stimulate drug metabolism through induction of hepatic microsomal enzymes. They bind to the cytosolic receptors in the hepatic endoplasmic reticulum to activate the **production of mono-oxygenase** (and some conjugation enzymes) (*see* Chapter 2). The induction of enzyme activity will lead to reduced effects of the drugs which are fast inactivated (Table 18.2). However, the effects of drugs which are activated by biotransformation will be increased. Enzyme induction is **slow in onset**, since protein synthesis is involved, and the process is **reversible** with the withdrawal of the enzyme-inducing agent. The latter is of clinical relevance since reduction in enzyme levels will result in a gradual increase in the plasma levels of the target drugs, resulting in toxicity. Thus, withdrawal of phenobarbitone, an enzyme inducer, will lead to increased toxicity of warfarin unless the dose of the latter is reduced.

(b) **Enzyme inhibition.** One drug may inhibit the metabolism of another drug leading to an increase in circulating levels of the active drug, and result in exaggerated and prolonged responses, with an increased risk of toxicity (*see* Chapter 2). As in enzyme induction, **hepatic microsomal enzymes** are involved. The enzyme inhibition, unlike induction, **occurs rapidly**, but is also **reversible**. **Such interactions are likely to be of clinical relevance when they co-exist with displacement interaction.** Drugs may also inhibit non-microsomal enzymes and induce interactions. The effects of those drugs, which are activated by biotransformation, are reduced by enzyme inhibitors. Drugs which undergo **substantial first-pass metabolism** in the liver, following oral administration, are more **vulnerable** to this type of drug interaction. In addition, the initial concen-tration of the target drug, the extent of inhibition, the susceptibility of the patient and the magnitude of the clinicai response, are major factors in enzyme inhibition-induced drug interaction. (Table 18.3).

An important example of **food-drug interaction** involves the inhibition of the enzyme

Table 18.1
Clinically relevant displacement interactions

Bound drug	*Displacing drug*	*Effect*
Phenytoin	Sodium valproate	Phenytoin toxicity
Methotrexate	Aspirin, probenecid, other NSAIDs	Methotrexate toxicity
Digoxin	Quinidine	Digoxin toxicity
Sulphonylureas	Sulphonamides	Hypoglycaemia
Warfarin	NSAIDS except paracetamol	Haemorrhage

Table 18.2
Drug interactions due to enzyme induction

Enzyme inducer	*Induces metabolism of*	*Effect*
Rifampicin	Oral contraceptives	Failure of contraception
NSAIDs, antiepileptics	Oral anticoagulants	Reduced effect, toxicity on withdrawal of inducing drug
Ethanol	Oral anticoagulants	Reduced effect
Rifampicin	Cyclosporine	Reduced immunosuppression
Carbamazepine	Phenytoin	Reduced effect
Rifampicin, phenytoin	Oral antidiabetics	Reduced effect

Table 18.3
Drug interactions due to enzyme inhibition

Enzyme inhibitor	*Inhibits metabolism of*	*Effect*
Cimetidine	Propranolol, warfarin theophylline	Increased toxicity
Erythromycin	Theophylline, warfarin, carbamazepine	Increased toxicity
	Astemizole, terfenadine	Cardiac arrhythmia
Enoxacin	**Theophylline**	Seizures
Verapamil	**Carbamazepine**	Increased toxicity
Allopurinol	**Azathioprine**	Increased toxicity
NSAIDs	**Warfarin**	Increased toxicity

monoamine oxidase (MAO) by a number of drugs, known as MAO inhibitors, earlier used for the treatment of endogenous depression. **Tyramine,** a dietary constituent, is normally metabolized by the gut and liver MAO. However, when MAO is inhibited, tyramine passes largely unchanged through the intestinal mucosa and liver, and can induce the release of large amounts of noradrenaline from the sympathetic neurones leading to a hypertensive crisis. Thus selective MAO-A inhibitors, like **clorgyline**, will induce hypertensive crisis with tyramine-containing foods such as cheese, meat, yeast extracts and wines, since tyramine is a substrate for MAO-A. However, MAO-B inhibitors, like **deprenyl,** will not induce the cheese reaction because tyramine will be inactivated by MAO-A

There are also some enzyme inhibition drug interactions which are **therapeutically useful. Disulfiram** (and other drugs like metronidazole, tinidazole, chlorpropamide, tolbutamide and nitrofurantoins) inhibit the enzyme aldehyde dehydrogenase so that the metabolism of ethanol is inhibited with accumulation of acetaldehyde. The unpleasant reactions induced by the latter form the basis of **'aversion therapy'** for alcoholics.

4. Drug excretion interactions

One drug may affect the renal excretion of another by affecting urinary pH, glomerular filtration, tubular reabsorption and tubular secretion (*see* Chapter 2). Competition for **renal tubular secretion** appears to be an important mechanism though alterations in the filtrate pH can influence drug reabsorption. Thus the excretion of acidic drugs such as warfarin, barbiturates, phenylbutazone, salicylates, sulphonamides and streptomycin is greater in *alkaline urine* because of **ionization** and **reduced reabsorption**, while the excretion of basic drugs such as atropine, ephedrine, amphetamine, chloroquine, mepacrine and pethidine is greater in *acidic urine*. The reverse is true for reabsorption. In fact, amphetamine abusers take bicarbonates to enhance reabsorption of the drug in an alkaline urine. Modulation of excretion kinetics of one drug by another has been used for the treatment of diseases, e.g. using penicillin with probenecid in gonococcal infections, and alkaline diuresis in barbiturate

poisoning. Some other examples of drug excretion interaction likely to be of clinical relevance are given in Table 18.4.

Table 18.4
Interactions due to drug excretion

Drug	*Inhibits excretion of*	*Effect*
Loop diuretics	Aminoglycosides	Renal toxicity
NSAIDs	Lithium	Increased toxicity
Probenecid	Penicillin, cephalosporins	Prolonged action
Phenylbutazone	Oral antidiabetics	Hypoglycaemia
Spironolactone	Digoxin	Increased toxicity

III. PHARMACODYNAMIC INTERACTIONS

The drug interactions involving additive, synergistic or antagonistic effects of drugs acting on the same receptors or physiological systems, account for most of the clinically important interactions .

1. Interactions at pharmacological receptors

Agonist-antagonist interaction has been discussed in Chapter 2). In most cases such interaction is predictable and avoidable. However, sometimes the antagonism appears **paradoxical**, viz. antagonism of morphine by pentazocine where the latter acts as a partial agonist, blocking the action of morphine on the opiate *mu* receptors and as an analgesic by acting on the *kappa* receptors. Similarly, the mutual antagonism between the two peripherally acting muscle relaxants, d-tubocurarine and succinylcholine, is based on the difference in their mechanism of action, the former acting by inhibiting depolarization and the latter by inducing persistent depolarization at the neuromuscular junction. Though some of these produce adverse reactions, this pharmacodynamic interaction is mainly **useful in the treatment of patients with drug overdosage.**

Drug synergism, involving the action of two drugs on the same or different receptor sites, can also lead to adverse drug interactions (Chapter 2). Thus, all central depressants can induce synergistic sedation when combined. The potentiation of ethanol-induced central depression by diazepam, antihistamines, phenothiazines, barbiturates, clonidine and methyldopa are well documented. This becomes more **important in elderly subjects**, where, due to their altered pharmacokinetics, toxic manifestations appear early and may become life threatening. Serious interactions characterized by extrapyramidal syndromes and irreversible dementia have been reported with lithium combined with haloperidol or α-methyldopa, and with a combination of α-methyldopa and haloperidol, possibly due to their action on dopamine receptors. The synergistic effects of β-adrenergic blockers and calcium channel antagonists, leading to atrioventricular conduction blocks, and the potentiation of neuromuscular blocking agents by verapamil are some other examples.

2. Interaction between drugs acting on the same physiological system

Interactions of this type may involve both synergism and antagonism. Thus, all aspirin-like drugs reduce platelet adhesiveness and potentiate warfarin anticoagulation. Aminoglycoside antibiotics potentiate neuromuscular blocking agents, while frusemide potentiates the ototoxicity of aminoglycosides. Ethanol-induced vasodilatation and hypotension can have serious synergistic consequences with antihypertensive agents. The synergistic gastric toxicity of paracetamol and ibuprofen combinations may be related to inhibition of PG synthesis. Some examples of this type of interaction are given in Table 18.5.

Table 18.5
Interactions of drugs acting on the same physiological system

Drugs	*Effect*
Carbenoxolone-spironolactone	Abolition of ulcer healing
Thiazides/propranolol-aspirin	Decreased antihypertensive effect
Phenytoin-reserpine	Decreased antiepileptic action
Oral hypoglycaemics-steroids/thiazides/frusemide	Decreased hypoglycaemic action